EXHIBIT

1

IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF TENNESSEE
AT CHATTANOOGA

AMERICAN COLLEGE OF PEDIATRICIANS, on behalf of itself and its members; **CATHOLIC MEDICAL ASSOCIATION**, on behalf of itself and its members; and **JEANIE DASSOW, M.D.**; *Plaintiffs,* v. **XAVIER BECERRA**, in his official capacity as Secretary of the United States Department of Health and Human Services; **UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES**; **LISA J. PINO**, in her official capacity as Director of the Office for Civil Rights of the U.S. Department of Health and Human Services; and **OFFICE FOR CIVIL RIGHTS OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**, *Defendants.*	Civil Action No. 1:21-cv-195

DECLARATION OF QUENTIN VAN METER, M.D.

I, QUENTIN VAN METER, M.D., pursuant to 28 U.S.C. § 1746, hereby declare as follows

1. I am over eighteen years of age and make this declaration on personal knowledge. If called as a witness, I could and would testify competently to the matters set for herein.

2. Currently, I am the President of the American College of Pediatricians ("ACPeds"). Given my involvement in ACPeds, I am familiar with the organization's history, the issues confronting it, the views of the organization, and its members' views and medical practices, including with respect to the gender identity mandate

(under Section 1557 or the 2016 Grants Rule) and its implications on medical practice at issue in this litigation.

3. I am a pediatric endocrinologist. In 1969 I graduated from the College of William and Mary. I attended the Medical College of Virginia and received my medical degree in 1973.

4. I did a pediatric internship in 1973, and a pediatric residency from 1974 to 1976, at the Naval Regional Medical Center in Oakland, through the University of California, San Francisco.

5. I completed a pediatric endocrinology fellowship from 1978 to 1980 at The Johns Hopkins Hospital.

6. I worked as a staff pediatric endocrinologist at the Naval Hospital in San Diego from 1980 to 1986.

7. I was Chairman and Director of the residency training program at the Naval Hospital Oakland from 1986 to 1991.

8. In 1991, I retired from a 20-year career in the Navy Medical Corps and moved to the Atlanta area where I joined the Fayette Medical Clinic as a Pediatrician and Pediatric Endocrinologist.

9. To better serve the ever-expanding population of pediatric patients with endocrine disorders, I developed a full-time endocrine practice, today called Van Meter Pediatric Endocrinology, P.C.

10. I am also an adjunct associate professor of Pediatrics at Emory University School of Medicine and an Associate Clinical Professor of Pediatrics at Morehouse Schools of Medicine.

11. I have campaigned around the world to educate health care professionals about the harm of affirmation of gender incongruence.

12. I and my wife of almost 50 years are active members of the parish of the Cathedral of Christ the King in Atlanta, where I am a member of the choir.

13. I am a member of the Catholic Medical Association.

14. I am not a member of the Christian Medical & Dental Associations.

15. Many members of ACPeds are not members of the Christian Medical & Dental Associations.

I. American College of Pediatricians and its membership.

16. ACPeds is a Tennessee not-for-profit corporation. In 2002, ACPeds was incorporated in Tennessee with its initial office located within this judicial district in Bristol, Tennessee. Since then, ACPeds has filed annual reports with the Tennessee Secretary of State, and the corporation is currently in good standing with the State of Tennessee.

17. ACPeds' registered agent for service of process is located in the State of Tennessee.

18. ACPeds' membership includes more than 600 physicians and other healthcare professionals drawn from 47 different States across the nation.

19. ACPeds has members within this judicial district and elsewhere in the State of Tennessee.

20. Though its origins are in Tennessee, and it continues to maintain a presence in this State through its members, ACPeds is a national organization of pediatricians and other healthcare professionals dedicated to the health and well-being of children. ACPeds has leadership and staff located throughout the country. Reflecting the current practices of modern virtual workplaces, it maintains a physical mailing address in Florida for administrative staff, although all staff work remotely.

21. Most ACPeds' members participate in health programs and activities receiving federal financial assistance.

22. Most ACPeds members treat patients who are members of federal healthcare programs such as Medicaid, Medicare, and CHIP, and are thus subject to Section 1557.

23. Many ACPeds members also work in hospitals that receive HHS grants, and some provide services in clinics serving rural or underserved populations.

24. Upon information and belief, the hospitals where ACPeds members provide care receive grants from HHS, as do the clinics serving rural or underserved populations.

II. American College of Pediatricians' and its members' views.

A. Introduction

25. Consistent with the Hippocratic Oath, ACPeds' mission is to enable all children to reach their optimal physical and emotional health and well-being from the moment of conception.

26. ACPeds' principles and activities are guided by the Hippocratic Oath and the similar traditions of the medical profession.

27. ACPeds is a scientific medical association in which our members share and discuss medical research, emerging treatments and trends related to caring for children. ACPeds conducts literature reviews and researches the literature, including preparing various reports, testimonies, or publications. Some members also may conduct clinical research studies.

28. Consistent with the Hippocratic Oath, ACPeds' mission is to enable all children to reach their optimal physical and emotional health and well-being from the moment of conception.

29. As a secular, scientific medical association, ACPeds' views are not religious as such, although some ACPeds members have religious beliefs consistent with their and ACPeds' scientific and medical ethics beliefs. ACPeds is welcoming both towards members who hold religious beliefs and towards those who do not. While

some of ACPeds' individual members are religious, others are non-religious and identify with no organized religion.

30. ACPeds and its members are dedicated to caring for all children regardless of their family structure, race, ethnicity, religious, ideology, sexual attractions, and gender identity. That commitment extends to caring for LGBTQ+ youth, parents, and families, including children who identify as a gender different from their biological sex; here I refer to such persons as "transgender youth" or "transgender-believing youth."

31. ACPeds' members care for transgender youth in a variety of ways ranging from setting broken bones, to conducting physicals, to treating acute and chronic illnesses. ACPeds is unaware of any of its members denying this critical, ordinary care to transgender youth. Anything less would be violation of the Hippocratic Oath and would also cause ACPeds to expel those members for not meeting our organization's ethical standards.

32. ACPeds and its members provide high-quality care to all people regardless of a given patient's "internal sense of gender," and believe that all people should be given the best medical care possible, regardless of their gender identity.

33. ACPeds and its members understand how individual teachers, educators, physicians, and therapists may be well-meaning when they encounter children with symptoms of depression or anxiety, but it opposes actions that can sterilize children as a way to address their anxiety.

34. ACPeds and its members sincerely believe that sex is a biological, immutable characteristic—a scientific reality, not a social construct.

35. ACPeds and its members are dedicated to doing what is best for all patients regardless of their varying backgrounds. This does not mean we are bound to provide, recommend, or prescribe a treatment on demand.

36. The Hippocratic Oath acknowledges this, in requiring us to "do no harm" to patients, and in specifying such requirements as, "Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course," the Oath requires. The bar on "suggest[ing] such a course" also limits our members' ability to refer patients for treatments they do not believe are in their patients' best interests.

B. Views on HHS's gender identity mandate.

37. HHS's gender identity mandate (under Section 1557 or the 2016 Grants Rule) conflict with our organization's foundational principles, and the core ethical beliefs of our members. The mandate violates our beliefs by requiring ACPeds' members to provide gender-transition interventions, treat patients as if their sex is their gender identity and not their actual biological sex, and engage in speech affirming gender identity regardless of the doctors' medical judgment and religious or ethical objections.

38. ACPeds members are predominately pediatricians and specialists, including but not limited to pediatric surgeons, family medicine physicians and pediatricians who are dual certified in pediatrics and adult internal medicine.

39. Many members have practices that may include adults, such as family medicine or internal medicine practices, or general surgery, and these practitioners object to these procedures for all adults as well as children.

40. ACPeds members thus seek protection from HHS's gender identity mandates for all aspects of their practices.

41. The HHS gender identity mandate requires ACPeds' members to engage in various practices to which our members object on medical and ethical grounds, including the following:

a. Prescribing puberty blockers off-label from the FDA-approved indication, in order to treat gender dysphoria or for the diagnosis of

gender dysphoria, and initiate or further transition in adults, young adults, and children;

b. Prescribing hormone therapies off-label from the FDA-approved indication, in order to treat gender dysphoria or for the diagnosis of gender dysphoria in adults, young adults, and children;

c. Providing other continuing or pharmacologic interventions to further gender transitions ongoing in both adults, young adults, and minors;

d. Performing hysterectomies or mastectomies on healthy women or healthy adolescent women who believe themselves to be men;

e. Removing the non-diseased ovaries of healthy women or healthy adolescent women who believe themselves to be men;

f. Removing the testicles of healthy men or healthy adolescent men who believe themselves to be women;

g. Performing a process called "de-gloving" to remove the skin of a man's penis and use it to create a faux vaginal opening;

h. Removing vaginal tissue from women to facilitate the creation of a faux or cosmetic penis;

i. Performing or participating in any of the above mutilating cosmetic procedures, or similar surgeries,[1] in order to place a patient somewhere along the socially constructed gender identity spectrum;

j. Offering to perform, provide, or prescribe any and all such interventions, procedures, services, or drugs;

k. Referring patients for any and all such interventions, procedures, services, or drugs;

[1] Similar objectionable surgeries include orchiectomy and penectomy (removal of testicles and penis); clitoroplasty, labiaplasty, and vaginoplasty (creation of a clitoris, labia, and vagina); vulvectomy and vaginectomy (removal of vulva and vagina); and metoidioplasty and phalloplasty (creation of penis).

l. Ending or modifying the policies, procedures, and practices of ACPeds' members to not refer for, offer, perform, or prescribe these procedures, drugs, and interventions;

m. Saying in their professional opinions that these gender intervention procedures are the standard of care, are safe, are beneficial, are not experimental, or should otherwise be recommended;

n. Treating patients according to gender identity and not sex;

o. Expressing views on gender interventions that they do not share;

p. Saying that sex is nonbinary or on a spectrum;

q. Using language affirming any self-professed gender identity that does not correspond to biological sex;

r. Using patients' preferred pronouns according to gender identity, rather than using no pronouns or using pronouns based on biological sex;

s. Creating medical records and coding patients and services according to gender identity not biological sex;

t. Providing to the government assurances of compliance with the gender identity mandate, providing compliance reports, and posting notices of compliance in prominent physical locations;

u. Refraining from expressing their medical, ethical, or religious views, options, and opinions to patients when those views disagree with gender identity theory or transitions; and

v. Allowing patients to access single-sex programs and facilities, such as mental health therapy groups, breastfeeding support groups, post-partum support groups, educational sessions, changing areas, restrooms, communal showers, and other single-sex programs and spaces, by gender identity and not by biological sex.

For ease of reference, these practices are referred to herein as the "objectionable practices."

C. Views on human sexuality.

42. ACPeds and its members have deep, substantial, science-based concerns about transgender interventions. I use the term "transgender interventions" here to refer to medical procedures such as surgery, and drug regimens such as puberty-blockers and hormone therapy, to facilitate a patient's "transition" from the sex they have biologically to the opposite sex or to another gender (or genders) with which the patient identifies, which I also refer to as a condition called "gender dysphoria."

43. Human sexuality is an objective biological binary trait: "XY" and "XX" are genetic markers of sex—not genetic markers of a disordered body. The norm for human design is to be conceived either male or female with the obvious purpose being the reproduction and flourishing of our species. This principle is self-evident. Children who identify as "feeling like the opposite sex" or "somewhere in between" do not comprise a third sex. They remain biological boys or biological girls.[2]

44. The idea that a child with gender dysphoria is born with a brain of the sex opposite that of the body is incorrect and biologically impossible, although this idea persists in the culture despite scientific objections by medical experts and researchers. Every cell of the human body contains identical copies of a person's sex chromosomes, and the brains of biologically normal infants are imprinted prenatally by their own endogenous sex hormones at eight weeks of age.

[2] For more details, see the ACPeds position statements, ACPeds, Sex is a Biological Trait of Medical Significance (March 2021), https://acpeds.org/position-statements/sex-is-a-biological-trait-of-medical-significancehttps://acpeds.org/position-statements/sex-is-a-biological-trait-of-medical-significance, & ACPeds, Gender Dysphoria in Children (November 2018), https://acpeds.org/position-statements/gender-dysphoria-in-childrenhttps://acpeds.org/position-statements/gender-dysphoria-in-children.

45. Every infant boy is born with a brain imprinted by testosterone; every infant girl is born with a brain imprinted by estrogen. Brain studies of transgender adults that purport to show differences in brain microstructures are of notoriously poor quality and more than likely reflect the fact that long-term transgender behavior alters brain microstructures. The latter is known as the well-established phenomenon of neuroplasticity, whereby behavior alters the chemical and physical structure of the brain. However, these brain cells remain biologically male or female.

46. Normalizing the myth of innate gender fluidity will cause psychological trauma to youth who are not confused about their gender identity.

47. Disorders of sex development (DSD), commonly referred to as intersex conditions, do not demonstrate the contrary. Disorders of sex development are maladies in which normal sexual differentiation and function are disrupted. Some argue that disorders of sex development demonstrate the existence of more than two sexes. But disorders of sex development do not represent additional reproductive organs, gonads, or gametes. Thus, by definition, disorders of sex development do not constitute additional sexes.

48. Human sex is a binary, not a spectrum, and disorders of sex development are rare congenital disorders affecting 0.02% of the population in which either genitalia are ambiguous in appearance, or an individual's sexual appearance fails to match what would be expected given the person's sex chromosomes. Reflecting the unfortunate nature of these conditions, all disorders of sex development are linked to impaired fertility.

D. Views on drug therapy in transgender interventions.

49. Puberty is not a disease. It is a critical window of normal development that is irreparably disrupted by puberty blockers. There are no long-term studies of Lupron (discussed below) or other puberty blockers for gender dysphoria. There is

thus no evidence that puberty blockers are reversible and harmless in gender incongruent youth as is claimed.

50. To the contrary, when normal puberty is artificially arrested, valuable time is forever stolen from these children, time that should be spent in normal development. This time period, during which highly significant and irreplaceable advances in bone, brain, and sexual development occur, is time—and development—that can never be recovered.

51. Among other things, there is not a single long-term study to demonstrate the safety or efficacy of transgender interventions such as puberty blockers, cross-sex hormones, and surgeries for transgender-believing youth who suffer from gender dysphoria.

52. By contrast, there is research indicating these interventions are harmful., resulting in infertility, heart attacks, strokes, and other chronic illnesses.[3]ACPeds and its members view such interventions to be both experimental and harmful, and therefore parents cannot provide informed consent for minors receiving them, nor can minors provide assent for these interventions.

53. Currently, in the United States, there are no drugs approved by the Food and Drug Administration (FDA) to treat gender dysphoria, much less to treat the

[3]Leena Nahata, et al., "Understudied and Under-Reported: Fertility Issues in Transgender Youth—A Narrative Review" Journal of Pediatrics 205:265-271 (February 2019); Jacqueline Ruttimann, "Blocking Puberty in Transgender Youth" Endocrine News (January 2013), https://endocrinenews.endocrine.org/blocking-puberty-in-transgender-youth/; Julie Compton, "Transgender men, eager to have biological kids, are freezing their eggs" NBC News (March 5, 2019), https://www.nbcnews.com/feature/nbc-out/transgender-men-eager-have-biological-kids-are-freezing-their-eggs-n975331;Darios Getahun, et al., "Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study" Annals of Internal Medicine 169(4):205-213 (August 21, 2018); Talal Alzahrani, et al., "Cardiovascular Disease Risk Factors and Myocardial Infarction in the Transgender Population" Circulation 12(4):e005597 (2019); Katrien Wierckx, et al., "Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study" European Journal of Endocrinology 169(4):471-478 (2013); Priyanka Boghani, "When Transgender Kids Transition, Medical Risks are Both Known and Unknown" Frontline (June 30, 2015), https://www.pbs.org/wgbh/frontline/article/when-transgender-kids-transition-medical-risks-are-both-known-and-unknown/.

condition through transgender interventions. The primary drug used for the purposes of blocking puberty to facilitate transgender interventions is LUPRON DEPOT-PED ("Lupron"). That drug is approved by FDA to treat pediatric patients with central precocious puberty. (Ex. A, Lupron Dep Label, at p. 1.) Central precious puberty is a condition which causes early sexual development in boys and girls. Lupron is not an FDA-approved treatment for gender dysphoria. To the extent the product is prescribed for gender dysphoria, it is prescribed outside the scope of or "off" the FDA-approved label.

54. The warnings and precautions section of the FDA-approved label for Lupron notes that "[p]sychiatric events have been reported in patients taking GnRH agonists, including LUPRON DEPOT-PED," and that "[p]ostmarking [sic] reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger and aggression." (*Id.* at 8.) As such, the label calls for "[m]onitoring for development or worsening of psychiatric symptoms during treatment with LUPRON DEPOT-PED." (*Id.*)

55. The Lupron label also notes "convulsions have been observed in patients receiving GnRH agonists, including LUPRON DEPOT-PED," that "[t]hese included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs," and that "[c]onvulsions have also been reported in patients in the absence of any of the conditions mentioned above." (*Id.*) Given that SSRIs or selective serotonin reuptake inhibitors are widely used to treat children suffering from depression,[4] this warning causes particular concern for ACPeds members.

[4]*See, e.g.*, Anne M. Libby et al., *Decline in Treatment of Pediatric Depression After FDA Advisory on Risk of Suicidality With SSRIs*, 164 Am. J. Psychiatry 844 (2007) (describing trends with respect to SSRI use prescribing in pediatric populations).

56. Under certain conditions, prescribing drugs off-label is an accepted part of medical practice. For off-label prescribing to be accepted though, there needs to be substantial clinical evidence supporting the off-label use in the form of peer-reviewed literature showing that a particular drug is safe and effective. The use must also be medically necessary in that there are no alternative therapies to treat the off-label indication. *See* American Academy of Pediatrics, *Policy Statement: Off-Label Use of Drugs in Children*, 133 Pediatrics 563, 566 (2014) (providing recommendations regarding use of drugs off-label in children).

57. With respect to puberty blockers to facilitate transgender interventions, the pre-conditions for off-label use are not present. ACPeds is aware of no single long-term study showing the safety and efficacy of puberty blockers to treat gender dysphoria. Further, alternatives to transgender interventions for gender dysphoria exist, including watchful waiting with counseling, which has proven successful for many children and young adults.[5]

58. Further, in addition to the harmful potential side effects listed above, all puberty blockers, including Lupron, arrest sexual development by acting on the brain. Boys are chemically castrated and girls chemically driven into premature menopause for as long as the puberty blockers are used. This developmental arrest may cause permanent sexual dysfunction, infertility, bone loss, and altered brain

[5]James Cantor, M.D., *Do trans- kids stay trans- when they grow up?* Sexology Today! (Jan. 11, 2016), http://www.sexologytoday.org/2016/01/do-trans-kids-stay-trans-when-they-grow_99.html ("Despite the differences in country, culture, decade, and follow-up length and method, all the studies have come to a remarkably similar conclusion: Only very few trans- kids still want to transition by the time they are adults. Instead, they generally turn out to be regular gay or lesbian folks. The exact number varies by study, but roughly 60–90% of trans- kids turn out no longer to be trans by adulthood."); ACPeds, Psychotherapeutic and behavioral approaches to treating gender dysphoria (including gender identity disorder & transsexualism) in adults and adolescents (2021)https://acpeds.org/assets/Psych-studies-gender-identity-final-17-June-2021.pdf (summarizing psychology studies); Andre Van Mol, The Scientific Case for Counseling Choice for LGBTQ Identified Youth, American College of Pediatricians,https://acpeds.org/blog/the-scientific-case-for-counseling-choice-for-lgbtq-identified-youth (collecting studies and reporting high-level conclusions of existing research).

development. In one report, gender-distressed girls exhibited greater self-harm, emotional problems, and body dissatisfaction while taking puberty blockers.[6]

59. Before these new procedures and interventions, the majority of gender-distressed children would embrace their bodies when supported through natural puberty. In contrast, all studies of gender dysphoric youth given puberty blockers reveal nearly 100% of them go on to identify as 'transgender' and request cross-sex hormones. This suggests that puberty blockers "lock" kids into their gender confusion. As a result, these children who have their development blocked in early puberty, and are later given cross-sex hormones, may be permanently sterilized, when they would otherwise naturally resolve their confusion.

60. Cross-sex hormones, namely testosterone and estrogen, are widely used in transgender interventions. *See* Cecile A. Unger, Hormone therapy for transgender patients, 2016 *Translational Andrology & Urology* 877 (2016) (listing hormone therapies in use). None of the FDA-approved hormone therapies identified in Unger's article as currently available are FDA-approved treatments for gender dysphoria. Further, as the analysis below shows, these therapies present significant risks, particularly with respect to the pediatric patients ACPeds members are obligated to protect and serve.

61. In table 1 of the Unger article, five formulations are listed as "Testosterone options for transgender men," four of which are available in the United States. I have reviewed the current FDA-approved labeling for currently marketed drugs for each of these formulations. From that review, I was able to determine the FDA-approved indications as follows:

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[6] Michael Biggs, Tavistock's Experimentation with Puberty Blockers: Scrutinizing the Evidence, Transgender Trend (March 2, 2019), https://www.transgendertrend.com/tavistock-experiment-puberty-blockers/.

a. The drug testosterone enanthate for injection which is indicated as a treatment for primary hypogonadism (congenital or acquired), hypogonadotropic hypogonadism (congenital or acquired), and delayed puberty in males, and metastatic mammary cancer in females, (Ex. B, Testosterone Enanthate injection, at pp. 2-3.);

b. The drug TESTOPEL which is approved to treat certain conditions such as primary hypogonadism, (Ex. C, Testopel Label, at p. 2); and

c.Transdermal gels containing testosterone such as AndroGel 1% which is indicated "replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone," (Ex. D, AndroGel Label, at p. 1); and

d. Transdermal patches containing testosterone such as ANDRODERM which is "indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone," (Ex. E, Androderm Label, at p. 1).

62. Each of these testosterone therapies have various limitations and warnings set forth on their FDA-approved labeling. I obtained these government-approved labels from DailyMed, an online database maintained by the National Institutes of Health, a component of HHS. Below is a non-exhaustive sample of the different warnings and precautions listed on the FDA-approved labeling for these medications:

a. Testerosterone ethanate "should be used very cautiously in pediatric patients and only by specialists who are aware of the adverse effects on bone maturation." Some of the side effects listed for biological females are "are amenorrhea and other menstrual irregularities, inhibition of gonadotropin secretion, and virilization, including deepening of the voice and clitoral enlargement." Voice deepening and clitoral enlargement "usually [are] not

reversible after androgens are discontinued." (Ex. B, Testosterone Enanthate Label, at p. 6.)

b. TESTOPEL's label states it should also be "used very cautiously in pediatric patients and only by specialists who are aware of the adverse effects on bone maturation." (Ex. C, Testopel Label, at p. 5.) TESTOPEL's label also states that "premature closure of bony epiphyses with termination of growth, and precocious puberty" has "been reported in male and female adolescents" using the therapy. (*Id.* at p. 6.)

c. AndroGel's labeling states flatly that "[t]he safety and efficacy of AndroGEl 1% in pediatric patients less than 18 years has not been established." (Ex. D, AndroGel Label at p 12.).

d. ANDRODERM's labeling states that "[d]ue to lack of controlled studies in women and potential virilizing effects, ANDRODERM is not indicated for use in women." (Ex. E, Androderm Label, at p. 5.)

63. Table 2 of Unger's article provides a list of "estrogen and anti-androgen options for transgender women." Table 2 lists nine different formulations. As with the drugs listed in Table 1, I reviewed the current FDA-approved labeling for currently marketed drugs within each of these nine formulation categories. The table below presents each of these nine drug categories below with their corresponding FDA-approved indication.

Drug	Indications	Source
Estradiol (Oral)	• Treatment of moderate to severe vasomotor symptoms associated with the menopause. • Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. • Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. • Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease. • Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only). • Prevention of osteoporosis.	Ex. F, Estradiol Label, at p. 5.
Estradiol valerate (injection)	• Treatment of moderate to severe vasomotor symptoms associated with the menopause. • Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. • Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. • Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).	Ex. G, Estradiol Valerate (injection) Label, at p. 4.

Drug	Indications	Source
Estradiol (transdermal)	• Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause. • Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause. • Treatment of Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure. • Prevention of Postmenopausal Osteoporosis.	Ex. H, Estradiol Transdermal Patch Label, at p. 1.
Progesterone	Progesterone Capsules are indicated for use in the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogens tablets. They arealso indicated for use in secondary amenorrhea.	Ex. I, Progesterone Label, at p. 8.
Medroxyprogesterone acetate (oral)	Treatment of secondary amenorrhea and abnormal uterinebleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterinecancer. They are also indicated for use in the prevention of endometrial hyperplasia innonhysterectomized postmenopausal women who are receiving daily oral conjugated estrogens 0.625mg tablets.	Ex. J, Medroxyprogesterone Acetate Label, at p. 6.
GnRH agonist (leuprolide)	Treatment of endometriosis and uterine leiomyomata.	Ex. K, Leuprolide Acetate Label, at p. 1.
Histrelin implant	Treatment of children with central precocious puberty.	Ex. L, Histrelin Acetate Label, at p. 1.
Spironolactone	Certain kinds of heart failure, management of edema, and primary hyperaldosternism.	Ex. M, Spironolactone Label, at p. 1.

Drug	Indications	Source
Finasteride	Male pattern baldness.	Ex. N, Finasteride Label, at p. 1.

64. As with the products listed in Table 1 of the Unger article, the labels for the products in the above table disclose numerous warnings and precautions, including but not limited to the following:

a. The labeling for estradiol, estradiol valerate, estradiol transdermal patch, progesterone, and medroxyprogesterone acetate all contain so-called "black-box" warnings related to the use of those therapies in combination with other therapies. (Ex. F, Estradiol Label, at 1; Ex. G, Estradiol Valerate (injection) Label at 1; Ex. H, Estradiol Transdermal Patch Label, at 1; Ex. I, Progesterone Label, at 1; Ex. J, Medroxyprogesterone Acetate Label, at 1.)

b. The labeling of estradiol and estradiol valerate states that "[s]afety and effectiveness in pediatric patients [has] not been established"—as in established for the labeled indications. (Ex. F, Estradiol Label, at 12; Ex. G, Estradiol Valerate (injection) Label at 10.)

c.The labeling for estradiol transdermal, progesterone, and medroxyprogesterone acetate states that those products "is not indicated in children." (Ex. H, Estradiol Transdermal Patch Label, at 14; Ex. I, Progesterone Label, at 12 Ex. J, Medroxyprogesterone Acetate Label, at 11.)

d. Leuprolide acetate product labeling states that the safety and effectiveness of that product has "not been established in premenarcheal pediatric patients." (Ex. K, Leuprolide Acetate Label, at 15.)

e.Histrelin's labeling discloses reports of psychiatric events and convulsions in some circumstances. (Ex. L, Histrelin Acetate Label, at 12.)

f. The labeling for spironolactone states that the "[s]afety and effectiveness in pediatric patients [has] not been established." (Ex. M, Spironolactone Label, at 9.)

g. Finasteride is expressly "not indicated for use in pediatric patients." (Ex. N, Finasteride Label, at 4.)

65. Cross-sex hormones also put youth at an increased risk of heart attacks, stroke, diabetes, blood clots, cancer and other serious diseases across their lifespan.

66. The best long-term evidence we have among adults shows medical intervention fails to reduce suicide. Studies cannot easily show whether gender dysphoria results from other underlying mental health issues, themselves correlated with high rates of suicide, or if those mental health issues are the result of the stresses of being a stigmatized minority. Indeed, some research has linked suicide for transgender people to issues arising out of romantic relationships rather than social stigma.[7]

67. Suicide risk among trans-identified youth is less than or comparable to that of other at-risk groups of youth; children with gender dysphoria often also have depression, anorexia, autism, and other psychological conditions predisposing them to suicide; and prevention of suicide for trans-identified youth is the same as for other youth: talk therapy and FDA-approved psychiatric medications. All in all, research shows that "there is no long-term evidence that puberty blockers, cross sex hormones or 'transition' surgeries prevent suicide. On the contrary, the best long-term research shows that individuals who do go through medical transition kill themselves at a rate 19 times greater than the general population."[8]

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[7] Mark L.Hatzenbuehler, et al, "RETRACTED: Structural stigma and all-cause mortality in sexual minority populations," Social Science & Medicine, https://doi.org/10.1016/j.socscimed.2013.06.005.

[8]Jane W. Robbins & Vernadette R. Broyles, Child & Parental Rights Campaign, The Myth About Suicide and Gender Dysphoric Children, https://acpeds.org/assets/for-GID-page-1-The-Myth-About-Suicide-and-Gender-Dysphoric-Children-handout.pdf (emphasis omitted) (summarizing research and

68. Again, while health care providers, including pediatricians, do prescribe drugs off-label, the requirements of peer-reviewed studies demonstrating the safety and efficacy of these treatments as well as the presence of alternatives as a treatment to gender dysphoria all weigh against prescribing these therapies to children. That would particularly be true in circumstances in which doctors would have to prescribe a therapy contraindicated by a drug's FDA-approved labeling, which would be the case for at least some of the therapies at issue.

69. Even so, ACPeds is unaware of any other medical area where HHS requires healthcare providers to provide a certain procedure or prescribe a particular drug, especially if that procedure or prescription conflicts with the provider's medical judgment, ethical concerns, or religious beliefs.

70. Nor are we aware of any effectively compulsory medical procedures or interventions that lack long-term efficacy studies or that effectively require off-label use of a particular drug, to include use of a drug which presents particular risks to children.

D. Views on transgender surgical interventions.

71. ACPeds and its members are aware of cases where pediatric patients are being treated with surgical interventions for gender dysphoria. Girls as young as 13 years-old are currently receiving double mastectomies to facilitate their transition to a trans-boy. Health care providers have removed the penises and testicles of boys as young as 16 years-old.

72. With respect to transitioning males, surgeons engage in a process called "de-gloving" of the penis. This procedure involves stripping the outer skin of the

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collecting sources). Puberty blockers actually cause depression and other emotional disturbances related to suicide; cross-sex hormones (testosterone for women; estrogen for men) may disrupt mental health; and the most reliable research shows that in the long run, medical transition does not reduce and may even exacerbate the psychological distress that could lead to suicide. *Id.*

penis and transplanting to the inside of an open wound in the pelvis area to create a simulated vaginal opening.

73. For transitioning females, surgeons remove vaginal tissue in order to create a faux or cosmetic penis.

74. Given the nature of these procedures, the consequences are traumatic, permanent, lifelong, and irreversible. There are no long-term studies establishing the safety and efficacy of these surgical interventions.

E. Views on international perspectives on transgender interventions for youth.

75. Transgender-affirmative interventions are not the international standard of care for youth.[9]

76. I have provided statements on international standards of care to bodies such as the Constitutional Court of Bulgaria and the Supreme Court of Cassation.

77. Many medical organizations around the world, including the Australian College of Physicians,[10] the Royal College of General Practitioners in the United Kingdom,[11] and the Swedish National Council for Medical Ethics[12] have criticized

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[9]Jane W. Robbins & Vernadette R. Broyles, Child & Parental Rights Campaign, *Do Physicians and Health Professionals Really Support "Gender-Affirming" Interventions in Minors?*, https://acpeds.org/assets/Do-Physicians-and-Health-Professionals-Really-Support-Gender-Affirming-Interventions-in-Minors-handout.pdf (Many "U.S. medical and mental health associations have identified these radical interventions as harmful to minors and advocate for extensive psychological evaluation and treatment of minors and families. Furthermore, medical societies in other industrialized nations have raised similar alarms about such interventions in minors.").

[10] Michael Cook, *Australia launches inquiry into safety and ethics of transgender medicine*, BioEdge.org, 18 Aug 2019. https://www.bioedge.org/bioethics/australia-launches-inquiry-into-safety-and-ethics-of-transgender-medicine/13182 ("A national inquiry into the safety and ethics of transgender medicine will be conducted by the Royal Australasian College of Physicians with the backing of Federal Health Minister Greg Hunt.").

[11] Royal College of General Practitioners, *The role of the GP in caring for gender-questioning and transgender patients*, RCGP Position Statement (June 2019), https://www.rcgp.org.uk/-/media/Files/Policy/A-Z-policy/2019/RCGP-position-statement-providing-care-for-gender-transgender-patients-june-2019.ashx?la=en ("There is an urgent need to increase the capacity of gender identity specialists and clinics and expand the understanding of gender variance issues across the entire health system, including more definitive knowledge about the causes of rapidly increasing referrals and the outcomes of interventions or 'wait and see' policies.").

the lack of research for prescribing puberty blockers and cross-sex hormones in youth, and have called for systemic review and studies, rather than confirming that these procedures are not experimental and dangerous.

78. World-renowned child psychiatrist Dr. Christopher Gillberg has referred to this as "possibly one of the greatest scandals in medical history."[13] His neuropsychiatry research group at Gothenburg University has called for "an immediate moratorium on the use of puberty blocker drugs because of their unknown long-term effects."[14]

79. The United Kingdom, Sweden, and Finland have taken steps to limit these interventions in youth. Sweden's Karolinska University Hospital restricted its use of the Dutch Protocol (transgender interventions) to children over 16 years old stating it is "potentially fraught with extensive and irreversible adverse consequences such as cardiovascular disease, osteoporosis, infertility, increased cancer risk, and thrombosis."[15] Finland, too has issued guidelines restricting these

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[12] Swedish National Council for Medical Ethics, (Apr. 26, 20219) https://www.transgendertrend.com/wp-content/uploads/2019/04/SMER-National-Council-for-Medical-Ethics-directive-March-2019.pdf ("The national commission for overseeing medical and social protocols and outcomes should be instructed to undertake a systematic review of the scientific evidential basis for assessment of children and young persons with gender dysphoria, and what is known about long-term effects on physical and mental health.").

[13] Jonathan Van Maren, *World-renowned child psychiatrist calls trans treatments "possibly one of the greatest scandals in medical history,"* The Bridgehead (Sept. 25, 2019), https://thebridgehead.ca/2019/09/25/world-renowned-child-psychiatrist-calls-trans-treatments-possibly-one-of-the-greatest-scandals-in-medical-history/ ("Professor Gillberg's neuro-psychiatry group at Sweden's Gothenburg University — which has research hubs in Britain, France and Japan — has called for an immediate moratorium on the use of puberty blocker drugs because of their unknown long-term effects.") (citing The Australian, https://www.theaustralian.com.au/nation/doctors-back-inquiry-on-kids-trans-care/news-story/6f352bc99da430b194620a2605e8a50d).

[14] *Id.*

[15] Cummings DM, *Swedish Hospital No Longer Gives Puberty Blockers or Sex Hormones to Children*,"Lifesite News (May 6, 2021), available at https://www.lifesitenews.com/news/swedish-hospital-no-longer-gives-puberty-blockers-sex-hormones-tochildren; Karolinska University Hospital Dutch Protocol Policy, https://segm.org/sites/default/files/Karolinska%20_Policy_Statement_English.pdf (last accessed Oct. 6, 2021) (concluding that from April 1, 2021 onwards, "hormonal treatments (i.e., puberty blocking and cross-sex hormones) will not be initiated in gender dysphoric patients under the age of 16").

interventions.[16]In December 2020, the High Court of the United Kingdom in the case of Keira Bell barred hormonal interventions in youth under the age of 16, and decreed physicians seek court approval for hormonal interventions in youth between 16 and 18 years old.[17] (This decision was overturned on appeal on the grounds that the case should not have reached these issues, and so permission to seek review by the UK's Supreme Court is forthcoming.) The UK is also undertaking a comprehensive review of these procedures, separate from litigation, to create new recommendations for the best standard of care.[18]

80. HHS's gender identity mandate ignored these international perspectives.

III. Effect of HHS's gender identity mandate on the members of American College of Pediatricians.

81. The issues identified above contribute to the deep, substantial, science-based concerns ACPeds and its members have about transgender interventions.[19]

82. HHS's gender identity mandate limits or prohibits the ability of ACPeds members to engage in speech advising patients of their medical judgment about gender-transition procedures, it forces them to offer services or facilities to further gender transitions, and it requires them to inaccurately refer to a patient's sex orally and in medical records.

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[16] Finland's Guidelines for Dutch Protocol in youth, available at https://palveluvalikoima.fi/documents/1237350/22895008/Summary_minors_en.pdf/aaf9a6e7-b970-9de9-165cabedfae46f2e/Summary_minors_en.pdf (accessed June 7, 2021).

[17] *R (on the application of) Quincy Bell and A v Tavistock and Portman NHS Trust and others*, [2020] EWHC 3274(Admin) (Dec. 1, 2020), (Ruling of U.K. High Court in Keira Bell Case), https://www.judiciary.uk/wp-content/uploads/2020/12/Bell-v-Tavistock-Clinic-and-ors-Summary.pdf (last accessed October 6, 2021).

[18] Eleanor Lawrie, *Ruling limiting under-16s puberty blockers overturned*, BBC (Sept. 17, 2021) https://www.bbc.com/news/uk-58598186.

[19] For more information, see the many resources at ACPeds, *Gender Confusion and Transgender Identity*, https://acpeds.org/topics/sexuality-issues-of-youth/gender-confusion-and-transgender-identity (last visited Aug. 23, 2021), & Family Watch International, *Transgender Issues Videos*, https://familywatch.org/transgenderissues/#.YRl6kohKg2x (last visited Aug. 23, 2021).

83. ACPeds and its members believe that the gender identity interventions described herein can be harmful to patients, particularly children, resulting in infertility, heart attacks, strokes, and other chronic illnesses, and that medical science does not support the provision of such procedures and interventions.

84. ACPeds members cannot perform or refer patients to other healthcare providers who will perform such procedures. ACPeds members believe it would violate their obligation to their patients as expressed in the Hippocratic Oath.

85. ACPeds has members who have treated or currently treat individuals who identify contrary to their biological sex, and these members would be liable for failure to engage in the objectionable practices under HHS's gender identity mandate.

86. ACPeds members thus include healthcare providers with medical, ethical, and conscientious objections to providing gender-transition interventions as being not in the best interests of patients, as well as members with religious objections.

87. ACPeds also believes that to eliminate sex-specific private spaces violates fundamental rights of all persons to privacy, safety, and a secure environment. In healthcare programs, as in schools, locker rooms, and restrooms, the facilities exist for the utilitarian purpose of hygiene, not to affirm the self-identified gender of certain individuals. These facilities are traditionally restricted to persons of the same sex for the sound and self-evident reason that such separation protects the bodily privacy of all. It also shields girls and women from offensive, criminal, or dangerous behaviors of voyeurs, exhibitionists, and rapists, whose claim to identify contrary to their biological sex may made as a pretext to take advantage of access given to persons who identify contrary to their biological sex.

88. Rather than end single-sex spaces by allowing persons of either sex to access them, there is a commonsense solution to respect the many individuals who are uncomfortable in public facilities for various reasons, including religious beliefs,

disability, deformity, or discomfort with their body, as well as gender dysphoria. A reasonable accommodation is a single-occupancy restroom available for all people who are uncomfortable with the standard arrangement of sex-specific bathrooms or locker rooms.

89. Defendants' gender identity mandate, if not enjoined, would cause ACPeds members to violate their oaths, their conscience, and cause them to engage in a course of procedures and interventions which is manifestly not in the best interests of patients.

90. ACPeds members are pediatricians whose practices are, by and large, limited to children and whose scope of practice would not include the gender interventions that pertain to adults. For these members, the objectionable practices primarily concern those provided to children, based on the scope of their practice, although many members have practices that may include adults, such as family medicine or internal medicine practices, or general surgery, and so these ACPeds practitioners object to these procedures for adults. ACPeds members thus seek relief for all aspects of their practices.

A. Impact on specific individual members of American College of Pediatricians.

91. ACPeds members practice in each of these various situations, and each would suffer the harm identified if HHS's gender identity mandate is fully enforced.

92. Some ACPeds members are self-censoring out of fear of enforcement of HHS's gender identity mandate.

93. Some ACPeds members continuing to practice consistent with their views and therefore face the danger of enforcement penalties as the result of HHS's gender identity mandate.

94. HHS's gender identity mandates jeopardize virtually every member of ACPeds, including, for example, subjecting to a risk of harm the following specific

and identified representative ACPeds members—each of whom continue to practice medicine without performing the HHS gender identity mandates' objectionable practices.

95. For example, ACPeds has a member who practices in Tennessee, referred to herein as Dr. Jane Doe 1. Dr. Jane Doe 1 is a member of ACPeds and shares ACPeds' views.

96. Dr. Jane Doe 1 is a pediatrician and has a private practice where she currently sees patients. Dr. Jane Doe 1 provides services to patients reimbursed by Medicaid and CoverKids Tennessee.

97. If her patients need hospitalization, Dr. Jane Doe 1 provides care in a hospital that receives federal financial assistance from HHS.

98. Dr. Jane Doe 1 is not a member of the Catholic Medical Association or the Christian Medical & Dental Associations.

99. Dr. Jane Doe 1 is therefore directly affected by the Section 1557 gender identity mandate in her practice but opposes engaging in the objectionable practices with respect to her patients.

100. Dr. Jane Doe 1 wishes to remain anonymous due to serious concerns of liability and harassment.

101. Dr. Jane Doe 1 has practiced and wishes to practice medicine consistent with the principles concerning gender identity she shares with ACPeds, but she fears liability from the Section 1557 gender identity mandate if she continues to practice and speak consistent with those principles.

102. As another example, Dr. Jane Doe 2 practices in Kentucky. Dr. Jane Doe 2 is a member of ACPeds and shares ACPeds' views.

103. Dr. Jane Doe 2 is a pediatrician who currently sees patients. Dr. Jane Doe 2 provides services to patients reimbursed by Medicaid.

104. Dr. Jane Doe 2 is not a member of the Catholic Medical Association or the Christian Medical & Dental Associations.

105. Dr. Jane Doe 2 is therefore directly affected by the Section 1557 gender transition mandate in her practice but opposes engaging in the objectionable practices with respect to her patients.

106. Dr. Jane Doe 2 wishes to remain anonymous due to serious concerns of liability and harassment.

107. Dr. Jane Doe 2 has practiced and wishes to practice medicine consistent with the principles concerning gender identity she shares with ACPeds but fears liability from the Section 1557 gender identity mandate if she continues to practice and speak consistent with those principles.

108. As another example, Dr. Jane Doe 3 practices in Ohio. Dr. Jane Doe 3 is a member of ACPeds and shares ACPeds' views.

109. Dr. Jane Doe 3 is a pediatrician who currently sees patients. Dr. Jane Doe 3 provides services to patients reimbursed by Medicaid.

110. Dr. Jane Doe 3 is not a member of the Catholic Medical Association or the Christian Medical & Dental Associations.

111. Dr. Jane Doe 3 is therefore directly affected by the Section 1557 gender transition mandate in her practice but opposes engaging in the objectionable practices with respect to her patients.

112. Dr. Jane Doe 3 wishes to remain anonymous due to serious concerns of liability and harassment.

113. Dr. Jane Doe 3 has practiced and wishes to practice medicine consistent with the principles concerning gender identity she shares with ACPeds but fears liability from the Section 1557 gender identity mandate if she continues to practice and speak consistent with those principles.

114. As another example, Dr. John Doe 1 practices in Michigan. Dr. John Doe 1 is a member of ACPeds and shares ACPeds' views.

115. Dr. John Doe 1 is a full-time pediatrician who currently sees patients. Dr. John Doe 1 provides services to patients reimbursed by Medicaid.

116. Dr. John Doe 1 is not a member of the Catholic Medical Association or the Christian Medical & Dental Associations.

117. Dr. John Doe 1 is therefore directly affected by the Section 1557 gender transition mandate in his practice but opposes engaging in the objectionable practices with respect to his patients. Dr. John Doe 1 wishes to remain anonymous due to serious concerns of liability and harassment.

118. Dr. John Doe 1 has practiced and wishes to practice medicine consistent with the principles concerning gender identity he shares with ACPeds but fears liability from the Section 1557 gender identity mandate if he continues to practice and speak consistent with those principles.

119. I, Dr. Quentin Van Meter, practice in Georgia.

120. As the President of ACPeds, I am a member of ACPeds and share ACPeds' views.

121. I am a pediatric endocrinologist who currently sees patients.

122. I run Van Meter Pediatric Endocrinology, P.C., in Atlanta, Georgia.

123. I provide services to patients reimbursed by Georgia Medicaid and PeachCare for Kids.

124. If my patients need hospitalization, I provide care in a hospital that receives federal financial assistance from HHS.

125. I am also an adjunct associate professor of Pediatrics at Emory School of Medicine at Emory University, and an Associate Clinical Professor of Pediatrics at Morehouse School of Medicine.

126. Emory School of Medicine, and Egleston Children's Hospital, both at Emory University, receive grants from HHS.[20]

127. Morehouse School of Medicine receives grants from HHS.[21]

128. I am a member of the Catholic Medical Association but not of the Christian Medical & Dental Associations.

129. I have campaigned around the world to educate health care professionals about the harm of affirmation of gender incongruences.

130. My objections to these practices include non-religious bases, such as the scientific fact, which informs my medical judgment, that puberty blockers and cross-sex hormones combined will sterilize many youth and cause them to develop serious chronic illnesses such as diabetes, heart disease, stroke and cancers that they otherwise would have never experienced.

131. I have practiced and wish to practice medicine consistent with the principles concerning gender identity I share with ACPeds and CMA but I fear liability from the Section 1557 gender identity mandate if I continue to practice and speak consistent with those principles.[22]

B. Impact of compliance or noncompliance with the gender identity mandate.

132. ACPeds members will never abandon a patient and they will discuss procedures and interventions used for altering biological sex characteristics under informed consent, but they oppose engaging in the objectionable practices.

133. The gender identity mandate presents our members with three choices: (1) not comply with the government's mandates, and risk significant government

[20] See https://taggs.hhs.gov/Detail/RecipDetail?arg_EntityId=LTAOtDJaByWI9stW6s6X9w%3D%3D ; https://taggs.hhs.gov/Detail/RecipDetail?arg_EntityId=zjGDHVo18kRSWbK0a1xgzA%3D%3D .
[21] See https://taggs.hhs.gov/Detail/RecipDetail?arg_EntityId=SF8WH7U3Ut3uJrGxjRfczw%3D%3D .
[22] For more information about me, see ACPeds, President Quentin Van Meter, MD (last accessed Oct. 29, 2021), https://acpeds.org/about/meet-our-board/president-quentin-van-meter-md.

enforcement and penalties, likely driving them out of much of the healthcare field and market; or (2) comply with the government's mandates, abandoning their medical, conscientious, and religious beliefs, and accept the dangers and burdens of compliance; or (3) exit most healthcare fields entirely, a penalty in and of itself.

134. Our members are susceptible to risk under the gender identity mandate at any moment.

135. If our members do not abide by HHS's mandates, they face losing access to federal healthcare program funds, potential civil lawsuits from plaintiffs, and being investigated by HHS's Office for Civil Rights or the Attorney General, imposing significant costs of time, money, attorney's fees, and diversion of resources our members could use to continue providing quality medical care and receive compensation for the same.

136. HHS's announcement of enforcement of Section 1557 gender identity mandate, as well as the gender identity language in the 2016 Section 1557 Rule and the 2016 Grants Rule, create substantial confusion and uncertainty for ACPeds' members.

137. If our members do not comply with the gender identity mandate, they risk expulsion from participation in Medicaid, Medicare, and CHIP, and from receiving, or participating in other programs receiving, federal financial assistance.

138. Failure to comply with the gender identity mandate threatens our members with loss of income and employment.

139. Our members will incur increased costs from the investigation and enforcement of claims against them, and they will suffer damaging barriers to their ability to participate in the marketplace as healthcare providers.

140. Many of our members cannot continue their healthcare practices if they are not eligible to participate in federal healthcare programs like Medicare, Medicaid, and CHIP.

141. The gender identity mandate requires our members to incur significant burdens of time and resources to plan for how they must either comply or risk loss of participation in federal programs.

142. The gender identity mandate has necessitated that our members spend time and money training staff, issuing guidance, and engaging in public education campaigns to mitigate the confusion caused by the mandate.

143. The gender identity mandate limits and compels the speech of our members, including what they can say to patients.

144. As the result of the gender identity mandate, many of our members are unlikely to express their full and frank views to patients for fear of liability.

145. If our members were to comply with the gender identity mandate, they would suffer the loss of their integrity and reputation because it will be perceived that they profess one thing but do another.

146. Such loss of integrity and reputation devastates conscientious medical professionals and their practices, and it makes patients less likely to trust them, which in turn drives patients away from their practices.

147. At the same time, all providers and members need assurance that they can provide complete, accurate information and timely and responsive medical care in an environment that protects their constitutional rights and does not expose them to stigma and harm because of their medical judgment, conscientious objections, and religious beliefs.

148. If our members comply with the gender identity mandate by performing gender transition interventions, they take on increased malpractice liability due to the risks and harms of those interventions, and of patients later regretting the decision to undergo those interventions. ACPeds members are thus stuck between HHS and a risk of litigation that is significant, but difficult to quantify.

149. At the same time the gender identity mandate constricts our members' ability to warn patients about the risks and harms of gender transition interventions, increasing our members' liability if they were to succumb to the gender identity mandate and perform such interventions in violation of their consciences.

150. Compliance with the gender identity mandate leads to medically unnecessary procedures, wasting the time and money of providers, patients, and insurers, and draining resources that could be better spent elsewhere, especially during a pandemic.

151. Compliance with the gender identity mandate presents risks to our members' patients, including life-threatening risks, by requiring that necessary procedures and inquiries be omitted by our members because those are associated with the patient's biological sex not the patient's gender identity.

152. Imposing the gender identity mandate on our members will deprive our members' patients, who want to receive care from them because of their ethical and religious beliefs, of their chosen doctor.

153. Imposing the gender identity mandate's penalties on our members will harm patients in low-income and underserved communities and regions because it will deprive those patients of our members' care.

C. Impact on patients, society, and the medical profession.

154. Based on my knowledge of doctors who practice medicine according to the Hippocratic Oath, the gender identity mandate will drive thousands of doctors out of the medical profession and out of the care of low-income and underserved patients, and it will dissuade students from choosing to practice medicine.

155. Driving our members out of the health care field by means of the gender identity mandate will place intense strain on the healthcare system in America, will

exacerbate disparities of care among low-income and underserved populations, and will cause immense human suffering and higher medical costs for all. Among other things, the consequences of driving our members out of the health care profession include the following:

a. Patients will experience limited choices for future care, creating likely delays in care and reduced access to care, and all patients will no longer receive care from doctors who share ACPeds' values;

b. Patients will be more likely to hesitate in seeking care because they feel that the doctors will not have their best medical interests or personal religious values at heart, or because they fear putting their doctor in legal jeopardy;

c. This delay will strain the other providers and increase costs for providers, patients, and the healthcare system as a whole;

d. HHS will also cause widespread health disparities by those who share the government's position and those who have other medical opinions, conscientious objections, or religious beliefs;

e. This limited access to care will cause unavoidable human suffering, higher medical costs for everyone, and the inefficient use of medical talents and energy;

f. It will also lead to a cultural disrespect for those with differing medical and religious views, causing discriminatory effects for those doctors and patients who do not share the government's position out of their own medical judgment, ethical positions, conscientious objections, or religious beliefs; and

g. Ultimately, most providers exist are willing to comply with HHS's view of the law and policy, this agency action will create many more health disparities than it will resolve.

156. Families have a right to know certain facts regarding documented harms associated with transgender interventions as well as the permanence of a decision to follow through with a gender transition.

157. In the past, our members have conveyed medical views and concerns, in appropriate and patient-sensitive ways, to their patients and their families in the context of their clinical practice, but by expressing views that under the gender identity mandate would consider harassment, hostile environment, or discrimination on the basis of gender identity.

158. The gender identity mandate prevents conversations between our members and their patients, and casts a credible threat of government prosecution over those conversations.

159. The gender identity mandate chills the speech of a health care professional of ordinary firmness, and it chills the speech of our members from (1) full and frank conversations on alternatives to gender procedures and interventions; (2) from using proper descriptions of sex in coding and medical records according to biological sex; and (3) from the spoken and written use of biologically correct pronouns.

160. Our members' views also prohibit them from telling patients that they should have healthcare treatments based on gender identity, rather than on biological sex.

161. Our members' medical judgment is that, in general, it is harmful to encourage a patient to undergo gender transition procedures, and so referring for or providing information affirming medical transition procedures is contrary to our members' best medical and ethical judgment.

162. Our members wish to keep using their best medical, ethical, and religious judgments in speaking and giving information to patients, but the gender identity mandate does not allow this.

163. But for the gender identity mandate, our members would continue to speak freely on these matters in healthcare each day in each clinical situation as they deem appropriate, as they have done throughout their careers until this mandate.

164. The gender identity mandate forces our members to participate in facilities, programs, and other healthcare-related endeavors contrary to their best medical judgment, religious beliefs, and expressive identities, and to associate with messages on these topics they disagree with.

165. The gender identity mandate chills the speech of all similarly situated healthcare providers who engage in private speech or religious expression through statements, notices, and other means in healthcare based on sex.

166. Our religious members' sincerely held religious beliefs prohibit them providing, offering, facilitating, or referring for gender transition interventions and also from engaging in or facilitating the objectionable practices.

167. Our religious members exercise their religious beliefs through providing healthcare and through expressing messages during their healthcare practices.

168. Our religious members exercise their religious beliefs through providing healthcare to low-income and underserved populations in health programs and activities funded by HHS, such as Medicaid, Medicare, CHIP, and federally qualified health centers.

169. Our religious members' compliance with these beliefs is a religious exercise.

170. Our religious members' speech about these beliefs is a religious exercise.

171. The gender identity mandate exerts significant pressure on them to violate their beliefs to continue providing healthcare in federally funded health programs and activities or else face exclusion from those programs, loss of funding, loss of livelihood, and investigatory burdens.

172. Our religious members' provision of healthcare in accord with their religious beliefs prevents no one from obtaining gender transition interventions from other providers.

IV. The Impact of the Delay of HHS's SUNSET Rule

173. The delay of the SUNSET Rule harms our members because it removes a procedural avenue for the repeal or modification of the gender identity mandate, and for our members' participation in that review process through the filing of comments by ACPeds.

174. If the Delay Rule itself were subject to notice and comment, our members would raise their concerns to the agency through comments by ACPeds.

175. ACPeds would comment on behalf of our members on several rules that would be offered for public comment because of the SUNSET Rule, including the Section 1557 rule, the Grants Rule, and rules protecting healthcare conscience at 45 C.F.R. Part 88.

176. Our members include small entities. More specifically, many of our employer members are independently owned medical practices organized for profit that are not dominant in their fields on a national basis.

177. ACPeds itself is a small entity.

178. The SUNSET Rule specifically calls for retrospective review of rules like the 2016 Rule which has a significant economic impact on a substantial number of small entities.

V. Verification

I, Quentin Van Meter, a citizen of the United States, hereby declare under penalty of perjury pursuant to 28 U.S.C. § 1746 that the foregoing Declaration is true and correct based on my personal knowledge.

Executed this 9th day of November, 2021.

Quentin L. Van Meter, MD
President, American College of
Pediatricians

Exhibit

A

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUPRON DEPOT-PED safely and effectively. See full prescribing information for LUPRON DEPOT-PED.

LUPRON DEPOT-PED (leuprolide acetate for depot suspension), for intramuscular use
Initial U.S. Approval: 1985

RECENT MAJOR CHANGES

Indications and Usage (1)	03/2021
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5)	03/2021
Contraindication (4)	03/2021
Warnings and Precautions (5.1)	03/2021

INDICATIONS AND USAGE

LUPRON DEPOT-PED is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of pediatric patients with central precocious puberty. (1)

DOSAGE AND ADMINISTRATION

- Must be administered by a healthcare professional. (2.1)
- LUPRON DEPOT-PED is administered as a single-dose intramuscular injection. The starting dose 7.5 mg, 11.25 mg, or 15 mg for 1-month administration is based on the child's weight. (2)
- LUPRON DEPOT-PED is administered as a single-dose intramuscular injection. The doses are either 11.25 mg or 30 mg for 3-month administration.(2)
- Hormonal and clinical parameters should be monitored during treatment to ensure adequate suppression. (2)
- The injection site should be varied periodically. (2)
- See Full Prescribing Information for administration and reconstitution instructions. (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

For depot suspension: leuprolide acetate as a lyophilized powder supplied in single-dose, prefilled dual-chamber syringe with diluent (3):

- For 1-month administration: 7.5 mg, 11.25 mg, or 15 mg
- For 3-month administration: 11.25 mg or 30 mg

CONTRAINDICATIONS

- Hypersensitivity reactions to GnRH, GnRH agonists or any of the excipients in LUPRON DEPOT-PED (4)
- Pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- *Initial Rise of Gonadotropins and Sex Steroid Levels:* During the early phase of therapy, gonadotropins and sex steroids may rise above baseline because of the initial stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms of puberty, including vaginal bleeding, may be observed during the first weeks of therapy or after subsequent doses. (5.1)
- *Psychiatric events:* Have been reported in patients taking GnRH agonists. Events include emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms. (5.2)
- *Convulsions*: Have been observed in patients with or without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions. (5.3)

ADVERSE REACTIONS

- Adverse events related to suppression of endogenous sex steroid secretion and injection site reactions including abscess may occur with LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration. (6.1, 6.2)
- In the clinical studies for LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15mg for 1-month administration the most common (≥2%) adverse reactions were: emotional lability, headache, general pain, acne/seborrhea, rash including erythema multiforme and vaginitis/vaginal bleeding/vaginal discharge. (6.1)
- In the clinical studies for LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration the most common (≥2%) adverse reactions were: injection site pain, weight increased, headache, mood altered, and injection site swelling. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUPRON DEPOT-PED is indicated for the treatment of pediatric patients with central precocious puberty (CPP).

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

- LUPRON DEPOT-PED must be administered by a healthcare professional.
- Individualize the dose of LUPRON DEPOT-PED for each patient.
- Each LUPRON DEPOT-PED strength and formulation has different release characteristics. Do not use partial syringes or a combination of syringes to achieve a particular dose.
- In the case of inadequate suppression of pituitary gonadotropins and peripheral sex steroids with a maximal dosage, consider other available gonadotropin releasing hormone (GnRH) agonists indicated for the treatment of central precocious puberty.
- Discontinue LUPRON DEPOT-PED at the appropriate age of onset of puberty.

2.2 Recommended Dosage and Monitoring for 1-Month Administration

- Administer LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-month administration as a single-dose intramuscular injection once every month.
- The starting dose is based on the patient's weight (see Table 1).

Table 1. Dosage Recommendations Based on Body Weight for LUPRON DEPOT-PED for 1-Month Administration

Body Weight	Once Monthly Recommended Dosage
Less than or equal to 25 kg	7.5 mg

Greater than 25 kg up to 37.5 kg	11.25 mg
Greater than 37.5 kg	15 mg

● The dosage may need to be adjusted with changes in body weight.

● If adequate hormonal and clinical suppression is not achieved with the starting dose, increase the dosage to the next available higher dose (e.g., 11.25 mg or 15 mg at the next monthly injection).

● Monitor response with a GnRH stimulation test, basal luteinizing hormone (LH) or serum concentration of sex steroid levels beginning 1 to 2 months following initiation of therapy, with changing doses, or further as judged clinically appropriate in order to confirm maintenance of efficacy.

● Assess height (for calculation of growth rate) and bone age every 6 to 12 months.

2.3 Recommended Dosage and Monitoring for 3-Month Administration

● Use LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration once every three months (12 weeks) as a single-dose intramuscular injection.

● Monitor response with a GnRH stimulation test, basal LH or serum concentration of sex steroid levels at months 2 to 3, month 6 and further as judged clinically appropriate, to confirm maintenance of efficacy.

● Assess height (for calculation of growth rate) and bone age every 6 to 12 months.

2.4 Administration

● Administer LUPRON DEPOT-PED as a single-dose intramuscular injection into the gluteal area, anterior thigh, or shoulder.

● Rotate injection sites within the same region from one injection to the next.

● Inject immediately after reconstitution. Discard if not used within 2 hours.

2.5 Reconstitution Instructions

1. Visually inspect the LUPRON DEPOT-PED powder and diluent. Do not use the syringe if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal prior to mixing with the diluent. The diluent should appear clear and free from particulate matter. Do not use the diluent if it is not clear or there is particulate matter.

2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn. (see Figure 1 and Figure 2)

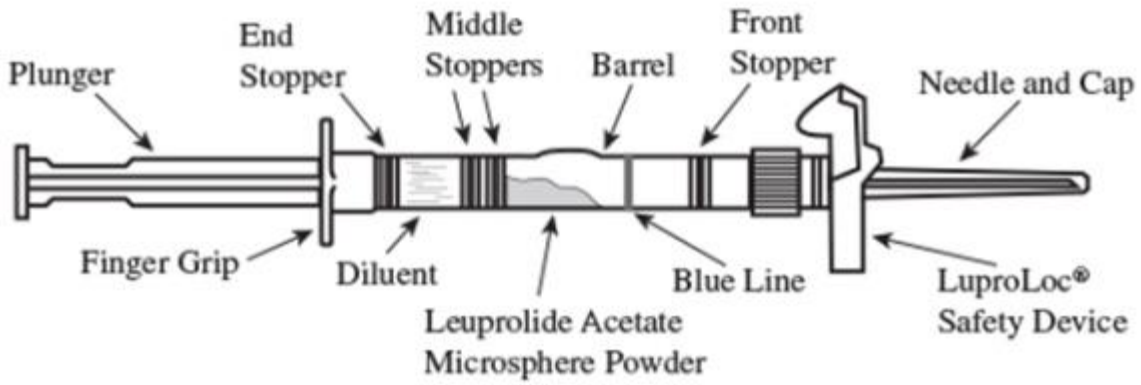


Figure 1

LuproLoc Safety Device should be activated after product injection, refer to Step 9 (Figure 7).

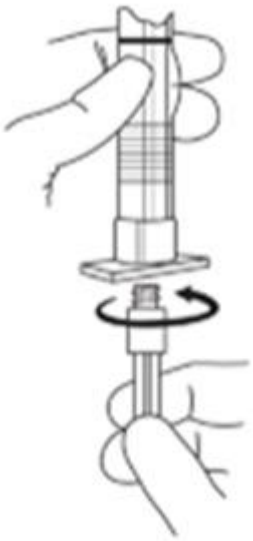


Figure 2

3. Hold the syringe upright. Release the diluent by slowly pushing the plunger for 6 to 8 seconds until the first stopper is at the blue line in the middle of the barrel. (Figure 3)

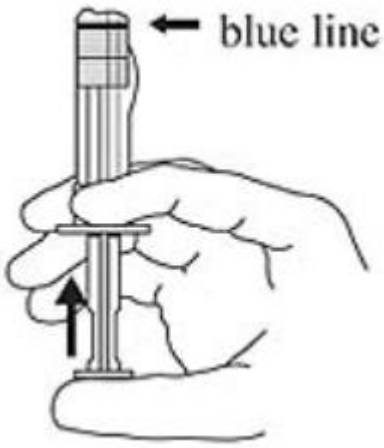


Figure 3

4. Keep the syringe upright. Mix the powder thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. Do not use if any of the powder has not gone into suspension. (Figure 4)

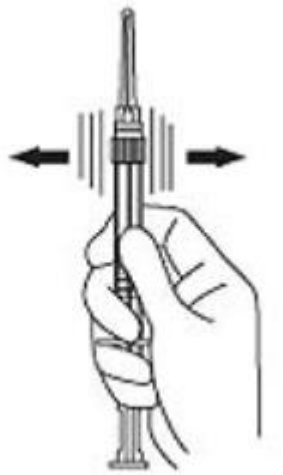


Figure 4

5. Hold the syringe upright. With the opposite hand pull the needle cap upward without twisting.

6. Keep the syringe upright. Advance the plunger to expel the air from the syringe.
Now the syringe is ready for injection.

7. After cleaning the injection site with an alcohol swab, administer the intramuscular injection by inserting the needle at a 90 degree angle into the deltoid, gluteal area, or anterior thigh. (Figure 5)

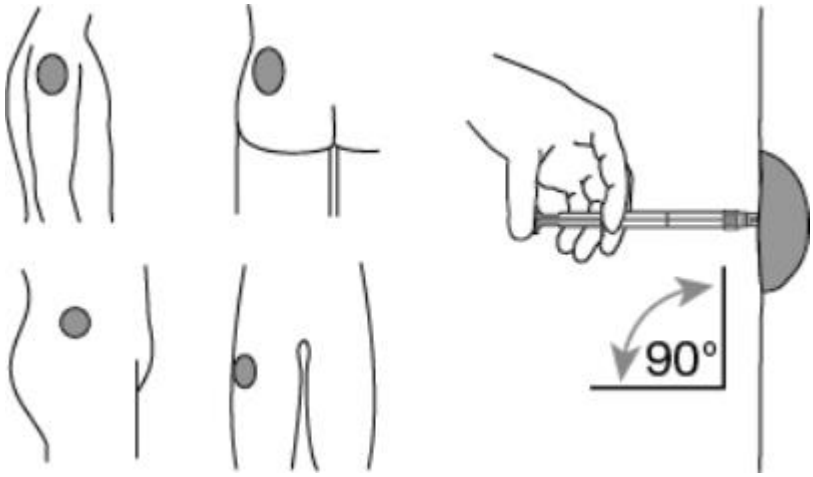


Figure 5

NOTE: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc® safety device. If blood is present remove the needle immediately. Do not inject the medication. (Figure 6)

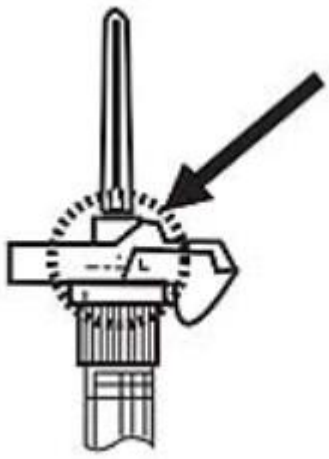


Figure 6

8. Inject the entire contents of the syringe intramuscularly immediately after reconstitution. The suspension settles very quickly following reconstitution.

9. Withdraw the needle. Once the syringe has been withdrawn, activate immediately the LuproLoc® safety device by pushing the arrow on the lock upward towards the needle tip with the thumb or finger, as illustrated, until the needle cover of the safety device is fully extended over the needle and a click is heard or felt. (Figure 7)

Figure 7

3 DOSAGE FORMS AND STRENGTHS

For depot suspension: a white lyophilized powder supplied in a single-dose, prefilled dual-chamber syringe with a colorless diluent is available as:

- For 1-month administration: 7.5 mg, 11.25 mg, or 15 mg of leuprolide acetate
- For 3-month administration: 11.25 mg or 30 mg of leuprolide acetate

4 CONTRAINDICATIONS

● Hypersensitivity to GnRH, GnRH agonists or any of the excipients in LUPRON DEPOT-PED. Anaphylactic reactions to synthetic GnRH or GnRH agonists have been reported *[see Adverse Reactions (6.2)]*.

● Pregnancy: LUPRON DEPOT-PED may cause fetal harm *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Initial Rise of Gonadotropins and Sex Steroid Levels

During the early phase of therapy or after subsequent doses, gonadotropins and sex steroids may rise above baseline because of a transient stimulatory effect of the drug *[see Clinical Pharmacology (12.2)]*. Therefore, an increase in clinical signs and symptoms of puberty, including vaginal bleeding, may be observed during the first weeks of therapy or after subsequent doses *[see Adverse Reactions (6)]*.

5.2 Psychiatric Events

Psychiatric events have been reported in patients taking GnRH agonists, including LUPRON DEPOT-PED. Postmarking reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with LUPRON DEPOT-PED *[see Adverse Reactions (6.2)]*.

5.3 Convulsions

Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, including LUPRON DEPOT-PED. These included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described here and elsewhere in the label:

- Initial rise in gonadotropin and sex steroid levels *[see Warnings and Precautions (5.1)]*.
- Psychiatric Events *[see Warnings and Precautions (5.2)]*.
- Convulsions *[see Warnings and Precautions (5.3)]*.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

LUPRON DEPOT-PED for 1-month administration

LUPRON DEPOT-PED 1-month administration was evaluated in a pivotal, open label, multicenter study in which 55 (49 female and 6 male) pediatric patients with central precocious puberty were enrolled. The age ranged from 1 to 8 years of age at the beginning of treatment; the mean age for females was 6.8 years (range: 1 to 9 years) and the mean age for males was 7.5 years (range: 4 to 9 years); 61.8% were Caucasian; 20% Black; 1.8% Oriental; and 16.4% Hispanic.

Adverse reactions that occurred in ≥2% of patients are shown in Table 2.

Table 2. Adverse Reactions Occurring in ≥2% in Pediatric Patients with CPP Receiving LUPRON DEPOT-PED 1-month

	% of Patients (N = 421)
Injection Site Reactions Including Abscess*	9
Emotional Lability	5
Headache	3
General Pain	3

Acne/Seborrhea	3
Rash Including Erythema Multiforme	3
Vaginitis/Vaginal Bleeding/Vaginal Discharge	3
Vasodilation	2
* Most events were mild or moderate in severity.	

Less Common Adverse Reactions

The following adverse reactions were reported in less than 2% of the patients and are listed below by body system.

Body as a Whole – aggravation of preexisting tumor and decreased vision, allergic reaction, body odor, fever, flu syndrome, hypertrophy, infection;

Cardiovascular System – bradycardia, hypertension, peripheral vascular disorder, syncope; *Digestive System* – constipation, dyspepsia, dysphagia, gingivitis, increased appetite, nausea/vomiting;

Endocrine System – accelerated sexual maturity, feminization, goiter;

Hemic and Lymphatic System – purpura;

Metabolic and Nutritional Disorders – growth retarded, peripheral edema, weight gain; *Musculoskeletal System* – arthralgia, joint disorder, myalgia, myopathy;

Nervous System – hyperkinesia, somnolence;

Psychiatric System – depression, nervousness;

Respiratory System – asthma, epistaxis, pharyngitis, rhinitis, sinusitis;

Integumentary System (Skin and Appendages) – alopecia, hair disorder, hirsutism, leukoderma, nail disorder, skin hypertrophy;

Urogenital System – cervix disorder/neoplasm, dysmenorrhea, gynecomastia/breast disorders, menstrual disorder, urinary incontinence.

Laboratory: The following laboratory events were reported as adverse reactions: antinuclear antibody present and increased sedimentation rate.

LUPRON DEPOT-PED for 3-month administration

LUPRON DEPOT-PED for 3-month administration was evaluated in a pivotal, open-label, multicenter, clinical study with 84 randomized pediatric patients with central precocious puberty; 76 (90.5%) were females and 8 (9.5%) were males. The age ranged from 1 to 11 years age at the beginning of treatment; 80/84 (95.2%) were 5 years or older, and female patients were younger than male; the mean age for 11.25 mg and 30 mg groups for females was 7.6 and 7.7 years, and for males 9.3 and 9.4 years, respectively; 58.3% were Caucasian; 22.6% were Black; 7.1% were Asian; 1.2% were Native Hawaiian or Other Pacific Islander; and 10.7% were Multi-race.

Adverse reactions that occurred in ≥2% of patients are shown in Table 3.

Table 3. Adverse Reactions Occurring in ≥2% in Pediatric Patients with CPP Receiving LUPRON DEPOT-PED for 3-month administration.

	% 11.25 mg every 3 Months N=42	**% 30 mg every 3 Months N=42**	**% Overall N = 84**
Injection site pain	19	21	20
Weight increased	7	7	7

Headache	2	7	5
Mood altered	5	5	5
Injection site swelling	2	2	2

Less Common Adverse Reactions

The following adverse reactions were reported in one patient and are listed below by system organ class:

Gastrointestinal Disorders – abdominal pain, nausea;

General Disorders and Administration Site Conditions – asthenia, gait disturbance, injection site abscess sterile, injection site hematoma, injection site induration, injection site warmth, irritability;

Metabolic and Nutritional Disorders – decreased appetite, obesity;

Musculoskeletal and Connective Tissue Disorders - musculoskeletal pain, pain in extremity; *Nervous System Disorders* – dizziness;

Psychiatric Disorders – crying, tearfulness;

Respiratory, Thoracic and Mediastinal Disorders – cough;

Skin and Subcutaneous Tissue Disorders – hyperhidrosis;

Vascular Disorders – pallor.

6.2 Postmarketing Experience

The following adverse events have been observed with post-approval use of leuprolide acetate in pediatric patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergic reactions: anaphylactic, rash, urticaria, and photosensitivity reactions.

General: chest pain, weight increase, decreased appetite, fatigue.

Laboratory Abnormalities: decreased WBC.

Metabolic: diabetes mellitus.

Musculoskeletal and Connective Tissue: tenosynovitis-like symptoms, severe muscle pain, arthralgia, epiphysiolysis, muscle spasms, myalgia.

Published literature and postmarketing reports indicate that bone mineral density may decrease during GnRH therapy in pediatric patients with central precocious puberty. Published studies indicate that after discontinuation of therapy, subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected.

Neurologic: neuropathy peripheral, convulsion, insomnia.

Psychiatric Disorders: Emotional lability, such as crying, irritability, impatience, anger, and aggression has been observed with GnRH agonists, including LUPRON DEPOT-PED; Depression, including rare reports of suicidal ideation and attempt, has been reported for GnRH agonists, including LUPRON DEPOT-PED, in children treated for central precocious puberty. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities with an increased risk of depression.

Reproductive System: vaginal bleeding, breast enlargement.

Respiratory: dyspnea.

Skin and Subcutaneous Tissue: injection site reactions including induration and abscess, flushing, hyperhidrosis.

Vascular Disorders: hypertension, hypotension.

7 DRUG INTERACTIONS

7.1 Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT-PED *[see Clinical Pharmacology (12.3)]* .

7.2 Drug-Laboratory Test Interactions

Administration of LUPRON DEPOT-PED in therapeutic doses results in suppression of the pituitary-gonadal system. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to six months after discontinuation of LUPRON DEPOT-PED may be affected. Normal pituitary-gonadal function is usually restored within six months after treatment with LUPRON DEPOT-PED is discontinued.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

LUPRON DEPOT-PED is contraindicated in pregnancy *[see Contraindications (4)]*.

LUPRON DEPOT-PED may cause fetal harm, when administered to a pregnant woman, based on findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. The available data from published clinical studies and case reports and from the pharmacovigilance database on exposure to LUPRON DEPOT-PED during pregnancy are insufficient to assess the risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on animal reproduction studies, LUPRON DEPOT-PED may be associated with an increased risk of pregnancy complications, including early pregnancy loss and fetal harm. In animal reproduction studies, subcutaneous administration of leuprolide acetate to rabbits during the period of organogenesis caused embryo-fetal toxicity, decreased fetal weights and a dose-dependent increase in major fetal abnormalities in animals at doses less than the recommended human dose based on body surface area using an estimated daily dose. A similar rat study also showed increased fetal mortality and decreased fetal weights but no major fetal abnormalities at doses less than the recommended human dose based on body surface area using an estimated daily dose *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% -20%, respectively.

Data

Animal Data

When administered on day 6 of pregnancy at test dosages of 0.00024 mg/kg, 0.0024 mg/kg, and 0.024 mg/kg (doses less than the recommended human dose) to rabbits, leuprolide acetate produced a dose-related increase in malformations comprised primarily of segmental and fusion defects of the skeleton and skull. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of leuprolide acetate in rabbits and with the highest dose (0.024 mg/kg) in rats.

8.2 Lactation

Risk Summary

There are no data on the presence of leuprolide acetate in either animal or human milk, the effects on the breastfed infants, or the effects on milk production. The developmental and health benefits of breastfeeding

should be considered along with the mother's clinical need for LUPRON DEPOT-PED and any potential adverse effects on the breastfed infant from LUPRON DEPOT-PED or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Exclude pregnancy in women of reproductive potential prior to initiating LUPRON DEPOT-PED if clinically indicated *[see Use in Specific Populations (8.1)]*.

Contraception

Females

LUPRON DEPOT-PED may cause embryo-fetal harm when administered during pregnancy. LUPRON DEPOT-PED is not a contraceptive. If contraception is indicated, advise females of reproductive potential to use a non-hormonal method of contraception during treatment with LUPRON DEPOT-PED *[see Use in Specific Populations (8.1)]*.

Infertility

Based on its pharmacodynamic effects of decreasing secretion of gonadal steroids, fertility is expected to be decreased while on treatment with LUPRON DEPOT-PED. Clinical and pharmacologic studies in adults (>18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks *[see Clinical Pharmacology (12.2)]*.

There is no evidence that pregnancy rates are affected following discontinuation of LUPRON DEPOT-PED.

Animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery of fertility suppression.

8.4 Pediatric Use

The safety and effectiveness of LUPRON DEPOT-PED for the treatment of CPP has been established in pediatric patients 1 years of age and older. Use of LUPRON DEPOT-PED for this indication is supported by evidence from two pivotal, open label clinical studies of 139 pediatric patients with central precocious puberty with an age range of 1 to 11 years *[see Clinical Studies (14)]*. The safety and effectiveness of LUPRON DEPOT-PED have not been established in pediatric patients less than 1 year old.

10 OVERDOSAGE

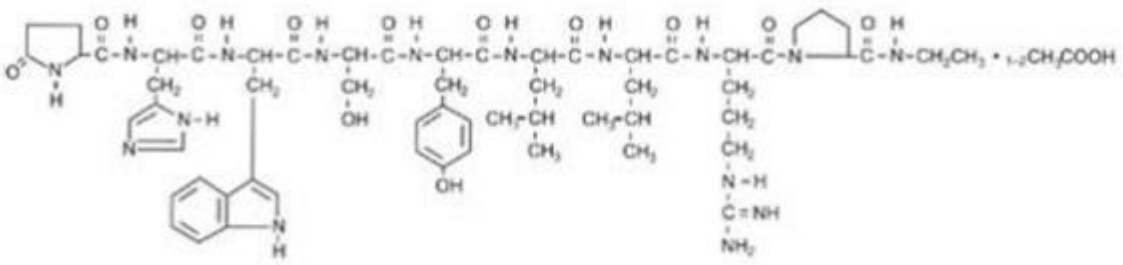
No specific antidotes for LUPRON DEPOT-PED are known. Contact Poison Control (1-800-222-1222) for latest recommendations.

In cases of overdosage, standard of care monitoring and management principles should be followed.

11 DESCRIPTION

LUPRON DEPOT-PED contains active ingredient, leuprolide, in the form of acetate salt, a gonadotropin-releasing hormone (GnRH) agonist. It is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name of leuprolide acetate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate, which has molecular formula of C59H84N16O12.(C2H4O2)n,

n=1 or 2, with the following structural formula:



LUPRON DEPOT-PED for 1-month administration

LUPRON DEPOT-PED is available in a prefilled dual-chamber single-dose syringe containing sterile lyophilized microsphere powder incorporated in a biodegradable lactic acid/glycolid acid copolymer which, when mixed with diluent, becomes a suspension for intramuscular injection. When mixed with 1 mililiter of accompanying diluent, LUPRON DEPOT-PED for 1-month administration is administered as a single-dose intramuscular injection.

The front chamber of LUPRON DEPOT-PED 7.5 mg, 11.25 mg, and 15 mg a prefilled dual-chamber syringe contains leuprolide acetate (7.5/11.25/15 mg), purified gelatin (1.3/1.95/2.6 mg), DL-lactic and glycolic acids copolymer (66.2/99.3/132.4 mg), and D-mannitol (13.2/19.8/26.4 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

LUPRON DEPOT-PED for 3-month administration

LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration is available in a prefilled dual-chamber single-dose syringe containing sterile lyophilized microsphere powder incorporated in a biodegradable lactic acid/glycolid acid copolymer which, when mixed with diluent, becomes a suspension for intramuscular injection. When mixed with 1.5 mililiters of accompanying diluent, LUPRON DEPOT-PED for 3-month administration is administered as a single-dose intramuscular injection.

The front chamber of LUPRON DEPOT-PED 11.25 mg for 3-month administration prefilled dual-chamber syringe contains leuprolide acetate (11.25 mg), polylactic acid (99.3 mg) and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

The front chamber of LUPRON DEPOT-PED 30 mg for 3-month administration prefilled dual-chamber syringe contains leuprolide acetate (30 mg), polylactic acid (264.8 mg) and D-mannitol (51.9 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide acetate, a GnRH agonist, acts as a potent inhibitor of gonadotropin secretion (LH and follicle stimulating hormone (FSH)) when given continuously in therapeutic doses.

12.2 Pharmacodynamics

Following an initial stimulation of GnRH receptors, chronic administration of leuprolide acetate results in downregulation of GnRH receptors, reduction in release of LH and FSH, and consequent suppression of ovarian and testicular production of estradiol and testosterone, respectively. This inhibitory effect is reversible upon discontinuation of drug therapy.

12.3 Pharmacokinetics

Absorption

LUPRON DEPOT-PED for 1-month administration

Following a single LUPRON DEPOT-PED 7.5 mg for 1-month administration to adult patients, mean peak leuprolide plasma concentration was almost 20 ng/mL at 4 hours and then declined to 0.36 ng/mL at 4 weeks. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. Nondetectable leuprolide plasma concentrations have been observed during chronic LUPRON DEPOT-PED 7.5 mg administration, but testosterone levels appear to be maintained at castrate levels.

In a study of pediatric patients with CPP, doses of 7.5 mg, 11.25 mg and 15.0 mg of LUPRON DEPOT-PED were given every 4 weeks. In 22 pediatric patients, trough leuprolide plasma levels were determined according to weight categories as summarized below:

Patient Weight Range (kg)	Group Weight Average (kg)	Dose (mg)	Trough Plasma Leuprolide Level Mean ±SD (ng/mL)*
20.2 - 27.0	22.7	7.5	0.77±0.033
28.4 - 36.8	32.5	11.25	1.25±1.06
39.3 - 57.5	44.2	15.0	1.59±0.65
* Group average values determined at Week 4 immediately prior to leuprolide injection. Drug levels at 12 and 24 weeks were similar to respective 4 week levels.			

LUPRON DEPOT-PED for 3-month administration

Following a single LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration to pediatric patients with CPP, leuprolide concentrations increased with increasing dose with mean peak leuprolide plasma concentration of 19.1 and 52.5 ng/mL at 1 hour for the 11.25 and 30 mg dose levels, respectively. The concentrations then declined to 0.08 and 0.25 ng/mL at 2 weeks after dosing for the 11.25 and 30 mg dose levels. Mean leuprolide plasma concentration remained constant from month 1 to month 3 for both 11.25 and 30 mg doses. The mean leuprolide concentrations 3 months after the first and second injections were similar indicating no accumulation of leuprolide from repeated administration.

Distribution

The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male subjects was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

Elimination

Metabolism

In healthy male subjects given an intravenous 1 mg bolus of leuprolide the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two-compartment model.

In rats and dogs, administration of ^{14}C-labeled leuprolide was shown to be metabolized to smaller inactive peptides; a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Excretion

Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Specific Populations

The pharmacokinetics of LUPRON DEPOT-PED has not been determined in patients with hepatic or renal impairment.

Drug-Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT-PED. Leuprolide acetate is a peptide that is not degraded by cytochrome P-450 enzymes; hence, drug interactions associated with cytochrome P-450 enzymes would not be expected to occur.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

14 CLINICAL STUDIES

14.1 LUPRON DEPOT-PED for 1-month administration

The efficacy of LUPRON DEPOT-PED was evaluated in a pivotal open-label, multicenter clinical trial in which 55 pediatric patients with central precocious puberty (49 females and 6 males, naïve to previous GnRHa treatment) were treated with LUPRON DEPOT-PED 1-month formulations until age was appropriate for entry into puberty (see treatment period data below)and a subset of 40 subjects were then followed post-treatment (see follow-up period data below). The mean ± SD age at the start of treatment was 7 ± 2 years and the duration of treatment was 4 ± 2 years. Study drug was administered intramuscularly (IM) every 28 days, with incremental adjustments of 3.75mg at each clinic visit, if necessary based on clinical and laboratory results. During the follow-up period, GnRHa stimulation test was performed every 6 months until a pubertal response was observed.

During the treatment period, LUPRON DEPOT-PED suppressed gonadotropins and sex steroids to prepubertal levels. Suppression of peak stimulated LH concentrations to < 1.75 mIU/mL was achieved in 96% of subjects by month 1. Five subjects required increased doses of study drug to achieve or retain LH suppression. The number and percentage of subjects with suppression of peak stimulated LH < 1.75 mIU/mL and mean ± SD peak stimulated LH over time is shown in Table 4. Six months after the treatment period was finished, the mean peak stimulated LH was 20.6 ± SD 13.7 mIU/mL (n=30).

The following effects have been noted with the chronic administration of leuprolide: cessation of menses (in girls), normalization and stabilization of linear growth and bone age advancement, stabilization of clinical signs and symptoms of puberty.

Table 4. The number and percentage of patients with peak stimulated LH < 1.75 mIU/mL and Mean (SD) peak LH at each clinic visit

Weeks on Study	n with peak stimulated LH < 1.75 mIU/mL/	Mean (SD) peak LH

	N with a LH measurement for that week		
	n/N	%	
	n/N	%	
Baseline	0/55	0%	35.0 (21.32)
Week 4	53/55	96.4%	0.8 (0.57)
Week 12	48/54	88.9%	1.1 (1.77)
Week 24	48/53	90.6%	0.8 (0.79)
Week 36	51/54	94.4%	0.6 (0.43)
Week 48	51/54	94.4%	0.6 (0.47)
Week 72	52/52	100%	0.5 (0.30)
Week 96	46/46	100%	0.4 (0.33)
Week 120	40/40	100%	0.4 (0.27)
Week 144	36/36	100%	0.4 (0.24)
Week 168	27/28	96.4%	1.2 (4.58)
Week 216	18/19	94.7%	0.5 (0.90)
Week 240	16/17	94.1%	0.4 (0.62)
Week 264	14/15	95.3%	0.4 (0.41)
Week 288	11/11	100%	0.3 (0.22)
Week 312	9/9	100%	0.4 (0.20)
Week 336	6/6	100%	0.3 (0.10)
Week 360	6/6	100%	0.3 (0.13)
Week 384	5/5	100%	0.2 (0.10)
Week 408	3/3	100%	0.2 (0.09)
Week 432	2/2	100%	0.3 (0.04)
Week 456	2/2	100%	0.2 (0.04)
Week 480	1/1	100%	0.2 (NA)
Week 504	1/1	100%	0.2 (NA)

Suppression (defined as regression or no change) of the clinical/physical signs of puberty was achieved in most patients. In females, suppression of breast development ranged from 66.7 to 90.6% of subjects during the first 5 years of treatment. The mean stimulated estradiol was 15.1 pg/mL at baseline, decreased to the lower level of detection (5.0 pg/mL) by Week 4 and was maintained there during the first 5 years of treatment. In males, suppression of genitalia development ranged from 60% to 100% of subjects during the first 5 years of treatment. The mean stimulated testosterone was 347.7 ng/dL at baseline and was maintained at levels no greater than 25.3 ng/dL during the first 5 years of treatment.

A “flare effect” of transient bleeding or spotting during the first 4 weeks of treatment was observed in 19.4% (7/36) females who had not reached menarche at baseline. After the first 4 weeks and for the remainder of the treatment period, no subject reported menstrual-like bleeding, and only rare spotting was noted.

The mean ratio of bone age to chronological age decreased from 1.5 at baseline to 1.1 by end of treatment. The mean height standard deviation z-score changed from 1.6 at baseline to 0.7 at the end of the treatment phase.

Thirty five (35) females and 5 males participated in a post-treatment follow-up period to assess reproductive function (in females) and final height. At 6 months post-treatment, most patients reverted to pubertal levels of LH (87.9%) and clinical signs of resumption of pubertal progression were evident with increase in breast development in girls (66.7%) and increase in genitalia development in boys (80%).

After stopping treatment, regular menses were reported for all female subjects who reached 12 years of age during follow-up; mean time to menses was approximately 1.5 years; mean age of onset of menstruation after stopping treatment was 12.9 years.

Of the 40 patients evaluated in the follow-up, 33 were observed until they reached final or near-final adult height. These patients had a mean increase in final adult height compared to baseline predicted adult height. The mean final adult height standard deviation score was -0.2.

14.2 LUPRON DEPOT-PED for 3-month administration

The efficacy was evaluated in a 6-month, randomized, open-label clinical study of LUPRON DEPOT-PED 3-Month formulations. 84 subjects (76 female, 8 male) between 1 and 11 years of age received the LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration formulation. Each dose group had an equal number of treatment-naïve patients who had pubertal LH levels and patients previously treated with GnRHa therapies who had prepubertal LH levels at the time of study entry. The percentage of subjects with suppression of peak-stimulated LH to < 4.0 mIU/mL, as determined by assessments at months 2, 3 and 6, is 78.6% in the 11.25 mg dose and 95.2% in the 30 mg dose as shown in Table 5.

Table 5. Suppression of Peak-Stimulated LH from Month 2 Through Month 6

	LUPRON DEPOT-PED 11.25 mg every 3 Months			LUPRON DEPOT-PED 30 mg every 3 Months		
Parameter	**Naïve N = 21**	**Prev Trt[a] N = 21**	**Total N = 42**	**Naïve N = 21**	**Prev Trt[a] N = 21**	**Total N = 42**
Percent with Suppression	76.2	81.0	78.6	90.5	100	95.2
2-sided 95% CI	52.8, 91.8	58.1, 94.6	63.2, 89.7	69.6, 98.8	83.9, 100	83.8, 99.4

a. Previously treated with GnRHa for at least 6 months prior to enrollment in pivotal Study L-CP07-167.

The mean peak stimulated LH levels for all visits are shown by dose and subgroup (naïve vs. previously treated subjects) in Figures 1 and 2.

Figure 1. Mean Peak Stimulated LH for LUPRON DEPOT-PED 11.25 mg for 3-month administration

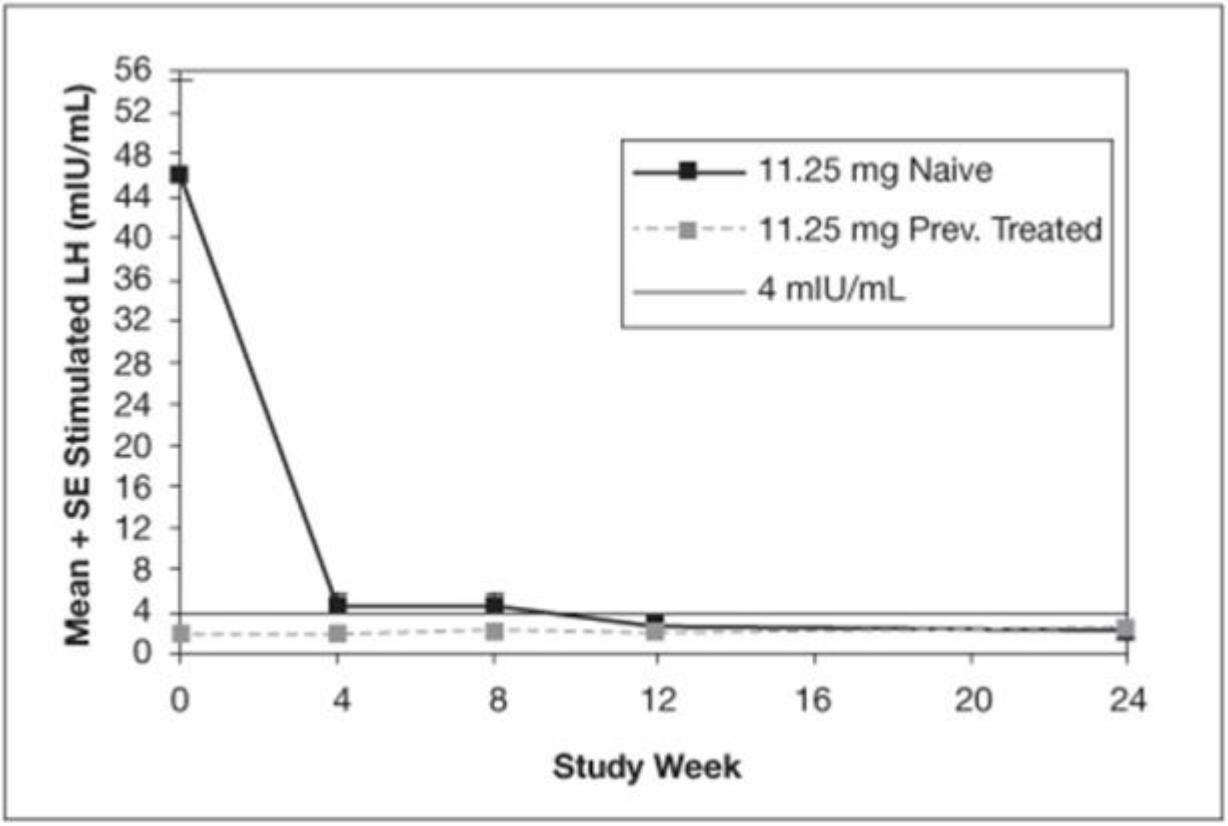
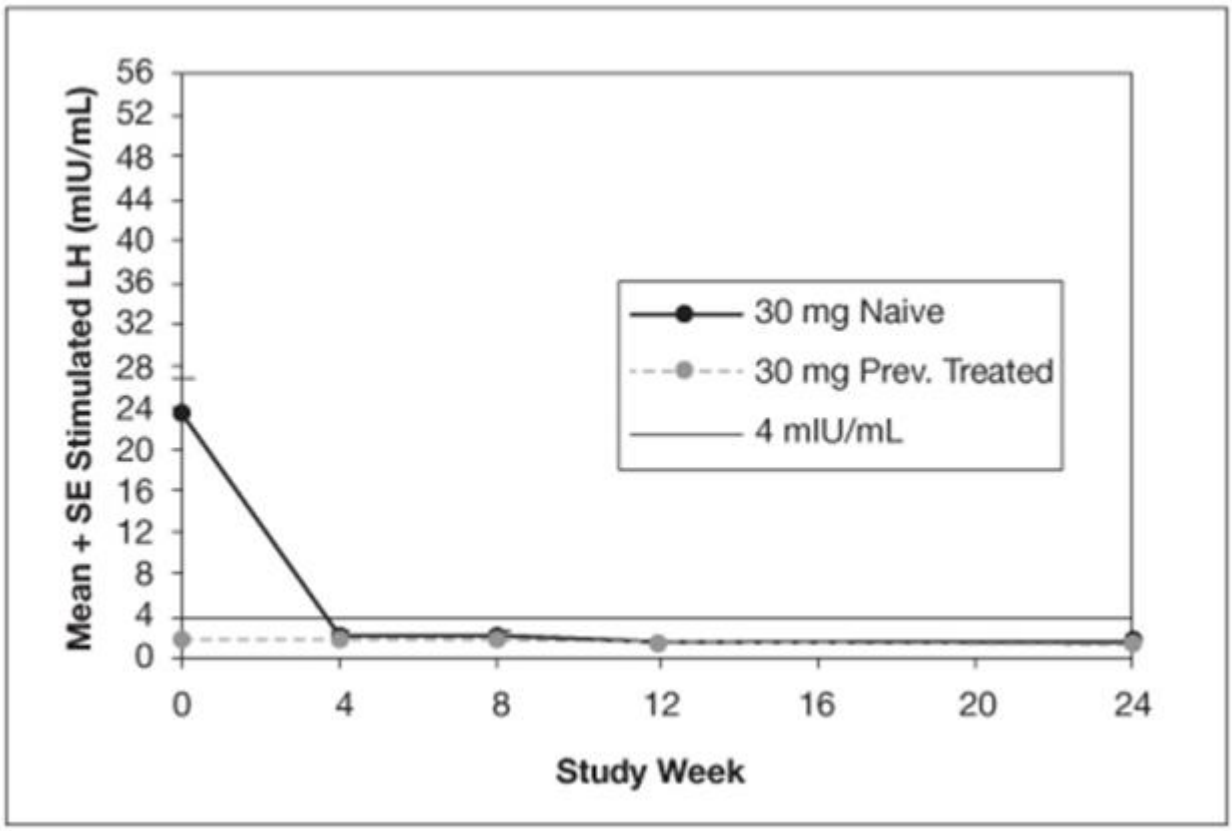


Figure 2. Mean Peak Stimulated LH for LUPRON DEPOT-PED 30 mg for 3-month administration



For the LUPRON DEPOT-PED 11.25 mg dose for 3-month administration, 93% (39/42) of subjects and for LUPRON DEPOT-PED 30 mg dose for 3-month administration, 100% (42/42) of subjects had sex steroid (estradiol or testosterone) suppressed to prepubertal levels at all visits. Clinical suppression of puberty in female patients was observed in 29 of 32 (90.6%) and 28 of 34 (82.4%) of patients in the 11.25 mg and 30 mg groups,

respectively, at month 6. Clinical suppression of puberty in males was observed in 1 of 2 (50%) and 2 of 5 (40%) patients in the 11.25 mg and 30 mg groups, respectively, at month 6. In subjects with complete data for bone age, 29 of 33 (88%) in the 11.25 mg group and 30 of 40 in the 30 mg group (75%) had a decrease in the ratio of bone age to chronological age at month 6 compared to screening.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LUPRON DEPOT-PED for depot suspension is supplied in a single dose, prefilled dual-chamber syringe containing a white lyophilized powder and a colorless diluent for reconstitution:

LUPRON DEPOT-PED 7.5 mg, 11.25 mg, or 15 mg for 1-Month Administration		
Kit Type	**Strength**	**NDC Number**
1-month kit	7.5 mg	NDC 0074-2108-03
	11.25 mg	NDC 0074-2282-03
	15 mg	NDC 0074-2440-03
LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-Month Administration		
3-month kit	11.25 mg	NDC 0074-3779-03
	30 mg	NDC 0074-9694-03

Each kit contains:

- one single-dose, prefilled dual-chamber syringe containing 23 gauge 1½ inch needle with LuproLoc® safety device
- one plunger
- two alcohol swabs
- population, dose and frequency confirmation insert
- a complete prescribing information enclosure

Storage

Prior to reconstitution, store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

After reconstitution, use immediately *[see Dosage and Administration (2.4, 2.5)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Symptoms After Initial LUPRON DEPOT-PED Administration

Inform patients and caregivers that during the early phase of therapy with LUPRON DEPOT-PED, gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms of puberty may be observed. Instruct patients and caregivers to notify the physician if these symptoms continue beyond the second month after LUPRON DEPOT-PED administration *[see Warnings and Precautions (5.1)]*.

Psychiatric Events

Inform patients and caregivers that psychiatric events have been reported in patients taking GnRH agonists, including leuprolide acetate. Events include emotional lability, such as crying, irritability, impatience, anger, and aggression. Instruct patients and caregivers to monitor for development or worsening of psychiatric

symptoms including depression during treatment with LUPRON DEPOT-PED *[see Warnings and Precautions (5.2)]*.

Convulsions

Inform patients and caregivers that reports of convulsions have been observed in patients receiving GnRH agonists, including leuprolide acetate. Patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions may be at increased risk *[see Warnings and Precautions (5.3)]*.

Injection Site Reactions

Inform patients and caregivers that injection site related adverse reactions may occur such as transient burning/stinging, pain, bruising, and redness. Advise patients to contact their healthcare provider if they experience rash or severe injection site reactions *[see Adverse Reactions (6.1)]*.

Pregnancy

LUPRON DEPOT-PED is contraindicated in pregnancy. If the patient becomes pregnant while taking the drug, the patient should be informed of the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

Compliance with the Dosing Schedule

Inform caregivers about the importance of adherence to the LUPRON DEPOT-PED dosing schedule *[see Dosage and Administration (2.2, 2.3)]*.

Manufactured for
AbbVie Inc.
North Chicago, IL 60064
by Takeda Pharmaceutical Company Limited
Osaka, Japan 540-8645

20065547 March, 2021

MEDICATION GUIDE
LUPRON DEPOT-PED® (loo-pron depo peed)
(leuprolide acetate for depot suspension)

What is the most important information I should know about LUPRON DEPOT-PED?

- During the first 2 to 4 weeks of treatment, LUPRON DEPOT-PED can cause an increase in some hormones. During this time you may notice more signs of puberty in your child, including vaginal bleeding. **Call your doctor if these signs continue after the second month of treatment with LUPRON DEPOT-PED.**
- Some people taking gonadotropin releasing hormone (GnRH) agonists like LUPRON DEPOT-PED have had new or worsened mental (psychiatric) problems. Mental (psychiatric) problems may include emotional symptoms such as:
  - crying
  - irritability
  - restlessness (impatience)

- anger
- acting aggressive

Call your child's doctor right away if your child has any new or worsening mental symptoms or problems while taking LUPRON DEPOT-PED.

- Some people taking GnRH agonists like LUPRON DEPOT-PED have had seizures. The risk of seizures may be higher in people who:
  - have a history of seizures
  - have a history of epilepsy
  - have a history of brain or brain vessel (cerebrovascular) problems or tumors
  - are taking a medicine that has been connected to seizures such as bupropion or selective serotonin reuptake inhibitors (SSRIs)

Seizures have also happened in people who have not had any of these problems. **Call your child's doctor right away if your child has a seizure while taking LUPRON DEPOT-PED**.

What is LUPRON DEPOT-PED?

- LUPRON DEPOT-PED is an injectable prescription gonadotropin releasing hormone (GnRH) medicine used for the treatment of children with central precocious puberty (CPP).
- It is not known if LUPRON DEPOT-PED is safe and effective in children under 2 years of age.

LUPRON DEPOT-PED should not be taken if your child is:

- allergic to GnRH, GnRH agonist medicines, or any ingredients in LUPRON DEPOT-PED. See the end of this Medication Guide for a complete list of ingredients in LUPRON DEPOT-PED.
- pregnant or becomes pregnant. LUPRON DEPOT-PED can cause birth defects or loss of the baby. If your child becomes pregnant call your doctor.

Before your child receives LUPRON DEPOT-PED, tell their doctor about all of your child's medical conditions including if they:

- have a history of mental (psychiatric) problems.
- have a history of seizures.
- have a history of epilepsy.
- have a history of brain or brain vessel (cerebrovascular) problems or tumors.
- are taking a medicine that has been connected to seizures such as bupropion or selective serotonin reuptake inhibitors (SSRIs).
- are breastfeeding or plans to breastfeed. It is not known if LUPRON DEPOT-PED passes into the breast milk.

Tell your doctor about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will your child receive LUPRON DEPOT-PED?

- Your child's doctor should do tests to make sure your child has CPP before treating them with LUPRON DEPOT-PED.
- LUPRON DEPOT-PED is given as a single-dose injection into your child's muscle each month or every 3 months by a doctor or trained nurse. Your doctor will decide how often your child will receive the injection.
- Keep all scheduled visits to the doctor. If a scheduled dose is missed, your child may start having signs of puberty again. The doctor will do regular exams and blood tests to check for signs of puberty.

What are the possible side effects of LUPRON DEPOT-PED?
LUPRON DEPOT-PED may cause serious side effects. See "What is the most important information I should know about LUPRON DEPOT-PED?"
The most common side effects of LUPRON DEPOT-PED received 1 time each month include:

- injection site reactions such as pain, swelling, and abscess
- weight gain
- pain throughout body
- headache
- acne or red, itchy, rash, and white scales (seborrhea)
- serious skin rash (erythema multiforme)
- mood changes
- swelling of vagina (vaginitis), vaginal bleeding, and vaginal discharge

The most common side effects of LUPRON DEPOT-PED received every 3 months include:

- injection site reactions such as pain and swelling
- weight gain
- headache
- mood changes

These are not all the possible side effects of LUPRON DEPOT-PED. **Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

How should I store LUPRON DEPOT-PED INJECTION?

- Store LUPRON DEPOT-PED INJECTION at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep LUPRON DEPOT-PED INJECTION and all medicines out of the reach of children.**

General information about the safe and effective use of LUPRON DEPOT-PED.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LUPRON DEPOT-PED for a condition for which it was not prescribed.
This Medication Guide summarizes the most important information about LUPRON DEPOT-PED. If you would like more information,

talk with your doctor. You can ask your pharmacist or doctor for information about LUPRON DEPOT-PED that is written for doctors or trained nurses.

What are the ingredients in LUPRON DEPOT-PED?
LUPRON DEPOT-PED 7.5 mg, 11.25 mg or 15 mg for 1-month administration:
Active Ingredients: leuprolide acetate for depot suspension
Inactive Ingredients: purified gelatin, DL-lactic and glycolic acids copolymer, D-mannitol, carboxymethylcellulose sodium, polysorbate 80, water for injection, USP, and glacial acetic acid, USP to control pH.
LUPRON DEPOT-PED 11.25 mg or 30 mg for 3-month administration:
Active Ingredients: leuprolide acetate for depot suspension
Inactive Ingredients: polylactic acid, D-mannitol, carboxymethylcellulose sodium, polysorbate 80, water for injection, USP, and glacial acetic acid, USP to control pH.
Manufactured for:
AbbVie Inc.
North Chicago, IL 60064
By Takeda Pharmaceutical Company Limited
Osaka, Japan 540-8645
For more information, go to www.lupronped.com or call 1-800-633-9110.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: March, 2021

20065547

NDC 0074-2282-03

PEDIATRIC USE ONLY 11.25 mg for 1-month administration

Single Dose Administration Kit with prefilled dual-chamber syringe.

LUPRON DEPOT-PED®

(Leuprolide Acetate for Depot Suspension)

Dispense the accompanying Medication Guide to each patient.

11.25 mg for 1-month administration

FOR INTRAMUSCULAR INJECTION

The front chamber contains: leuprolide acetate 11.25 mg • purified gelatin 1.95 mg • DL-lactic & glycolic acids copolymer 99.3 mg • D-mannitol 19.8 mg

The second chamber contains: D-mannitol 50 mg • carboxymethylcellulose sodium 5 mg • polysorbate 80 1 mg • water for injection, USP, and glacial acetic acid, USP to control pH

Rx only

NDC 0074-3779-03

PEDIATRIC USE ONLY 11.25 mg for 3-month administration

Single Dose Administration Kit with prefilled dual-chamber syringe.

LUPRON DEPOT-PED® (Leuprolide Acetate for Depot Suspension)

Dispense the accompanying Medication Guide to each patient.

11.25 mg for 3-month administration

FOR INTRAMUSCULAR INJECTION

The front chamber contains: leuprolide acetate 11.25 mg • polylactic acid 99.3 mg • D-mannitol 19.45 mg

The second chamber contains: carboxymethylcellulose sodium 7.5 mg • D-mannitol 75.0 mg • polysorbate 80 1.5 mg • water for injection, USP, and glacial acetic acid, USP to control pH

Rx only

NDC 0074-9694-03

PEDIATRIC USE ONLY 30 mg for 3-month administration

Single Dose Administration Kit with prefilled dual-chamber syringe

LUPRON DEPOT-PED®

(Leuprolide Acetate for Depot Suspension)

30 mg for 3-month administration

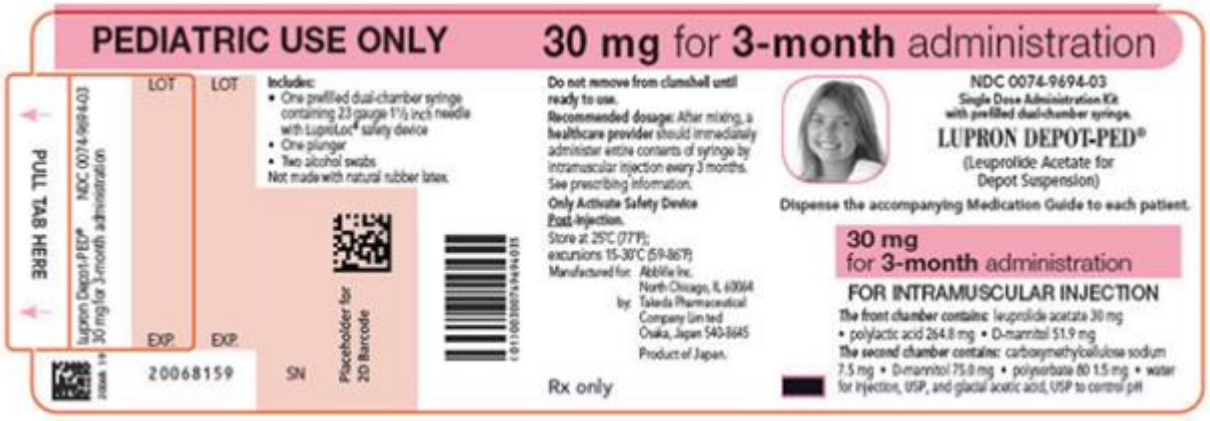
FOR INTRAMUSCULAR INJECTION

Dispense the accompanying Medication Guide to each patient.

The front chamber contains: leuprolide acetate 30 mg • polylactic acid 264.8 mg • D-mannitol 51.9 mg

The second chamber contains: carboxymethylcellulose sodium 7.5 mg • D-mannitol 75.0 mg • polysorbate 80 1.5 mg • water for injection, USP, and glacial acetic acid, USP to control pH

Rx only



NDC 0074-2108-03

PEDIATRIC USE ONLY 7.5 mg for 1-month administration

Single Dose Administration Kit with prefilled dual-chamber syringe.

LUPRON DEPOT-PED®

(Leuprolide Acetate for Depot Suspension)

Dispense the accompanying Medication Guide to each patient.

7.5 mg for 1-month administration

FOR INTRAMUSCULAR INJECTION

The front chamber contains: leuprolide acetate 7.5 mg • purified gelatin 1.3 mg • DL-lactic & glycolic acids copolymer 66.2 mg • D-mannitol 13.2 mg

The second chamber contains: D-mannitol 50 mg • carboxymethylcellulose sodium 5 mg • polysorbate 80 1 mg • water for injection, USP and glacial acetic acid, USP to control pH

Rx only

NDC 0074-2440-03

PEDIATRIC USE ONLY 15 mg for 1-month administration

Single Dose Administration Kit with prefilled dual-chamber syringe.

LUPRON DEPOT-PED®

(Leuprolide Acetate for Depot Suspension)

Dispense the accompanying Medication Guide to each patient.

15 mg for 1-month administration

FOR INTRAMUSCULAR INJECTION

The front chamber contains: leuprolide acetate 15 mg • purified gelatin 2.6 mg • DL-lactic & glycolic acids copolymer 132.4 mg • D-mannitol 26.4 mg

The second chamber contains: D-mannitol 50 mg • carboxymethylcellulose sodium 5 mg • polysorbate 80 1 mg • water for injection, USP and glacial acetic acid, USP to control pH

Rx only

LUPRON DEPOT-PED

leuprolide acetate kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0074-2282

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0074-2282-03	1 in 1 CARTON; Type 0: Not a Combination Product	04/16/1993	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 SYRINGE	1 mL
Part 2	2 PACKET	2

Part 1 of 2

LUPRON DEPOT-PED

leuprolide acetate injection, powder, lyophilized, for suspension

Product Information

Route of Administration	INTRAMUSCULAR

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEUPROLIDE ACETATE (UNII: 37JNS02E7V) (LEUPROLIDE - UNII:EFY6W0M8TG)	LEUPROLIDE ACETATE	11.25 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	
ACETIC ACID (UNII: Q40Q9N063P)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	1 mg in 1 mL
MANNITOL (UNII: 3OWL53L36A)	69.8 mg in 1 mL
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	1.95 mg in 1 mL
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM (UNII: K679OBS311)	5 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020263	04/16/1993	

Part 2 of 2

ALCOHOL

isopropyl alcohol swab

Product Information

Route of Administration	TOPICAL

Inactive Ingredients

Ingredient Name	Strength
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC monograph final	part333	10/12/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020263	04/16/1993	

LUPRON DEPOT-PED

leuprolide acetate kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0074-2440

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0074-2440-03	1 in 1 CARTON; Type 0: Not a Combination Product	04/16/1993	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 SYRINGE	1 mL
Part 2	2 PACKET	2

Part 1 of 2

LUPRON DEPOT-PED

leuprolide acetate injection, powder, lyophilized, for suspension

Product Information

Route of Administration	INTRAMUSCULAR

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEUPROLIDE ACETATE (UNII: 37JNS02E7V) (LEUPROLIDE - UNII:EFY6W0M8TG)	LEUPROLIDE ACETATE	15 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
ACETIC ACID (UNII: Q40Q9N063P)	
WATER (UNII: 059QF0KO0R)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	1 mg in 1 mL
MANNITOL (UNII: 3OWL53L36A)	76.4 mg in 1 mL
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	2.6 mg in 1 mL
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM (UNII: K679OBS311)	5 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020263	04/16/1993	

Part 2 of 2

ALCOHOL

isopropyl alcohol swab

Product Information

Route of Administration	TOPICAL

Inactive Ingredients

Ingredient Name	Strength
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC monograph final	part333	10/12/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020263	04/16/1993	

LUPRON DEPOT-PED

leuprolide acetate kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0074-2108

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0074-2108-03	1 in 1 CARTON; Type 0: Not a Combination Product	04/16/1993	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 SYRINGE	1 mL
Part 2	2 PACKET	2

Part 1 of 2

LUPRON DEPOT-PED

leuprolide acetate injection, powder, lyophilized, for suspension

Product Information

Route of Administration	INTRAMUSCULAR

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEUPROLIDE ACETATE (UNII: 37JNS02E7V) (LEUPROLIDE - UNII:EFY6W0M8TG)	LEUPROLIDE ACETATE	7.5 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
ACETIC ACID (UNII: Q40Q9N063P)	
WATER (UNII: 059QF0KO0R)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	1 mg in 1 mL
MANNITOL (UNII: 3OWL53L36A)	63.2 mg in 1 mL
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	1.3 mg in 1 mL
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM (UNII: K679OBS311)	5 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020263	08/16/1993	

Part 2 of 2

ALCOHOL

isopropyl alcohol swab

Product Information

Route of Administration	TOPICAL

Inactive Ingredients

Ingredient Name	Strength
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC monograph final	part333	10/12/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020263	04/16/1993	

LUPRON DEPOT-PED

leuprolide acetate kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0074-3779

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0074-3779-03	1 in 1 CARTON; Type 0: Not a Combination Product	04/16/1993	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 SYRINGE	1.5 mL
Part 2	2 PACKET	2

Part 1 of 2

LUPRON DEPOT-PED

leuprolide acetate injection, powder, lyophilized, for suspension

Product Information

Route of Administration	INTRAMUSCULAR

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEUPROLIDE ACETATE (UNII: 37JNS02E7V) (LEUPROLIDE - UNII:EFY6W0M8TG)	LEUPROLIDE ACETATE	11.25 mg in 1.5 mL

Inactive Ingredients

Ingredient Name	Strength
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	1.5 mg in 1.5 mL
WATER (UNII: 059QF0KO0R)	
ACETIC ACID (UNII: Q40Q9N063P)	
POLYLACTIDE (UNII: 459TN2L5F5)	99.3 mL in 1.5 mL
MANNITOL (UNII: 3OWL53L36A)	94.5 mg in 1.5 mL

CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM (UNII: K679OBS311)	7.5 mg in 1.5 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1.5 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020263	04/16/1993	

Part 2 of 2

ALCOHOL

isopropyl alcohol swab

Product Information

Route of Administration	TOPICAL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC monograph final	part333	08/16/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020263	04/16/1993	

LUPRON DEPOT-PED

leuprolide acetate kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0074-9694

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0074-9694-03	1 in 1 CARTON; Type 0: Not a Combination Product	04/16/1993	

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 SYRINGE	1.5 mL
Part 2	2 PACKET	2

Part 1 of 2

LUPRON DEPOT-PED

leuprolide acetate injection, powder, lyophilized, for suspension

Product Information

Route of Administration	INTRAMUSCULAR

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEUPROLIDE ACETATE (UNII: 37JNS02E7V) (LEUPROLIDE - UNII:EFY6W0M8TG)	LEUPROLIDE ACETATE	30 mg in 1.5 mL

Inactive Ingredients

Ingredient Name	Strength
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	1.5 mg in 1.5 mL
ACETIC ACID (UNII: Q40Q9N063P)	
POLYLACTIDE (UNII: 459TN2L5F5)	99.3 mg in 1.5 mL
MANNITOL (UNII: 3OWL53L36A)	126.9 mg in 1.5 mL
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED FORM (UNII: K679OBS311)	7.5 mg in 1.5 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1.5 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020263	04/16/1993	

Part 2 of 2

ALCOHOL

isopropyl alcohol swab

Product Information

Route of Administration	TOPICAL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		1 in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC monograph not final	part333	05/16/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020263	04/16/1993	

Labeler - AbbVie Inc. (078458370)

Revised: 3/2021 AbbVie Inc.

Exhibit

B

TESTOSTERONE ENANTHATE- testosterone enanthate injection, solution
West-Ward Pharmaceuticals Corp

TESTOSTERONE ENANTHATE INJECTION, USP

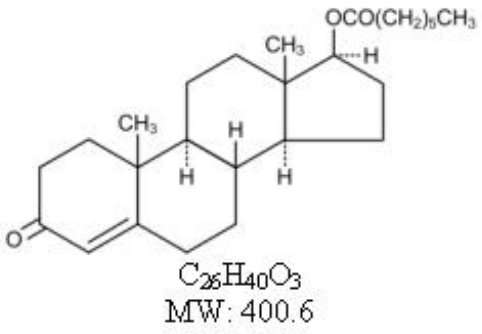
Rx ONLY

CIII

DESCRIPTION

Testosterone Enanthate Injection, USP provides Testosterone Enanthate, USP, a derivative of the primary endogenous androgen testosterone, for intramuscular administration. In their active form, androgens have a 17-beta-hydroxy group. Esterification of the 17-beta-hydroxy group increases the duration of action of testosterone; hydrolysis to free testosterone occurs *in vivo*. Each mL of sterile, colorless to pale yellow, solution provides 200 mg Testosterone Enanthate, USP in sesame oil with 5 mg chlorobutanol (chloral derivative) as a preservative.

Testosterone Enanthate, USP is designated chemically as androst-4-en-3-one, 17-[(1-oxoheptyl)-oxy]-, (17β)-. Structural formula:



$C_{26}H_{40}O_3$
MW: 400.6

CLINICAL PHARMACOLOGY

Endogenous androgens are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include growth and maturation of prostate, seminal vesicles, penis, and scrotum; development of male hair distribution, such as beard, pubic, chest, and axillary hair; laryngeal enlargement; vocal chord thickening; alterations in body musculature; and fat distribution.

Androgens also cause retention of nitrogen, sodium, potassium, and phosphorus, and decreased urinary excretion of calcium. Androgens have been reported to increase protein anabolism and decrease protein catabolism. Nitrogen balance is improved only when there is sufficient intake of calories and protein.

Androgens are responsible for the growth spurt of adolescence and for the eventual termination of linear growth which is brought about by fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of the growth process. Androgens have been reported to stimulate the production of red blood cells by enhancing the production of erythropoietic stimulating factor.

During exogenous administration of androgens, endogenous testosterone release is inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens,

spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle stimulating hormone (FSH).

There is a lack of substantial evidence that androgens are effective in fractures, surgery, convalescence, and functional uterine bleeding.

PHARMACOKINETICS

Testosterone esters are less polar than free testosterone. Testosterone esters in oil injected intramuscularly are absorbed slowly from the lipid phase; thus testosterone enanthate can be given at intervals of two to four weeks.

Testosterone in plasma is 98 percent bound to a specific testosterone-estradiol binding globulin, and about two percent is free. Generally, the amount of this sex-hormone binding globulin (SHBG) in the plasma will determine the distribution of testosterone between free and bound forms, and the free testosterone concentration will determine its half-life.

About 90 percent of a dose of testosterone is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about six percent of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolized to various 17-keto steroids through two different pathways. There are considerable variations of the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes.

In responsive tissues, the activity of testosterone appears to depend on reduction to dihydrotestosterone (DHT), which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription events and cellular changes related to androgen action.

INDICATIONS AND USAGE

Males

Testosterone Enanthate Injection, USP is indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.

Primary hypogonadism (congenital or acquired) – Testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy.

Hypogonadotropic hypogonadism (congenital or acquired) – Gonadotropin or luteinizing hormone releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation. (Appropriate adrenal cortical and thyroid hormone replacement therapy are still necessary, however, and are actually of primary importance.)

If the above conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sexual characteristics. Prolonged androgen treatment will be required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.

Safety and efficacy of Testosterone Enanthate Injection, USP in men with age-related hypogonadism have not been established.

Delayed puberty – Testosterone Enanthate Injection, USP may be used to stimulate puberty in carefully selected males with clearly delayed puberty. These patients usually have a familial pattern of delayed puberty that is not secondary to a pathological disorder; puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An X-ray of the hand and wrist to determine bone age should be obtained every six months to assess the effect of treatment on the epiphyseal centers (see **WARNINGS**).

Females

Metastatic mammary cancer – Testosterone Enanthate Injection, USP may be used secondarily in women with advancing inoperable metastatic (skeletal) mammary cancer who are one to five years postmenopausal. Primary goals of therapy in these women include ablation of the ovaries. Other methods of counteracting estrogen activity are adrenalectomy, hypophysectomy, and/or antiestrogen therapy. This treatment has also been used in premenopausal women with breast cancer who have benefited from oophorectomy and are considered to have a hormone-responsive tumor. Judgment concerning androgen therapy should be made by an oncologist with expertise in this field.

CONTRAINDICATIONS

Androgens are contraindicated in men with carcinomas of the breast or with known or suspected carcinomas of the prostate and in women who are or may become pregnant. When administered to pregnant women, androgens cause virilization of the external genitalia of the female fetus. This virilization includes clitoromegaly, abnormal vaginal development, and fusion of genital folds to form a scrotal-like structure. The degree of masculinization is related to the amount of drug given and the age of the fetus and is most likely to occur in the female fetus when the drugs are given in the first trimester. If the patient becomes pregnant while taking androgens, she should be apprised of the potential hazard to the fetus.

This preparation is also contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS

In patients with breast cancer and in immobilized patients, androgen therapy may cause hypercalcemia by stimulating osteolysis. In patients with cancer, hypercalcemia may indicate progression of bony metastasis. If hypercalcemia occurs, the drug should be discontinued and appropriate measures instituted.

Prolonged use of high doses of androgens has been associated with the development of peliosis hepatis and hepatic neoplasms including hepatocellular carcinoma (see **PRECAUTIONS, Carcinogenesis**). Peliosis hepatis can be a life-threatening or fatal complication.

If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, the androgen should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as testosterone enanthate injection. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with testosterone enanthate injection and initiate appropriate workup and management.

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use testosterone enanthate injection.

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions (see **DRUG ABUSE AND DEPENDENCE**).

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic steroids. Conversely, consider the possibility of testosterone and anabolic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

Due to sodium and water retention, edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required. If the administration of testosterone enanthate is restarted, a lower dose should be used.

Gynecomastia frequently develops and occasionally persists in patients being treated for hypogonadism.

Androgen therapy should be used cautiously in healthy males with delayed puberty. The effect on bone maturation should be monitored by assessing bone age of the wrist and hand every six months. In children, androgen treatment may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature. The younger the child the greater the risk of compromising final mature height.

PRECAUTIONS

General

Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly, and menstrual irregularities). Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization. Such virilization is usual following androgen use at high doses and is not prevented by concomitant use of estrogens. A decision may be made by the patient and the physician that some virilization will be tolerated during treatment for breast carcinoma.

Because androgens may alter serum cholesterol concentration, caution should be used when administering these drugs to patients with a history of myocardial infarction or coronary artery disease. Serial determinations of serum cholesterol should be made and therapy adjusted accordingly. A causal relationship between myocardial infarction and hypercholesterolemia has not been established.

Information for Patients

Male adolescent patients receiving androgens for delayed puberty should have bone development checked every six months.

The physician should instruct patients to report any of the following side effects of androgens:

Adult or adolescent males – too frequent or persistent erections of the penis.

Women – hoarseness, acne, changes in menstrual periods, or more facial hair.

All patients – any nausea, vomiting, changes in skin color, or ankle swelling.

Geriatric Use

Clinical studies of testosterone enanthate did not include sufficient numbers of subjects, aged 65 and older, to determine whether they respond differently from younger subjects. Testosterone replacement is not indicated in geriatric patients who have age‐related hypogonadism only (“andropause”), because

there is insufficient safety and efficacy information to support such use. Current studies do not assess whether testosterone use increases risks of prostate cancer, prostate hyperplasia, and cardiovascular disease in the geriatric population.

Intramuscular Administration

When properly given, injections of testosterone enanthate are well tolerated. Care should be taken to slowly inject the preparation deeply into the gluteal muscle, being sure to follow the usual precautions for intramuscular administration, such as the avoidance of intravascular injection. There have been rare post-marketing reports of transient reactions involving urge to cough, coughing fits, and respiratory distress immediately after the injection of testosterone enanthate, an oil-based depot preparation (see **DOSAGE AND ADMINISTRATION**).

Laboratory Tests

Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of androgen therapy (see **WARNINGS**).

Periodic (every six months) X-ray examinations of bone age should be made during treatment of pre-pubertal males to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.

Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of androgens.

Drug Interactions

When administered concurrently, the following drugs may interact with androgens:

Anticoagulants, oral – C-17 substituted derivatives of testosterone, such as methandrostenolone, have been reported to decrease the anticoagulant requirement. Patients receiving oral anticoagulant therapy require close monitoring especially when androgens are started or stopped.

Antidiabetic drugs and insulin – In diabetic patients, the metabolic effects of androgens may decrease blood glucose and insulin requirements.

ACTH and corticosteroids – Enhanced tendency toward edema. Use caution when giving these drugs together, especially in patients with hepatic or cardiac disease.

Oxyphenbutazone – Elevated serum levels of oxyphenbutazone may result.

Drug/Laboratory Test Interferences

Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased total T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

Carcinogenesis

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Pregnancy: Teratogenic Effects

Category X (see CONTRAINDICATIONS).

Nursing Mothers

It is not known whether androgens are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from androgens, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Androgen therapy should be used very cautiously in pediatric patients and only by specialists who are aware of the adverse effects on bone maturation. Skeletal maturation must be monitored every six months by an X-ray of the hand and wrist (see **INDICATIONS AND USAGE** and **WARNINGS**).

ADVERSE REACTIONS

Endocrine and Urogenital, Female – The most common side effects of androgen therapy are amenorrhea and other menstrual irregularities, inhibition of gonadotropin secretion, and virilization, including deepening of the voice and clitoral enlargement. The latter usually is not reversible after androgens are discontinued. When administered to a pregnant woman, androgens cause virilization of the external genitalia of the female fetus.

Male – Gynecomastia, and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages (see **CLINICAL PHARMACOLOGY**).

Skin and Appendages – Hirsutism, male pattern baldness, and acne.

Cardiovascular Disorders – Myocardial infarction, stroke.

Fluid and Electrolyte Disturbances – Retention of sodium, chloride, water, potassium, calcium (see **WARNINGS**), and inorganic phosphates.

Gastrointestinal – Nausea, cholestatic jaundice, alterations in liver function tests; rarely, hepatocellular neoplasms, peliosis hepatis (see **WARNINGS**).

Hematologic – Suppression of clotting factors II, V, VII, and X; bleeding in patients on concomitant anticoagulant therapy; polycythemia.

Nervous System – Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.

Metabolic – Increased serum cholesterol.

Vascular Disorders – venous thromboembolism

Miscellaneous – Rarely, anaphylactoid reactions; inflammation and pain at injection site.

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceutical Corp. at 1-877233-2001 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Testosterone enanthate contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

Abuse

Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids (AAS), and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse of men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids, and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dependence

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations
- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism.

Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

OVERDOSAGE

There have been no reports of acute overdosage with androgens.

DOSAGE AND ADMINISTRATION

Prior to initiating testosterone enanthate injection, confirm the diagnosis of hypogonadism by ensuring

that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

Dosage and duration of therapy with testosterone enanthate injection will depend on age, sex, diagnosis, patient's response to treatment, and appearance of adverse effects. When properly given, injections of testosterone enanthate, are well tolerated. Care should be taken to slowly inject the preparation deeply into the gluteal muscle, being sure to follow the usual precautions for intramuscular administration, such as the avoidance of intravascular injection (see **PRECAUTIONS**).

In general, total doses above 400 mg per month are not required because of the prolonged action of the preparation. Injections more frequently than every two weeks are rarely indicated. **NOTE:** Use of a wet needle or wet syringe may cause the solution to become cloudy; however this does not affect the potency of the material. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Testosterone enanthate injection is a clear, colorless to pale yellow solution.

Male hypogonadism: As replacement therapy, i.e., for eunuchism, the suggested dosage is 50 to 400 mg every 2 to 4 weeks.

In males with delayed puberty: Various dosage regimens have been used; some call for lower dosages initially with gradual increases as puberty progresses, with or without a decrease to maintenance levels. Other regimens call for higher dosage to induce pubertal changes and lower dosage for maintenance after puberty. The chronological and skeletal ages must be taken into consideration, both in determining the initial dose and in adjusting the dose. Dosage is within the range of 50 to 200 mg every 2 to 4 weeks for a limited duration, for example, 4 to 6 months. X-rays should be taken at appropriate intervals to determine the amount of bone maturation and skeletal development (see **INDICATIONS AND USAGE** and **WARNINGS**).

Palliation of inoperable mammary cancer in women: A dosage of 200 to 400 mg every 2 to 4 weeks is recommended. Women with metastatic breast carcinoma must be followed closely because androgen therapy occasionally appears to accelerate the disease.

HOW SUPPLIED

Testosterone Enanthate Injection, USP 200 mg/mL is available as:

5 mL Multiple Dose vial, Cartons of 1 vial NDC 0143-9750-01

STORAGE

Testosterone Enanthate Injection should be stored at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Warming and rotating the vial between the palms of the hands will redissolve any crystals that may have formed during storage at low temperatures.

For prescription Use Only

Manufactured by: HIKMA FARMACÊUTICA (PORTUGAL), S.A.
Estrada do Rio da Mó, nº 8, 8A e 8B - Fervença, - 2705 – 906 Terrugem SNT - PORTUGAL

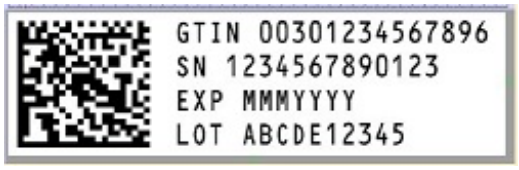
Distributed by:
WEST-WARD
A HIKMA COMPANY
Eatontown, NJ 07724 USA

PIN308-WES/4
Revised: November 2016

Principal Display Panel

NDC 0143-9750-01
Testosterone
Enanthate
Injection, USP
CIII
1,000 mg/5 mL
(200 mg/mL)
STERILE
For Intramuscular Use Only
Rx ONLY
5 mL Multiple Dose Vial
Each mL contains 200 mg Testosterone Enanthate, USP in sesame oil with 5 mg chlorobutanol (chloral derivative) as preservative.
USUAL DOSAGE: See package insert.
Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].
Warming and rotating the vial between the palms of the hands will redissolve any crystals that may have formed during storage at low temperatures.

SERIALIZATION IMAGE



TESTOSTERONE ENANTHATE

testosterone enanthate injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-9750
Route of Administration	INTRAMUSCULAR	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TESTOSTERONE ENANTHATE (UNII: 7Z6522T8N9) (TESTOSTERONE - UNII:3XMK78S47O)	TESTOSTERONE ENANTHATE	200 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SESAME OIL (UNII: QX10HYY4QV)	
CHLOROBUTANOL (UNII: HM4YQM8WRC)	5 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0143-9750-01	5 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product	09/18/2012	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091120	09/18/2012	

Labeler - West-Ward Pharmaceuticals Corp (001230762)

Establishment

Name	Address	ID/FEI	Business Operations
HIKMA FARMACEUTICA (PORTUGAL), S.A		452742943	ANALYSIS(0143-9750) , LABEL(0143-9750) , MANUFACTURE(0143-9750) , PACK(0143-9750)

Revised: 12/2018 West-Ward Pharmaceuticals Corp

Exhibit C

TESTOPEL- testosterone pellet
Endo Pharmaceuticals Inc.

TESTOPEL®
(testosterone pellets)
C-III

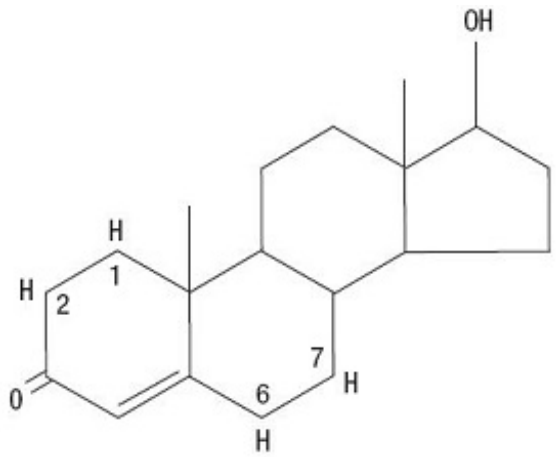
DESCRIPTION

TESTOPEL® (testosterone pellets) are cylindrically shaped pellets 3.2mm (1/8 inch) in diameter and approximately 9mm in length. Each sterile pellet weighs approximately 78mg (75mg testosterone) and is ready for implantation.

Androgens are steroids that develop and maintain primary and secondary male sex characteristics. Testosterone is a member of this class.

Structural formula for testosterone follows:

TESTOSTERONE
$C_{19}H_{28}O_2$ MW288.43
17β -Hydroxyandrost-4-en-3-one



INGREDIENTS

Each **TESTOPEL®** (testosterone pellets) for subcutaneous implantation contains 75mg testosterone. In addition each pellet contains the following inactive ingredients: stearic acid NF 0.97mg and polyvinylpyrrolidone USP 2mg.

TESTOPEL® (testosterone pellets) consist of crystalline testosterone. When implanted subcutaneously, the pellets slowly release the hormone for a long acting androgenic effect.

CLINICAL PHARMACOLOGY

Endogenous androgens are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution such as beard, pubic, chest and axillary hair, laryngeal enlargements, vocal cord thickening, alterations in body musculature and fat distribution. Drugs in this class can also cause retention of nitrogen, sodium, potassium, phosphorus, and decreased urinary excretion of calcium.

Androgens have been reported to increase protein anabolism and decrease protein catabolism.

Nitrogen balance is improved only when there is sufficient intake of calories and protein.

Androgens are responsible for the growth spurt of adolescence and for the eventual termination of

linear growth which is brought about by the fusion of the epiphyseal growth centers. In children, exogenous androgens accelerate linear growth rates, but may cause a disproportionate advancement in bone maturation. Use over long periods may result in fusion of the epiphyseal growth centers and termination of growth process. Androgens have been reported to stimulate the production of red blood cells by enhancing the production of erythropoietic stimulating factor.

During exogenous administration of androgens, endogenous testosterone release is inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle stimulating hormone (FSH).

There is a lack of substantial evidence that androgens are effective in fractures, surgery, convalescence, and functional uterine bleeding.

PHARMACOKINETICS

Testosterone in plasma is 98 percent bound to a specific testosterone-estradiol binding globulin, and about 2 percent is free. Generally, the amount of this sex-hormone binding globulin in the plasma will determine the distribution of testosterone between the free and bound forms, and the free testosterone concentration will determine its half-life.

About 90 percent of a dose of testosterone is excreted as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6 percent of a dose is excreted in feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver. Testosterone is metabolized to various 17-keto steroids through two different pathways. There are considerable variations of the half-life as reported in the literature, ranging from 10-100 minutes.

In many tissues the activity of testosterone appears to depend on reduction to dihydrotestosterone, which binds to cytosol receptor proteins. The steroid-receptor complex is transported to the nucleus where it initiates transcription events and cellular changes related to androgen action.

INDICATIONS AND USAGE

MALES

Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.

- a.Primary hypogonadism (congenital or acquired) - testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testes syndrome; or orchiectomy.
- b.Hypogonadotropic hypogonadism (congenital or acquired) - gonadotropic LHRH deficiency, or pituitary - hypothalamic injury from tumors, trauma or radiation.

If the above conditions occur prior to puberty, androgen replacement therapy will be needed during the adolescent years for development of secondary sex characteristics. Prolonged androgen treatment will be required to maintain sexual characteristics in these and other males who develop testosterone deficiency after puberty.

Safety and efficacy of Testopel® (testosterone pellets) in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.

- c.Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty. These patients usually have a familial pattern of delayed puberty that is not secondary to a pathological disorder; puberty is expected to occur spontaneously at a relatively late date. Brief treatment with conservative doses may occasionally be justified in these patients if they do not respond to psychological support. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. An x-ray of the hand and wrist to determine bone age should be taken every 6 months to assess the effect of treatment on epiphyseal centers (see WARNINGS).

CONTRAINDICATIONS

Androgens are contraindicated in men with carcinomas of the breast or with known or suspected carcinomas of the prostate. If administered to pregnant women, androgens cause virilization of the external genitalia of the female fetus. The virilization includes clitoromegaly, abnormal vaginal development, and fusion of genital folds to form a scrotal-like structure. The degree of masculinization is related to the amount of drug given and the age of the fetus, and is most likely to occur in the female fetus when the drugs are given in the first trimester. If the patient becomes pregnant while taking these drugs she should be apprised of the potential hazard to the fetus.

WARNINGS

In patients with breast cancer, androgen therapy may cause hypercalcemia by stimulating osteolysis. In this case, the drug should be discontinued.

Prolonged use of high doses of androgens has been associated with the development of peliosis hepatis and hepatic neoplasms including hepatocellular carcinoma (see PRECAUTIONS - Carcinogenesis, Mutagenesis, Impairment of Fertility). Peliosis hepatis can be a life-threatening or fatal complication.

Men treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as Testopel® (testosterone pellets). Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with Testopel® (testosterone pellets) and initiate appropriate workup and management [see ADVERSE REACTIONS.

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use Testopel® (testosterone pellets).

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions (see DRUG ABUSE AND DEPENDENCE).

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

Edema with or without congestive heart failure may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

Gynecomastia frequently develops in patients and occasionally persists in patients being treated for hypogonadism.

Androgen therapy should be used cautiously in healthy males with delayed puberty. The effect on bone maturation should be monitored by assessing bone age of the wrist and hand every 6 months. In children, androgen treatment may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect may result in compromised adult stature. The younger the child the greater the risk of compromising final mature height.

Post-marketing cases associate TESTOPEL® pellet(s) insertion with implant site infection (cellulitis and abscess), and/or pellet extrusion at or near the implantation site. Infection and extrusion may occur concurrently or separately. Reported signs and symptoms of infection and/or extrusion at the implant site included induration, inflammation, fibrosis, bleeding, bruising, wound drainage, pain, itching, and pellet extrusion. Although cases of infection and/or extrusion may occur at any time, most reported cases occurred within the first month after TESTOPEL® implantation. Infection and/or extrusion may require further treatment (see ADVERSE REACTIONS).

This drug has not been shown to be safe and effective for the enhancement of athletic performance. Because of the potential risk for serious adverse health effects, this drug should not be used for such purpose.

PRECAUTIONS

GENERAL

Pellet implantation is much less flexible for dosage adjustment than is oral administration of or intramuscular injections of oil solutions or aqueous suspensions. Therefore, great care should be used when estimating the amount of testosterone needed.

In the face of complications where the effects of testosterone should be discontinued, the pellets would have to be removed.

INFORMATION FOR THE PATIENT

The physician should instruct patients to report any of the following side effects of androgens:

Adult or adolescent males: Too frequent or persistent erections of the penis. Any nausea, vomiting, changes in skin color, ankle swelling.

Implantation site infection and/or pellet extrusion can occur and may be associated with implant site induration, inflammation, fibrosis, bleeding, bruising, wound drainage, pain, itching, and pellet extrusion. (see WARNINGS and ADVERSE REACTIONS).

Any male adolescent patient receiving androgens for delayed puberty should have bone development checked every 6 months.

LABORATORY TESTS

1. Because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.
2. Periodic (every 6 months) x-ray examinations of the bone age should be made during treatment of prepubertal males to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.
3. Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of androgens.

DRUG INTERACTIONS

1. Anticoagulants. C-17 substituted derivatives of testosterone, such as methandrostenolone have been reported to decrease the anticoagulant requirements of patients receiving oral anticoagulants. Patients receiving oral anticoagulant therapy require close monitoring, especially when androgens are started or stopped.
2. Oxyphenbutazone. Concurrent administration of oxyphenbutazone and androgens may result in

elevated serum levels of oxyphenbutazone.

3. Insulin. In diabetic patients the metabolic effects of androgens may decrease blood glucose and insulin requirements.

DRUG/LABORATORY TEST INTERFERENCES

Androgens may decrease levels of thyroxine-binding globulin, resulting in decreased total T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Animal Data. Testosterone has been tested by subcutaneous injection and implantation in mice and rats. The implant induced cervical-uterine tumors in mice, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of liver in rats.

Human Data. There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgens may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

PREGNANCY

Teratogenic Effects. Pregnancy Category X (see CONTRAINDICATIONS).

NURSING MOTHERS

It is not known whether androgens are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from androgens, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Androgen therapy should be used very cautiously in children and only by specialists who are aware of the adverse effects on bone maturation. Skeletal maturation must be monitored every 6 months by an x-ray of the hand and wrist (see INDICATIONS AND USAGE and WARNINGS).

ADVERSE REACTIONS

The following adverse reactions have been identified during post-approval use of testosterone replacement therapy, including TESTOPEL®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Implantation Site Infection and Pellet Extrusion: (see WARNINGS)

Endocrine and Urogenital, Male. Gynecomastia and excessive frequency and duration of penile erections. Oligospermia may occur at high dosages (see CLINICAL PHARMACOLOGY).

Skin and Appendages. Hirsutism, male pattern of baldness, and acne.

Cardiovascular Disorders. Myocardial infarction, stroke.

Fluid and Electrolyte Disturbances. Retention of sodium, chloride, water, potassium, calcium and inorganic phosphates.

Gastrointestinal. Nausea, cholestatic jaundice, alterations in liver function tests, rarely hepatocellular

neoplasms and peliosis hepatis (see WARNINGS).

Hematologic. Suppression of clotting factors II, V, VII, and X, bleeding in patients on concomitant anticoagulant therapy, and polycythemia.

Nervous System. Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia.

Metabolic. Increased serum cholesterol.

Vascular Disorders: Venous thromboembolism (see WARNINGS)

Miscellaneous. Rarely anaphylactoid reactions.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

TESTOPEL® contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

Abuse

Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids (AAS), and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse of men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids, and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dependence

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations
- Having difficulty in discontinuing the drug despite desires and attempts to do so

- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism.

Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

OVERDOSAGE

There have been no reports of acute overdosage with the androgens.

DOSAGE AND ADMINISTRATION

Prior to initiating, Testopel® (testosterone pellets) confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

The suggested dosage for androgens varies depending on the age, and diagnosis of the individual patient. Dosage is adjusted according to the patient's response and the appearance of adverse reactions. The dosage guideline for the testosterone pellets for replacement therapy in androgen-deficient males is 150mg to 450mg subcutaneously every 3 to 6 months. Various dosage regimens have been used to induce pubertal changes in hypogonadal males; some experts have advocated lower doses initially, gradually increasing the dose as puberty progresses, with or without a decrease in maintenance levels. Other experts emphasize that higher dosages are needed to induce pubertal changes and lower dosages can be used for maintenance after puberty. The chronological and skeletal ages must be taken into consideration, both in determining the initial dose and in adjusting the dose.

Dosages in delayed puberty generally are in the lower range of that listed above and, for a limited duration, for example 4 to 6 months.

The number of pellets to be implanted depends upon the minimal daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally. The usual dosage is as follows: implant two 75mg pellets for each 25mg testosterone propionate required weekly. Thus when a patient requires injections of 75mg per week, it is usually necessary to implant 450mg (6 pellets). With injections of 50mg per week, implantation of 300mg (4 pellets) may suffice for approximately three months. With lower requirements by injection, correspondingly lower amounts may be implanted. It has been found that approximately one-third of the material is absorbed in the first month, one-fourth in the second month and one-sixth in the third month. Adequate effect of the pellets ordinarily continues for three to four months, sometimes as long as six months.

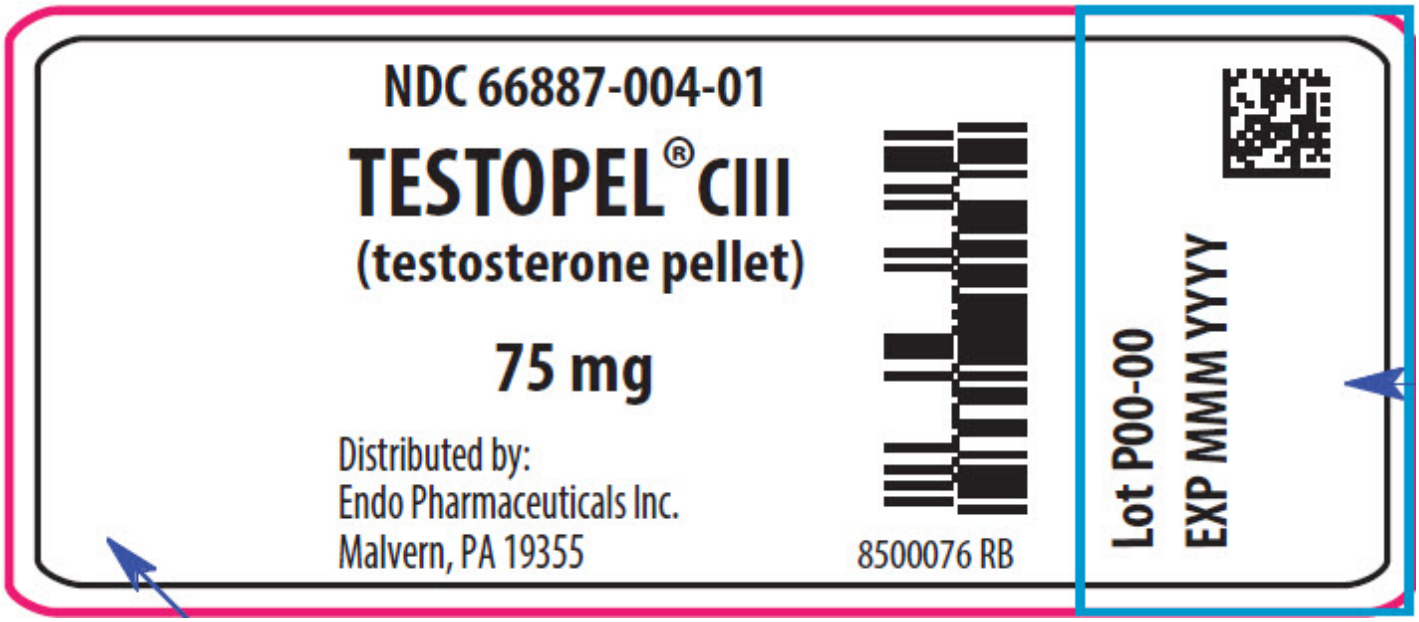
HOW SUPPLIED

Testosterone pellets each containing 75mg testosterone. One pellet per vial in boxes of 10 (NDC: 66887-004-10) and 100 (NDC: 66887-004-20). Store at 25°C (77°F), excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].

Rx Only

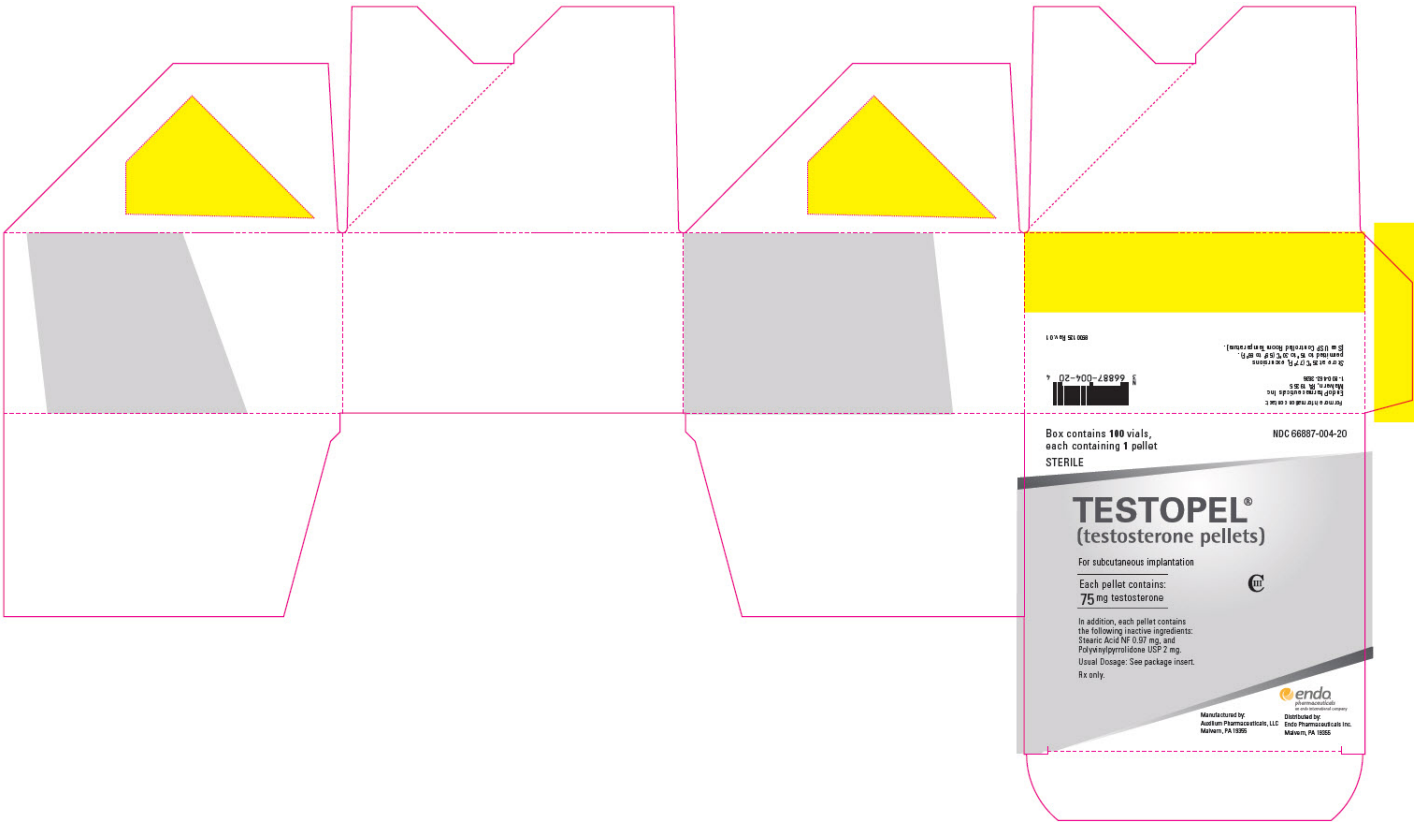
Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355

Principal Display Panel – Vial Label



Principal Display Panel – Box of 10 Vials


N 3 66887-004-10 5
Box contains 10 vials, each containing 1 pellet
NDC 66887-004-10
STERILE
TESTOPEL®
(testosterone pellets)
For subcutaneous implantation
Each pellet contains:
75 mg testosterone
C III
In addition, each pellet contains the following inactive ingredients: Stearic Acid NF 0.97 mg, and Polyvinylpyrrolidone USP 2 mg.
Usual Dosage: See package insert.
Rx only.
For more information contact:
Endo Pharmaceuticals Inc.
Malvern, PA 19355
1-800-462-3636
Store at 25°C (77°F), excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].
8500050 Rev. 03
Manufactured by:
Auxilium Pharmaceuticals, LLC
Malvern, PA 19355
Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355
endo pharmaceuticals
an endo international company



Principal Display Panel – Box of 100 Vials

TESTOPEL

testosterone pellet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:66887-004
Route of Administration	SUBCUTANEOUS	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TESTOSTERONE (UNII: 3XMK78S47O) (TESTOSTERONE - UNII:3XMK78S47O)	TESTOSTERONE	75 mg

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	BULLET	**Size**	9mm
Flavor		**Imprint Code**	
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:66887-004-10	10 in 1 BOX	10/31/2014	

1	NDC:66887-004-01	1 in 1 AMPULE; Type 0: Not a Combination Product		
2	NDC:66887-004-20	100 in 1 BOX	10/31/2014	
2	NDC:66887-004-01	1 in 1 AMPULE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA080911	10/31/2014	

Labeler - Endo Pharmaceuticals Inc. (178074951)

Revised: 8/2018 Endo Pharmaceuticals Inc.

Exhibit D

ANDROGEL- testosterone gel
AbbVie Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AndroGel 1% safely and effectively. See full prescribing information for AndroGel 1%.

AndroGel® (testosterone gel) 1% for topical use CIII
Initial U.S. Approval: 1953

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

See full prescribing information for complete boxed warning.

- **Virilization has been reported in children who were secondarily exposed to testosterone gel. (5.2, 6.2)**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel. (2.2, 5.2)**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use. (2.2, 5.2, 17)**

INDICATIONS AND USAGE

AndroGel 1% is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired). (1)
- Hypogonadotropic hypogonadism (congenital or acquired). (1)

Limitations of use:

- Safety and efficacy of AndroGel 1% in men with "age-related hypogonadism" have not been established. (1)
- Safety and efficacy of AndroGel 1% in males less than 18 years old have not been established. (8.4)
- Topical testosterone products may have different doses, strengths or application instructions that may result in different systemic exposure. (1, 12.3)

DOSAGE AND ADMINISTRATION

- **Dosage and Administration for AndroGel 1% differs from AndroGel 1.62 %. For dosage and administration of AndroGel 1.62% refer to its full prescribing information. (2)**
- Prior to initiating AndroGel 1%., confirm the diagnosis of hypogonadism by ensuring that serum testosterone has been measured in the morning on at least two separate days and that these concentrations are below the normal range (2).
- Starting dose of AndroGel 1% is 50 mg of testosterone (two 25 mg packets or one 50 mg packet), applied once daily in the morning. (2.1)
- Apply to clean, dry, intact skin of shoulders and upper arms and/or abdomen. Do NOT apply AndroGel 1% to any other parts of the body including the genitals, chest, armpits (axillae), knees, or back. (2.2)
- Dose adjustment: AndroGel 1% can be dose adjusted using 50 mg, 75 mg, or 100 mg of testosterone on the basis of total serum testosterone concentration. The dose should be titrated based on the serum testosterone concentration. Additionally, serum testosterone concentration should be assessed periodically. (2.1)
- Patients should wash hands immediately with soap and water after applying AndroGel 1% and cover the application site(s) with clothing after the gel has dried. Wash the application site thoroughly with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated. (2.2)

DOSAGE FORMS AND STRENGTHS

AndroGel (testosterone gel) 1% for topical use is available as follows:

- Packets containing 25 mg of testosterone. (3)
- Packets containing 50 mg of testosterone. (3)

CONTRAINDICATIONS

- Men with carcinoma of the breast or known or suspected prostate cancer. (4, 5.1)
- Women who are pregnant. Testosterone may cause fetal harm. (4, 8.1)

WARNINGS AND PRECAUTIONS

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. (5.1)
- Avoid unintentional exposure of women or children to AndroGel 1%. Secondary exposure to testosterone can produce

signs of virilization. AndroGel 1% should be discontinued until the cause of virilization is identified. (5.2)

- Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE. (5.4)
- Some postmarketing studies have shown an increased risk of myocardial infarction and stroke associated with use of testosterone replacement therapy. (5.5)
- Exogenous administration of androgens may lead to azoospermia. (5.8)
- Edema, with or without congestive heart failure (CHF), may be a complication in patients with preexisting cardiac, renal, or hepatic disease. (5.10, 6.2)
- Sleep apnea may occur in those with risk factors. (5.12)
- Monitor serum testosterone, prostate specific antigen (PSA), hemoglobin, hematocrit, liver function tests, and lipid concentrations periodically. (5.1, 5.3, 5.9, 5.13)
- AndroGel 1% is flammable until dry. (5.16)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 5%) are acne, application site reaction, abnormal lab tests, and prostatic disorders. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Androgens may decrease blood glucose and therefore may decrease insulin requirements in diabetic patients. (7.1)
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended. (7.2)
- Use of testosterone with adrenocorticotrophic hormone (ACTH) or corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease. (7.3)

USE IN SPECIFIC POPULATIONS

There are insufficient long-term safety data in geriatric patients using AndroGel 1% to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Patient Counseling Information (17)]*.**

1 INDICATIONS AND USAGE

AndroGel 1% is indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

Limitations of use:

- Safety and efficacy of AndroGel 1% in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established.
- Safety and efficacy of AndroGel 1% in males less than 18 years old have not been established *[see Use in Specific Populations (8.4)]*.
- Topical testosterone products may have different doses, strengths or application instructions that may result in different systemic exposure (1, 12.3).

2 DOSAGE AND ADMINISTRATION

Dosage and Administration for AndroGel 1% differs from AndroGel 1.62%. For dosage and administration of AndroGel 1.62% refer to its full prescribing information. (2)

Prior to initiating AndroGel 1%, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone concentrations are below the normal range.

2.1 Dosing and Dose Adjustment

The recommended starting dose of AndroGel 1% is 50 mg of testosterone (two 25 mg packets or one 50 mg packet), applied topically once daily in the morning to the shoulders and upper arms and/or abdomen area (preferably at the same time every day).

Dose Adjustment

To ensure proper dosing, serum testosterone concentrations should be measured at intervals. If the serum testosterone concentration is below the normal range, the daily AndroGel 1% dose may be increased from 50 mg to 75 mg and from 75 mg to 100 mg for adult males as instructed by the physician. If the serum testosterone concentration exceeds the normal range, the daily AndroGel 1% dose may be

decreased. If the serum testosterone concentration consistently exceeds the normal range at a daily dose of 50 mg, AndroGel 1% therapy should be discontinued. In addition, serum testosterone concentrations should be assessed periodically.

The application site and dose of AndroGel 1% are not interchangeable with other topical testosterone products.

2.2 Administration Instructions

AndroGel 1% should be applied to clean, dry, healthy, intact skin of the right and left upper arms/shoulders and/or right and left abdomen. Area of application should be limited to the area that will be covered by the patient's short sleeve T-shirt. Do not apply AndroGel 1% to any other part of the body including the genitals, chest, armpits (axillae), knees, or back. AndroGel 1% should be evenly distributed between the right and left upper arms/shoulders or both sides of the abdomen.

The prescribed daily dose of AndroGel 1% should be applied to the right and left upper arms/shoulders and/or right/left abdomen as shown in the shaded areas in the figure below.

After applying the gel, the application site should be allowed to dry prior to dressing. Hands should be washed thoroughly with soap and water after application. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including AndroGel 1%, are flammable.

The patient should be advised to avoid swimming or showering for at least 5 hours after the application of AndroGel 1%.

Packets

The entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. Alternately, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until entire contents have been applied.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from AndroGel 1%-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using AndroGel 1%.
- Patients should wash hands with soap and water immediately after application of AndroGel 1%.
- Patients should cover the application site(s) with clothing (e.g., a T-shirt) after the gel has dried.
- Prior to situation in which direct skin-to-skin contact is anticipated, patients should wash the application site thoroughly with soap and water to remove any testosterone residue.
- In the event that unwashed or unclothed skin to which AndroGel 1% has been applied comes in direct contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible.

3 DOSAGE FORMS AND STRENGTHS

AndroGel (testosterone gel) 1% for topical use is available as follows:

- A unit dose packet containing 25 mg of testosterone provided in 2.5 g of gel.
- A unit dose packet containing 50 mg of testosterone provided in 5 g of gel.

4 CONTRAINDICATIONS

- AndroGel 1% is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.1), Adverse Reactions (6.1),* and *Nonclinical Toxicology (13.1)]*.
- AndroGel 1% is contraindicated in women who are pregnant. AndroGel 1% can cause virilization of the female fetus when administered to a pregnant woman. Pregnant women need to be aware of the potential for transfer of testosterone from men treated with AndroGel 1%. If a pregnant woman is exposed to AndroGel 1%, she should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.2)* and *Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

- Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.
- Patients treated with androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating and during treatment with androgens *[see Contraindications (4), Adverse Reactions (6.1)* and *Nonclinical Toxicology (13.1)]*.

5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance. Signs and symptoms have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases, these signs and symptoms regressed with removal of the exposure to testosterone gel. In a few cases, however, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of transfer was increased in some of these cases by not adhering to precautions for the appropriate use of the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using AndroGel 1% *[see Dosage and Administration (2.2), Use in Specific Populations (8.1)* and *Clinical Pharmacology (12.3)]*.

Inappropriate changes in genital size or development of pubic hair or libido in children, or changes in body hair distribution, significant increase in acne, or other signs of virilization in adult women should be brought to the attention of a physician and the possibility of secondary exposure to testosterone gel should also be brought to the attention of a physician. Testosterone gel should be promptly discontinued until the cause of virilization has been identified.

5.3 Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating treatment. It would also be appropriate to re-evaluate the hematocrit 3 to 6 months after starting treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable concentration. An increase in red blood cell mass may increase the risk of thromboembolic events.

5.4 Venous Thromboembolism

There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products such as AndroGel 1%. Evaluate patients who report symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous

thromboembolic event is suspected, discontinue treatment with AndroGel 1% and initiate appropriate workup and management *[see Adverse Reactions (6.2)]*.

5.5 Cardiovascular Risk

Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men.

Patients should be informed of this possible risk when deciding whether to use or to continue to use AndroGel 1%.

5.6 Abuse of Testosterone and Monitoring of Serum Testosterone Concentrations

Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions *[see Drug Abuse and Dependence (9)]*.

If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

5.7 Use in Women

Due to lack of controlled evaluations in women and potential virilizing effects, AndroGel 1% is not indicated for use in women *[see Contraindications (4)* and *Use in Specific Populations (8.1, 8.2)]*.

5.8 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including AndroGel 1%, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) which could possibly lead to adverse effects on semen parameters including sperm count.

5.9 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate has produced multiple hepatic adenomas. AndroGel 1% is not known to cause these adverse effects.

5.10 Edema

Androgens, including AndroGel 1%, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease *[see Adverse Reactions (6.2)]*.

5.11 Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including AndroGel 1%, for hypogonadism.

5.12 Sleep Apnea

The treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors such as obesity or chronic lung diseases *[see Adverse Reactions (6.2)]*.

5.13 Lipids

Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

5.14 Hypercalcemia

Androgens, including AndroGel 1%, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

5.15 Decreased Thyroxine-binding Globulin

Androgens, including AndroGel 1%, may decrease concentrations of thyroxin-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

5.16 Flammability

Alcohol based products, including AndroGel 1%, are flammable; therefore, patients should be advised to avoid fire, flame or smoking until the AndroGel 1% has dried.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Hypogonadal Men

Table 1 shows the incidence of all adverse events judged by the investigator to be at least possibly related to treatment with AndroGel 1% and reported by >1% of patients in a 180 Day, Phase 3 study.

Table 1: Adverse Events Possibly, Probably or Definitely Related to Use of AndroGel 1% in the 180-Day Controlled Clinical Trial

Adverse Event	Dose of AndroGel 1%		
	50 mg	75 mg	100 mg
	N = 77	N = 40	N = 78
Acne	1%	3%	8%
Alopecia	1%	0%	1%
Application Site Reaction	5%	3%	4%
Asthenia	0%	3%	1%
Depression	1%	0%	1%
Emotional Lability	0%	3%	3%
Gynecomastia	1%	0%	3%
Headache	4%	3%	0%
Hypertension	3%	0%	3%
Lab Test Abnormal*	6%	5%	3%

Libido Decreased	0%	3%	1%
Nervousness	0%	3%	1%
Pain Breast	1%	3%	1%
Prostate Disorder**	3%	3%	5%
Testis Disorder***	3%	0%	0%
*_Lab test abnormal_ occurred in nine patients with one or more of the following events reported: elevated hemoglobin or hematocrit, hyperlipidemia, elevated triglycerides, hypokalemia, decreased HDL, elevated glucose, elevated creatinine, elevated total bilirubin.			
**_Prostate disorders_ included five patients with enlarged prostate, one with BPH, and one with elevated PSA results.			
***_Testis disorders_ were reported in two patients: one with left varicocele and one with slight sensitivity of left testis.			

Other less common adverse reactions, reported in fewer than 1% of patients included: amnesia, anxiety, discolored hair, dizziness, dry skin, hirsutism, hostility, impaired urination, paresthesia, penis disorder, peripheral edema, sweating, and vasodilation.

In this 180 day clinical trial, skin reactions at the site of application were reported with AndroGel 1%, but none was severe enough to require treatment or discontinuation of drug.

Six patients (4%) in this trial had adverse events that led to discontinuation of AndroGel 1%. These events included: cerebral hemorrhage, convulsion (neither of which were considered related to AndroGel 1% administration), depression, sadness, memory loss, elevated prostate specific antigen, and hypertension. No AndroGel 1% patient discontinued due to skin reactions.

In a separate uncontrolled pharmacokinetic study of 10 patients, two had adverse events associated with AndroGel 1%; these were asthenia and depression in one patient and increased libido and hyperkinesia in the other.

In a 3 year, flexible dose, extension study, the incidence of all adverse events judged by the investigator to be at least possibly related to treatment with AndroGel 1% and reported by > 1% of patients is shown in Table 2.

Table 2: Adverse Events Possibly, Probably or Definitely Related to Use of AndroGel 1% in the 3 Year, Flexible Dose, Extension Study

Adverse Event	Percent of Subjects
	(N = 162)
Lab Test Abnormal+	9.3
Skin dry	1.9
Application Site Reaction	5.6
Acne	3.1
Pruritus	1.9
Enlarged Prostate	11.7
Carcinoma of Prostate	1.2
Urinary Symptoms*	3.7
Testis Disorder**	1.9
Gynecomastia	2.5
Anemia	2.5
+_Lab test abnormal_ occurred in 15 patients with one or more of the following events reported: elevated AST, elevated ALT, elevated testosterone, elevated hemoglobin or hematocrit, elevated cholesterol, elevated cholesterol/HDL ratio, elevated triglycerides, elevated HDL, elevated serum creatinine.	

**Urinary symptoms* included nocturia, urinary hesitancy, urinary incontinence, urinary retention, urinary urgency and weak urinary stream.
***Testis disorders* included three patients. There were two with a non-palpable testis and one with slight right testicular tenderness.

Two patients reported serious adverse events considered possibly related to treatment: deep vein thrombosis (DVT) and prostate disorder requiring a transurethral resection of the prostate (TURP).

Discontinuation for adverse events in this study included: two patients with application site reactions, one with kidney failure, and five with prostate disorders (including increase in serum PSA in 4 patients, and increase in PSA with prostate enlargement in a fifth patient).

Increases in Serum PSA Observed in Clinical Trials of Hypogonadal Men

During the initial 6-month study, the mean change in PSA values had a statistically significant increase of 0.26 ng/mL. Serum PSA was measured every 6 months thereafter in the 162 hypogonadal men on AndroGel 1% in the 3-year extension study. There was no additional statistically significant increase observed in mean PSA from 6 months through 36 months. However, there were increases in serum PSA observed in approximately 18% of individual patients. The overall mean change from baseline in serum PSA values for the entire group from month 6 to 36 was 0.11 ng/mL.

Twenty-nine patients (18%) met the per-protocol criterion for increase in serum PSA, defined as >2X the baseline or any single serum PSA >6 ng/mL. Most of these (25/29) met this criterion by at least doubling of their PSA from baseline. In most cases where PSA at least doubled (22/25), the maximum serum PSA value was still <2 ng/mL. The first occurrence of a pre-specified, post-baseline increase in serum PSA was seen at or prior to Month 12 in most of the patients who met this criterion (23 of 29; 79%).

Four patients met this criterion by having a serum PSA >6 ng/mL and in these, maximum serum PSA values were 6.2 ng/mL, 6.6 ng/mL, 6.7 ng/mL, and 10.7 ng/mL. In two of these patients, prostate cancer was detected on biopsy. The first patient's PSA levels were 4.7 ng/mL and 6.2 ng/mL at baseline and at Month 6/Final, respectively. The second patient's PSA levels were 4.2 ng/mL, 5.2 ng/mL, 5.8 ng/mL, and 6.6 ng/mL at baseline, Month 6, Month 12, and Final, respectively.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AndroGel 1%. Because the reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure (Table 3).

Table 3: Adverse Drug Reactions from Postmarketing Experience of AndroGel 1% by MedDRA System Organ Class

Blood and the lymphatic system disorders:	Elevated Hgb, Hct (polycythemia)
Cardiovascular disorders:	Myocardial infarction, stroke
Endocrine disorders:	Hirsutism
Gastrointestinal disorders:	Nausea
General disorders and administration site reactions:	Asthenia, edema, malaise
Genitourinary disorders:	Impaired urination
Hepatobiliary disorders:	Abnormal liver function tests (e.g. transaminases, elevated GGTP, bilirubin)
	Elevated PSA, electrolyte changes (nitrogen, calcium, potassium, phosphorus, sodium), changes

Investigations:	in serum lipids (hyperlipidemia, elevated triglycerides, decreased HDL), impaired glucose tolerance, fluctuating testosterone concentrations, weight increase
Neoplasms benign, malignant and unspecified (cysts and polyps):	Prostate cancer
Nervous system:	Headache, dizziness, sleep apnea, insomnia
Psychiatric disorders:	Depression, emotional lability, decreased libido, nervousness, hostility, amnesia, anxiety
Reproductive system and breast disorders:	Gynecomastia, mastodynia, prostatic enlargement, testicular atrophy, oligospermia, priapism (frequent or prolonged erections)
Respiratory disorders:	Dyspnea
Skin and subcutaneous tissue disorders:	Acne, alopecia, application site reaction (pruritus, dry skin, erythema, rash, discolored hair, paresthesia), sweating
Vascular disorders:	Hypertension, vasodilation (hot flushes), venous thromboembolism

Secondary Exposure to Testosterone in Children

Cases of secondary exposure to testosterone resulting in virilization of children have been reported in postmarket surveillance. Signs and symptoms of these reported cases have included enlargement of the clitoris (with surgical intervention) or the penis, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. In most cases with a reported outcome, these signs and symptoms were reported to have regressed with removal of the testosterone gel exposure. In a few cases, however, enlarged genitalia did not fully return to age appropriate normal size, and bone age remained modestly greater than chronological age. In some of the cases, direct contact with the sites of application on the skin of men using testosterone gel was reported. In at least one reported case, the reporter considered the possibility of secondary exposure from items such as the testosterone gel user's shirts and/or other fabric, such as towels and sheets *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may decrease insulin requirements.

7.2 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens, therefore more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal or hepatic disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

AndroGel 1% is contraindicated in pregnant women. Testosterone is teratogenic and may cause fetal harm when administered to a pregnant woman based on data from animal studies and its mechanism of action *[see Contraindications (4) and Clinical Pharmacology (12.1)]*. Exposure of a female fetus to androgens may result in varying degrees of virilization. In animal developmental studies, exposure to testosterone in utero resulted in hormonal and behavioral changes in offspring and structural impairments of reproductive tissues in female and male offspring. These studies did not meet current standards for nonclinical development toxicity studies.

Data

Animal Data

In developmental studies conducted in rats, rabbits, pigs, sheep and rhesus monkeys, pregnant animals received intramuscular injection of testosterone during the period of organogenesis. Testosterone treatment at doses that were comparable to those used for testosterone replacement therapy resulted in structural impairments in both female and male offspring. Structural impairments observed in females included increased ano-genital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment. Structural impairments seen in male offspring included increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen. Increased pituitary weight was seen in both sexes.

Testosterone exposure in utero also resulted in hormonal and behavioral changes in offspring. Hypertension was observed in pregnant female rats and their offspring exposed to doses approximately twice those used fortestosterone replacement therapy.

8.2 Lactation

Risk Summary

AndroGel 1% is not indicated for use in women.

8.3 Females and Males of Reproductive Potential

Infertility

Testis disorder, testicular atrophy, and oligospermia have been identified during use of AndroGel 1% *[see Adverse Reactions (6.1, 6.2)]*.

During treatment with large doses of exogenous androgens, including AndroGel 1%, spermatogenesis may be suppressed through feedback inhibition of the hypothalamic-pituitary-testicular axis *[see Warnings and Precautions (5.8)]*. Reduced fertility is observed in some men taking testosterone replacement therapy. Testicular atrophy, subfertility, and infertility have also been reported in men who abuse anabolic androgenic steroids *[see Drug Abuse and Dependence (9.2)]*. With either type of use, the impact on fertility may be irreversible.

8.4 Pediatric Use

The safety and efficacy of AndroGel 1% in pediatric patients less than 18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing AndroGel 1% to determine whether efficacy in those over 65 years of age differs from younger subjects. Additionally, there is insufficient long-term safety data in geriatric patients to assess

the potential risks of cardiovascular disease and prostate cancer.

Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of BPH.

8.6 Renal Impairment

No studies were conducted in patients with renal impairment.

8.7 Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

AndroGel 1% contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

9.2 Abuse

Drug abuse is intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Abuse and misuse of testosterone are seen in male and female adults and adolescents. Testosterone, often in combination with other anabolic androgenic steroids (AAS), and not obtained by prescription through a pharmacy, may be abused by athletes and bodybuilders. There have been reports of misuse by men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice.

Abuse-Related Adverse Reactions

Serious adverse reactions have been reported in individuals who abuse anabolic androgenic steroids and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilization, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

9.3 Dependence

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

- Taking greater dosages than prescribed
- Continued drug use despite medical and social problems due to drug use
- Spending significant time to obtain the drug when supplies of the drug are interrupted
- Giving a higher priority to drug use than other obligations

- Having difficulty in discontinuing the drug despite desires and attempts to do so
- Experiencing withdrawal symptoms upon abrupt discontinuation of use

Physical dependence is characterized by withdrawal symptoms after abrupt drug discontinuation or a significant dose reduction of a drug. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism.

Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented.

10 OVERDOSAGE

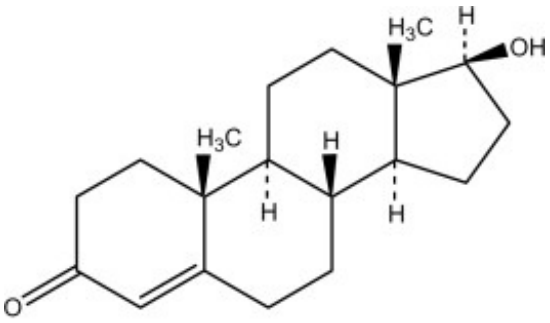
There is one report of acute overdosage with use of an approved injectable testosterone product: this subject had serum testosterone concentrations of up to 11,400 ng/dL with a cerebrovascular accident.

Treatment of overdosage would consist of discontinuation of AndroGel 1%, washing the application site with soap and water, and appropriate symptomatic and supportive care.

11 DESCRIPTION

AndroGel (testosterone gel) 1% is a clear, colorless hydroalcoholic gel containing testosterone.

The active pharmacologic ingredient in AndroGel 1% is testosterone, an androgen. Testosterone USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:



Testosterone

$C_{19}H_{28}O_2$ MW 288.42

Pharmacologically inactive ingredients in AndroGel 1% are carbomer 980, ethanol 67.0%, isopropyl myristate, purified water, and sodium hydroxide. These ingredients are not pharmacologically active.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal chord thickening, alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted using AndroGel 1%.

12.3 Pharmacokinetics

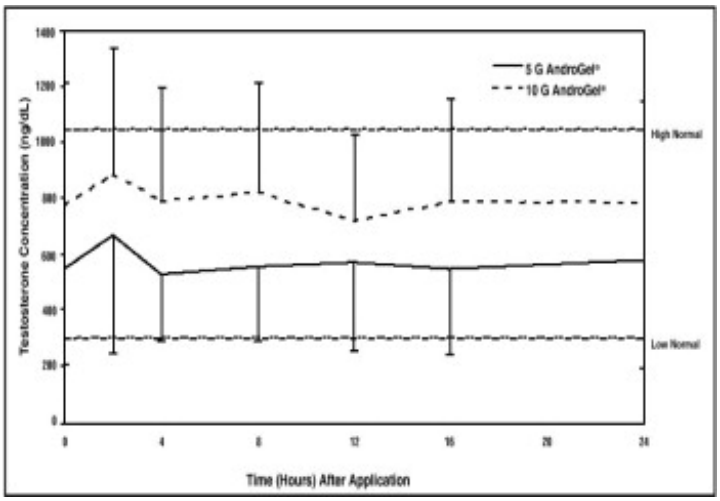
Absorption

AndroGel 1% delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal concentrations (298 - 1043 ng/dL) seen in healthy men. AndroGel 1% provides continuous transdermal delivery of testosterone for 24 hours following a single application to intact, clean, dry skin of the shoulders, upper arms and/or abdomen.

AndroGel 1% is a hydroalcoholic formulation that dries quickly when applied to the skin surface. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone dose applied on the skin surface from AndroGel is absorbed into systemic circulation. In a study with AndroGel 1% 100 mg , all patients showed an increase in serum testosterone within 30 minutes, and eight of nine patients had a serum testosterone concentration within normal range by 4 hours after the initial application. Absorption of testosterone into the blood continues for the entire 24-hour dosing interval. Serum concentrations approximate the steady-state concentration by the end of the first 24 hours and are at steady state by the second or third day of dosing.

With single daily applications of AndroGel 1%, follow-up measurements 30, 90 and 180 days after starting treatment have confirmed that serum testosterone concentrations are generally maintained within the eugonadal range. Figure 1 summarizes the 24-hour pharmacokinetic profiles of testosterone for hypogonadal men (less than 300 ng/dL) maintained on AndroGel 1% 50 mg or 100 mg for 30 days. The average (± SD) daily testosterone concentration produced by AndroGel 1% 100 mg on Day 30 was 792 (± 294) ng/dL and by AndroGel 1% 50 mg 566 (± 262) ng/dL.

Figure 1: Mean (± SD) Steady-State Serum Testosterone Concentrations on Day 30 in Patients Applying AndroGel 1% Once Daily



Distribution

Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free)

and the rest is bound to albumin and other proteins.

Metabolism

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT).

DHT concentrations increased in parallel with testosterone concentrations during AndroGel 1% treatment. The mean steady-state DHT/T ratio during 180 days of AndroGel treatment ranged from 0.23 to 0.29 (50 mg of AndroGel 1%/day) and from 0.27 to 0.33 (100 mg of AndroGel 1%/day).

Excretion

There is considerable variation in the half-life of testosterone concentration as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

When AndroGel 1% treatment is discontinued after achieving steady state, serum testosterone concentrations remain in the normal range for 24 to 48 hours but return to their pretreatment concentrations by the fifth day after the last application.

Testosterone Transfer from Male Patients to Female Partners

The potential for dermal testosterone transfer following AndroGel 1% use was evaluated in a clinical study between males dosed with AndroGel 1% and their untreated female partners. Two (2) to 12 hours after application of 100 mg of testosterone administered as AndroGel 1% by the male subjects, the couples (N = 38 couples) engaged in daily, 15-minute sessions of vigorous skin-to-skin contact so that the female partners gained maximum exposure to the AndroGel 1% application sites. Under these study conditions, all unprotected female partners had a serum testosterone concentration >2 times the baseline value at some time during the study. When a shirt covered the application site(s), the transfer of testosterone from the males to the female partners was completely prevented.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats.

Mutagenesis

Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays.

Impairment of Fertility

The administration of exogenous testosterone has been reported to suppress spermatogenesis in rats, dogs, and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adult Hypogonadal Males

AndroGel 1% was evaluated in a multi-center, randomized, parallel-group, active-controlled, 180-day

trial in 227 hypogonadal men. The study was conducted in 2 phases. During the Initial Treatment Period (Days 1-90), 73 patients were randomized to AndroGel 1% 50 mg daily, 78 patients to AndroGel 1% 100 mg daily, and 76 patients to a non-scrotal testosterone transdermal system. The study was double-blind for dose of AndroGel 1% but open-label for active control. Patients who were originally randomized to AndroGel 1% and who had single-sample serum testosterone concentrations above or below the normal range on Day 60 were titrated to 75 mg daily on Day 91. During the Extended Treatment Period (Days 91-180), 51 patients continued on AndroGel 1% 50 mg daily, 52 patients continued on AndroGel 1% 100 mg daily, 41 patients continued on a non-scrotal testosterone transdermal system (5 mg daily), and 40 patients received AndroGel 1% 75 mg daily. Upon completion of the initial study, 163 enrolled and 162 patients received treatment in an open-label extension study of AndroGel 1% for an additional period of up to 3 years.

Mean peak, trough and average serum testosterone concentrations within the normal range (298-1043 ng/dL) were achieved on the first day of treatment with doses of 50 mg and 100 mg of AndroGel 1%. In patients continuing on AndroGel 1% 50 mg and 100 mg, these mean testosterone concentrations were maintained within the normal range for the 180-day duration of the original study. Figure 2 summarizes the 24-hour pharmacokinetic profiles of testosterone administered as AndroGel 1% for 30, 90 and 180 days. Testosterone concentrations were maintained as long as the patient continued to properly apply the prescribed AndroGel 1% treatment.

Figure 2: Mean Steady-State Testosterone Concentrations in Patients with Once-Daily AndroGel 1% Therapy

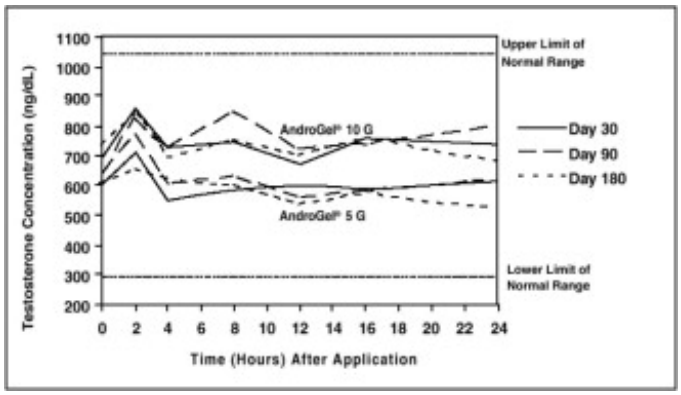


Table 4 summarizes the mean testosterone concentrations on Treatment Day 180 for patients receiving 50 mg, 75 mg, or 100 mg of AndroGel 1%. The 75 mg dose produced mean concentrations intermediate to those produced by 50 mg and 100 mg of AndroGel 1%.

Table 4: Mean (± SD) Steady-State Serum Testosterone Concentrations During Therapy (Day 180)

	50 mg	**75 mg**	**100 mg**
	N = 44	N = 37	N = 48
C_{avg}	555 ± 225	601 ± 309	713 ± 209
C_{max}	830 ± 347	901 ± 471	1083 ± 434
C_{min}	371 ± 165	406 ± 220	485 ± 156

Of 129 hypogonadal men who were appropriately titrated with AndroGel 1% and who had sufficient data for analysis, 87% achieved an average serum testosterone concentration within the normal range on Treatment Day 180.

In patients treated with AndroGel 1%, there were no observed differences in the average daily serum

testosterone concentrations at steady-state based on age, cause of hypogonadism, or body mass index.

DHT concentrations increased in parallel with testosterone concentrations at AndroGel 1% doses of 50 mg/day and 100 mg/day, but the DHT/T ratio stayed within the normal range, indicating enhanced availability of the major physiologically active androgen. Serum estradiol (E2) concentrations increased significantly within 30 days of starting treatment with AndroGel 1% 50 or 100 mg/day and remained elevated throughout the treatment period but remained within the normal range for eugonadal men. Serum levels of SHBG decreased very slightly (1 to 11%) during AndroGel 1% treatment. In men with hypergonadotropic hypogonadism, serum levels of LH and FSH fell in a dose- and time-dependent manner during treatment with AndroGel 1%.

14.2 Phototoxicity in Humans

The phototoxic potential of AndroGel 1% was evaluated in a double-blind, single-dose study in 27 subjects with photosensitive skin types. The Minimal Erythema Dose (MED) of ultraviolet radiation was determined for each subject. A single 24 (+1) hour application of duplicate patches containing test articles (placebo gel, testosterone gel, or saline) was made to naive skin sites on Day 1. On Day 2, each subject received five exposure times of ultraviolet radiation, each exposure being 25% greater than the previous one. Skin evaluations were made on Days 2 to 5. Exposure of test and control article application sites to ultraviolet light did not produce increased inflammation relative to non-irradiated sites, indicating no phototoxic effect.

16 HOW SUPPLIED/STORAGE AND HANDLING

AndroGel 1% is supplied in unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5 g gel contains 25 mg or 50 mg testosterone, respectively.

NDC Number	Package Size
0051-8425-30	30 packets (a unit dose packet containing 25 mg of testosterone provided in 2.5 g of gel)
0051-8450-30	30 packets (a unit dose packet containing 50 mg of testosterone provided in 5 g of gel)

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Disposal

Used AndroGel 1% packets should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide)

Patients should be informed of the following:

17.1 Use in Men with Known or Suspected Prostate or Breast Cancer

Men with known or suspected prostate or breast cancer should not use AndroGel 1% *[see Contraindications (4)* and *Warnings and Precautions (5.1)]*.

17.2 Potential for Secondary Exposure to Testosterone and Steps to Prevent Secondary Exposure

Secondary exposure to testosterone in children and women can occur with the use of testosterone gel in men *[see Warnings and Precautions (5.2)]*. Cases of secondary exposure to testosterone have been reported in children.

Physicians should advise patients of the reported signs and symptoms of secondary exposure which may include the following:

- In children; unexpected sexual development including inappropriate enlargement of the penis or clitoris, premature development of pubic hair, increased erections, and aggressive behavior
- In women; changes in hair distribution, increase in acne, or other signs of testosterone effects
- The possibility of secondary exposure to testosterone gel should be brought to the attention of a healthcare provider
- AndroGel 1% should be promptly discontinued until the cause of virilization is identified

Strict adherence to the following precautions is advised to minimize the potential for secondary exposure to testosterone from testosterone gel in men *[see Medication Guide]*:

- **Children and women should avoid contact with unwashed or unclothed application site(s)** of men using testosterone gel
- Patients using AndroGel 1% should apply the product as directed and strictly adhere to the following:
  - **Wash hands** with soap and water after application
  - **Cover the application site(s)** with clothing after the gel has dried
  - **Wash the application site(s) thoroughly** with soap and water prior to any situation where skin-to-skin contact of the application site with another person is anticipated
  - In the event that unwashed or unclothed skin to which AndroGel 1% has been applied comes in contact with the skin of another person, the general area of contact on the other person should be washed with soap and water as soon as possible *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)]*.

17.3 Potential Adverse Reactions with Androgens

Patients should be informed that treatment with androgens may lead to adverse reactions which include:

- Changes in urinary habits such as increased urination at night, trouble starting your urine stream, passing urine many times during the day, having an urge that you have to go to the bathroom right away, having a urine accident, being unable to pass urine and weak urine flow.
- Breathing disturbances, including those associated with sleep, or excessive daytime sleepiness.
- Too frequent or persistent erections of the penis.
- Nausea, vomiting, changes in skin color, or ankle swelling.

17.4 Patients Should Be Advised of the Following Instructions for Use:

- **Read the Medication Guide before starting AndroGel 1% therapy and to reread it each time the prescription is renewed**
- **AndroGel 1% should be applied and used appropriately to maximize the benefits and to minimize the risk of secondary exposure in children and women**
- **Keep AndroGel 1% out of the reach of children**
- **AndroGel 1% is an alcohol based product and is flammable; therefore avoid fire, flame or smoking until the gel has dried**
- **It is important to adhere to all recommended monitoring**
- **Report any changes in their state of health, such as changes in urinary habits, breathing, sleep, and mood**
- AndroGel 1% is prescribed to meet the patient's specific needs; therefore, the patient should never share AndroGel 1% with anyone.
- Wait 5 hours before swimming or washing following application of AndroGel 1%. This will ensure that the greatest amount of AndroGel 1% is absorbed into their system.

Marketed by:

AbbVie Inc.
North Chicago, IL 60064, USA

5044279 Revised May, 2019

MEDICATION GUIDE
ANDROGEL® (AN DROW JEL) CIII
(testosterone gel) 1% for topical use

What is the most important information I should know about ANDROGEL 1%?

1. **ANDROGEL 1% can transfer from your body to others including, children and women.** Children and women should avoid contact with the unwashed or not covered (unclothed) areas where ANDROGEL 1% has been applied to your skin. Early signs and symptoms of puberty have occurred in young children who have come in direct contact with testosterone by touching areas where men have used ANDROGEL 1%.
   - **Children**
   - **Signs and symptoms of early puberty in a child when they come in direct contact with ANDROGEL 1% may include:**
     - **Abnormal sexual changes:**
       - enlarged penis or clitoris.
       - early growth of hair near the vagina or around the penis (pubic hair).
       - erections or acting out sexual urges (sex drive).
     - **Behavior problems:**
       - acting aggressively, behaving in an angry or violent way.

   Women

   Signs and symptoms in women when they come in direct contact with ANDROGEL 1% may include:
   - changes in body hair.
   - an abnormal increase in pimples (acne).

   Stop using ANDROGEL 1% and call your healthcare provider right away if you see any signs and symptoms in a child or a woman that may have happened through accidental touching of the area where you have applied ANDROGEL 1%.
2. **To lower the risk of transfer of ANDROGEL 1% from your body to others, follow these important instructions:**
   - Apply ANDROGEL 1% only to areas of your shoulders, upper arms, or stomach area (abdomen) that will be covered by a short sleeve t-shirt.
   - Wash your hands right away with soap and water after applying ANDROGEL 1%.
   - After the gel has dried, cover the application area with clothing. Keep the area covered until you have washed the gel off the application area well or have showered.
   - If you expect to have skin-to-skin contact with another person, first wash the application area well with soap and water.
   - If a child or woman touches the area where you have applied ANDROGEL 1%, that area on the child or woman should be washed well with soap and water right away.

What is ANDROGEL 1%?

ANDROGEL 1% is a prescription medicine that contains testosterone. ANDROGEL 1% is used to treat adult males who have low or no testosterone due to certain medical conditions.

- Your healthcare provider will test your blood before you start and while you are using ANDROGEL 1%.
- It is not known if ANDROGEL 1% is safe or effective to treat men who have low testosterone due

to aging.
- It is not known if ANDROGEL 1% is safe or effective in children younger than 18 years old. Improper use of ANDROGEL 1% may affect bone growth in children.

ANDROGEL 1% is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your ANDROGEL 1% in a safe place to protect it. Never give your ANDROGEL 1% to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and is against the law.
ANDROGEL 1% is not meant for use in women.

Do not use ANDROGEL 1% if you:
- have breast cancer.
- have or might have prostate cancer.
- are pregnant. ANDROGEL 1% may harm your unborn baby.
- Women who are pregnant should avoid contact with the area of skin where ANDROGEL 1% has been applied.

Before using ANDROGEL 1%, tell your healthcare provider about all of your medical conditions, including if you:
- have breast cancer.
- have or might have prostate cancer.
- have urinary problems due to an enlarged prostate.
- have heart problems.
- have liver or kidney problems.
- have problems breathing while you sleep (sleep apnea).

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using ANDROGEL 1% with certain other medicines can affect each other.
Especially, tell your healthcare provider if you take:
- insulin
- corticosteroids
- medicines that decrease blood clotting (blood thinners)

How should I use ANDROGEL 1%?
- See the detailed **Instructions for Use** for information about how to use ANDROGEL 1% at the end of this Medication Guide.
- It is important that you apply ANDROGEL 1% exactly as your healthcare provider tells you to.
- Your healthcare provider may change your ANDROGEL 1% dose. **Do not** change your ANDROGEL 1% dose without talking to your healthcare provider.
- Apply ANDROGEL 1% at the same time each morning. ANDROGEL 1% should be applied after showering or bathing.

What are the possible side effects of ANDROGEL 1%?
ANDROGEL 1% can cause serious side effects including:
See **"What is the most important information I should know about ANDROGEL 1%?"**
- **If you already have an enlarged prostate, your symptoms can get worse while using ANDROGEL 1%.** This can include:
  - increased urination at night.
  - trouble starting your urine stream.
  - having to pass urine many times during the day.
  - having an urge to go to the bathroom right away.
  - having a urine accident.

- being unable to pass urine or weak urine flow.

- **Possible increased risk of prostate cancer.** Your healthcare provider should check you for prostate cancer or any other prostate problems before you start and while you use ANDROGEL 1%.
- **Blood clots in the legs or lungs.** Signs and symptoms of a blood clot in your leg can include leg pain, swelling or redness. Signs and symptoms of a blood clot in your lungs can include difficulty breathing or chest pain.
- **Possible increased risk of heart attack or stroke.**
- **In large doses ANDROGEL 1% may lower your sperm count.**
- **Swelling of your ankles, feet, or body, with or without heart failure.**
- **Enlarged or painful breasts.**
- **Have problems breathing while you sleep (sleep apnea).**

Call your healthcare provider right away if you have any of the serious side effects listed above.
The most common side effects of ANDROGEL 1% include:

- acne
- skin irritation where ANDROGEL 1% is applied
- lab test changes
- increased prostate specific antigen (a test used to screen for prostate cancer).

Other side effects include more erections than are normal for you or erections that last a long time. Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of ANDROGEL 1%. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ANDROGEL 1%
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ANDROGEL 1% for a condition for which it was not prescribed. Do not give ANDROGEL 1% to other people, even if they have the same symptoms you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about ANDROGEL 1% that is written for health professionals.

What are the ingredients in ANDROGEL 1%?
Active ingredient: testosterone
Inactive ingredients: carbomer 980, ethyl alcohol 67.0%, isopropyl myristate, purified water and sodium hydroxide.
Marketed by: AbbVie Inc., North Chicago, IL 60064, USA

For more information, go to www.ANDROGEL.com or call 1-800-633-9110.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: 05/2019

5044279

INSTRUCTIONS FOR USE
ANDROGEL® (AN DROW JEL) CIII
(testosterone gel) 1%
for topical use

Read this Instructions for Use for ANDROGEL 1% before you start using it and each time you get a

refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

Applying ANDROGEL 1%:

- Before applying ANDROGEL 1%, make sure that your shoulders, upper arms or stomach are clean, dry, and there is no broken skin.
- The application sites for ANDROGEL 1% are the shoulders, upper arms or stomach area (abdomen) that will be covered by a short sleeve t-shirt (see Figure A). **Do not** apply ANDROGEL 1% to any other parts of your body such as your penis, scrotum, chest, armpits (axillae), knees, or back.

(Figure A)

- Tear open the packet completely at the dotted line. Squeeze from the bottom of the packet to the top.
- Squeeze all of the ANDROGEL 1% out of the packet into the palm of your hand.
- Apply ANDROGEL 1% to the application site. You may also apply ANDROGEL 1% from the packet directly to the application site.
- **Let the application areas dry completely before putting on a t-shirt.**
- **ANDROGEL 1% is flammable until dry. Let ANDROGEL 1% dry before smoking or going near an open flame.**
- **Wash your hands with soap and water right away** after applying ANDROGEL 1%.
- Avoid showering, swimming, or bathing for at least 5 hours after you apply ANDROGEL 1%.

How should I store ANDROGEL 1%?

- Store ANDROGEL 1% at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away used ANDROGEL 1% in the household trash. Be careful to prevent accidental exposure of children or pets.
- Keep ANDROGEL 1% away from fire.

Keep ANDROGEL 1% and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Revised: 05/2019

5044279

NDC 0051–8425–30

CIII

AndroGel®(testosterone gel) 1%

30 Unit-dose Packets

Contains 25 mg of testosterone in 2.5 Grams of gel per unit dose

Clear, colorless gel provides transdermal delivery of testosterone through the skin of the shoulders, upper arms, or abdomen.*

Rx Only

For Topical Use Only

Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure.

Dispense the enclosed Medication Guide to each patient.

*See accompanying package insert.

abbvie

NDC 0051–8450–30

CIII

AndroGel® (testosterone gel) 1%

30 Unit-dose Packets

Contains 50 mg of testosterone in 5 Grams of gel per unit dose

Clear, colorless gel provides transdermal delivery of testosterone through the skin of the shoulders, upper arms, or abdomen.*

Rx Only

For Topical Use Only

Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure.

Dispense the enclosed Medication Guide to each patient.

*See accompanying package insert.

abbvie

NDC 0051–8488–88

ANDROGEL

testosterone gel

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0051-8488
Route of Administration	TRANSDERMAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
testosterone (UNII: 3XMK78S47O) (testosterone - UNII:3XMK78S47O)	testosterone	10 mg in 1 g

Inactive Ingredients	
Ingredient Name	**Strength**
isopropyl myristate (UNII: 0RE8K4LNJS)	
water (UNII: 059QF0KO0R)	
sodium hydroxide (UNII: 55X04QC32I)	
alcohol (UNII: 3K9958V90M)	
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED) (UNII: 4Q93RCW27E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0051-8488-88	2 in 1 CARTON	03/14/2011	08/31/2015
1	NDC:0051-8488-33	75 g in 1 BOTTLE, PUMP; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

NDA	NDA021015	03/14/2011	08/31/2015

ANDROGEL

testosterone gel

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0051-8425
Route of Administration	TRANSDERMAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
testosterone (UNII: 3XMK78S47O) (testosterone - UNII:3XMK78S47O)	testosterone	10 mg in 1 g

Inactive Ingredients	
Ingredient Name	**Strength**
alcohol (UNII: 3K9958V90M)	
isopropyl myristate (UNII: 0RE8K4LNJS)	
water (UNII: 059QF0KO0R)	
sodium hydroxide (UNII: 55X04QC32I)	
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED) (UNII: 4Q93RCW27E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0051-8425-30	30 in 1 CARTON	03/14/2011	
1	NDC:0051-8425-01	2.5 g in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021015	03/14/2011	

ANDROGEL

testosterone gel

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0051-8450
Route of Administration	TRANSDERMAL	**DEA Schedule**	CIII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
testosterone (UNII: 3XMK78S47O) (testosterone - UNII:3XMK78S47O)	testosterone	10 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
alcohol (UNII: 3K9958V90M)	
isopropyl myristate (UNII: 0RE8K4LNJS)	
water (UNII: 059QF0KO0R)	
sodium hydroxide (UNII: 55X04QC32I)	
CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED) (UNII: 4Q93RCW27E)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0051-8450-30	30 in 1 CARTON	03/14/2011	
1	NDC:0051-8450-01	5 g in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021015	03/14/2011	

Labeler - AbbVie Inc. (078458370)

Revised: 4/2020 AbbVie Inc.

Exhibit

E

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANDRODERM safely and effectively. See full prescribing information for ANDRODERM.

ANDRODERM® (testosterone transdermal system), for topical use CIII

Initial U.S. Approval: 1995

----------INDICATIONS AND USAGE----------

ANDRODERM is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired) (1)
- Hypogonadotropic hypogonadism (congenital or acquired) (1)

Important limitations of use: Safety and efficacy of ANDRODERM in males < 18 years old have not been established. (1, 8.4)

----------DOSAGE AND ADMINISTRATION----------

ANDRODERM 2 mg/day and 4 mg/day system: The recommended starting dose is one ANDRODERM 4 mg/day system (not two 2 mg/day systems) applied nightly for 24 hours, delivering approximately 4 mg of testosterone per day. Serum testosterone concentrations measured in the early morning outside the range of 400 – 930 ng/dL require increasing the daily dose to 6 mg (i.e., one 4 mg/day and one 2 mg/day system) or decreasing the daily dose to 2 mg (i.e., one 2 mg/day system), maintaining nightly application. (2.1)

ANDRODERM 2.5 mg/day and 5 mg/day system: The recommended starting dose is one ANDRODERM 5 mg/day system (or two 2.5 mg/day systems) applied nightly for 24 hours, delivering approximately 5 mg of testosterone per day. Confirmed serum testosterone concentrations outside the normal range (300 – 1030 ng/dL) require increasing the daily dose to 7.5 mg (i.e., one 5 mg/day and one 2.5 mg/day system) or decreasing the daily dose to 2.5 mg (i.e., one 2.5 mg/day system), maintaining nightly application. (2.1)

To ensure proper dosing, approximately 2 weeks after starting therapy, the early morning serum testosterone concentration should be measured following system application in the previous evening. (2.1, 12.3)

Patients switching from Androderm 2.5 mg/day, 5 mg/day, and 7.5 mg/day system to Androderm 2 mg/day, 4 mg/day, and 6 mg/day system: Patients currently maintained on ANDRODERM 2.5 mg/day systems applied once daily may be switched to ANDRODERM 2 mg/day systems applied once daily in the evening at the next scheduled dose. (2.1)

Patients currently maintained on ANDRODERM 5 mg/day systems applied once daily may be switched to ANDRODERM 4 mg/day systems applied once daily in the evening at the next scheduled dose. (2.1)
Patients currently maintained on ANDRODERM 7.5 mg (2.5 mg/day and 5 mg/day systems) applied once daily may be switched to ANDRODERM 6 mg (2 mg/day and 4 mg/day systems) applied once daily in the evening at the next scheduled dose. (2.1)
To ensure proper dosing, approximately 2 weeks after switching therapy an early morning serum testosterone concentration should be measured following system application the previous evening. (2.1, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------

Transdermal system: 2 mg/day, 2.5 mg/day, 4 mg/day and 5 mg/day. (3)

----------CONTRAINDICATIONS----------

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate. (4, 5.1)
- Pregnant or breastfeeding women. Testosterone may cause fetal harm. (4, 8.1, 8.3)

----------WARNINGS AND PRECAUTIONS----------

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. (5.1)
- Avoid exposure of women or children to ANDRODERM. (5.3)
- Exogenous administration of testosterone may lead to azoospermia. (5.4)
- Edema with or without congestive heart failure, may be a complication in patients with pre-existing cardiac, renal, or hepatic disease. (5.6)
- Sleep apnea may occur in those with risk factors. (5.8)
- Monitor serum testosterone, prostate specific antigen (PSA), liver function, lipid concentrations, hematocrit and hemoglobin periodically. (5.1, 5.2, 5.5, 5.9)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence > 3%) are application site reactions, and back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Watson Laboratories, Inc. at 1-800-272-5525 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Androgens may decrease blood glucose and insulin requirement in diabetic patients. (7.1)
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended. (7.2)
- Use of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

There are insufficient long-term safety data in geriatric patients using ANDRODERM to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 10/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ANDRODERM is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

- **Primary hypogonadism (congenital or acquired):** testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter Syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.

- **Hypogonadotropic hypogonadism (congenital or acquired):** idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Important limitations of use – Safety and efficacy of ANDRODERM in males <18 years old have not been established [*see Use in Specific Populations (8.4)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

ANDRODERM 2 mg/day and 4 mg/day system: The recommended starting dose is one ANDRODERM 4 mg/day system (not two 2 mg/day systems) applied nightly for 24 hours, delivering approximately 4 mg of testosterone per day. To ensure proper dosing, approximately 2 weeks after starting therapy, the early morning serum testosterone concentration should be measured following system application the previous evening. Serum concentrations outside the range of 400 – 930 ng/dL require increasing the daily dose to 6 mg (i.e., one 4 mg/day and one 2 mg/day system) or decreasing the daily dose to 2 mg (i.e., one 2 mg/day system), maintaining nightly application.

ANDRODERM 2.5 mg/day and 5 mg/day system: The recommended starting dose is one ANDRODERM 5 mg/day system (or two 2.5 mg/day systems) applied nightly for 24 hours, delivering approximately 5 mg of testosterone per day. To ensure proper dosing, approximately 2 weeks after starting therapy the early morning serum testosterone concentration should be measured following system application the previous evening. If the serum concentration is outside the normal range (300 – 1030 ng/dL), sampling should be repeated with assurance of proper system adhesion as well as appropriate application time. Confirmed serum concentrations outside the normal range requires increasing the daily dose to 7.5 mg (i.e., one 5 mg/day and one 2.5 mg/day system) or decreasing the daily dose to 2.5 mg (i.e., one 2.5 mg/day system), maintaining nightly application.

Patients Switching from ANDRODERM 2.5 mg/day, 5 mg/day, and 7.5 mg/day system to ANDRODERM 2 mg/day, 4 mg/day, and 6 mg/day system: Patients currently maintained on

ANDRODERM 2.5 mg/day, 5 mg/day, and 7.5 mg/day may be switched to the 2 mg/day, 4 mg/day and 6 mg/day dosage using the following schema:

- Patients using 2.5 mg daily may be switched to 2 mg/day systems at the next scheduled dose.
- Patients using 5 mg daily may be switched to 4 mg/day systems at the next scheduled dose.
- Patients using 7.5 mg daily may be switched to 6 mg (2 mg/day and 4 mg/day systems) at the next scheduled dose.

To ensure proper dosing, approximately 2 weeks after switching therapy, the early morning serum testosterone concentration should be measured following system application the previous evening.

The adhesive side of the ANDRODERM system should be applied to a clean, dry area of the skin on the back, abdomen, upper arms, or thighs. Avoid application over bony prominences or on a part of the body that may be subject to prolonged pressure during sleep or sitting (e.g., the deltoid region of the upper arm, the greater trochanter of the femur, and the ischial tuberosity). DO NOT APPLY TO THE SCROTUM. The sites of application should be rotated, with an interval of 7 days between applications to the same site. The area selected should not be oily, damaged, or irritated.

The system should be applied immediately after opening the pouch and removing the protective release liner. The system should be pressed firmly in place, making sure there is good contact with the skin, especially around the edges.

The patient should avoid swimming, showering, or washing the administration site for a minimum of 3 hours after application *[see Clinical Pharmacology (12.3)]*.

Mild skin irritation may be ameliorated by treatment of the affected skin with over-the-counter topical hydrocortisone cream applied after system removal. Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the ANDRODERM system has been shown to reduce the incidence and severity of skin irritation.

3 DOSAGE FORMS AND STRENGTHS

Transdermal system: 2 mg/day, 2.5 mg/day, 4 mg/day, and 5 mg/day.

4 CONTRAINDICATIONS

- ANDRODERM is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.1)]*.

- ANDRODERM is contraindicated in women who are, or who may become pregnant, or who are breastfeeding. ANDRODERM may cause fetal harm when administered to a pregnant woman. ANDRODERM may cause serious adverse reactions in nursing

infants. If a pregnant woman is exposed to ANDRODERM, she should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1, 8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening of Benign Prostatic Hyperplasia and Potential Risk of Prostate Cancer

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH.

- Patients treated with androgens may be at increased risk for prostate cancer. Evaluate patients for prostate cancer prior to initiating treatment. It is appropriate to re-evaluate patients 3 to 6 months after initiation of treatment, and then in accordance with prostate cancer screening practices *[see Contraindications (4)]*.

5.2 Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating testosterone treatment. It is appropriate to re-evaluate the hematocrit 3 to 6 months after starting testosterone treatment, and then monitor annually. Discontinue testosterone therapy if the hematocrit becomes elevated. Testosterone therapy may be restarted when the hematocrit decreases to an acceptable level. An increase in red blood cell mass may increase the risk of thromboembolic events.

5.3 Use in Women and Children

Women and children should not use ANDRODERM. Use in women and children has not been studied with ANDRODERM.

Due to lack of controlled studies in women and potential virilizing effects, ANDRODERM is not indicated for use in women and children *[see Contraindications (4) and Use in Specific Populations (8.1, 8.3, 8.4)]*.

5.4 Potential for Adverse Effects on Spermatogenesis

At large doses of exogenous androgens, including ANDRODERM, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) that could lead to adverse effects on semen parameters including reduction of sperm count.

5.5 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal

complication. Long-term therapy with intramuscular testosterone enanthate has produced multiple hepatic adenomas. ANDRODERM is not known to cause these adverse effects.

5.6 Edema

Androgens, including ANDRODERM, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease *[see Adverse Reactions (6)]*.

5.7 Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including ANDRODERM, for hypogonadism.

5.8 Sleep Apnea

The treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors such as obesity and chronic lung disease.

5.9 Lipids

Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

5.10 Hypercalcemia

Androgens, including ANDRODERM, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

5.11 Decreased Thyroxine-Binding Globulin

Androgens, including ANDRODERM, may decrease concentrations of thyroxine-binding globulins, resulting in decreased total T4 serum concentration and increased resin uptake of T3 and T4. Free thyroid hormone concentration remains unchanged and there is no clinical evidence of thyroid dysfunction.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 1 shows the adverse reactions that were reported by > 3% of 36 hypogonadal men who were treated with ANDRODERM 2 mg/day, 4 mg/day, or 6 mg/day for 28 days. Of note, all hypogonadal men studied had been stable users of topical testosterone replacement products

prior to the study and there was no washout period between therapies. Furthermore, there was only one subject titrated to 6 mg/day and he withdrew from the study prematurely.

Table 1. Adverse Reactions Seen With the Use of ANDRODERM 2 mg/day, 4 mg/day, or 6 mg/day (> 3%)

Adverse Reaction	Overall N = 36 %
Application site pruritus	17
Application site vesicles	6
Back pain	6

Other less common adverse reactions reported by < 3% of patients included: application site erythema, application site exfoliation, chills, diarrhea, fatigue, gastroesophageal reflux disease, hemarthrosis, hematuria, headache, polyuria, and prostatitis. The overall incidence of application site reactions of any kind was 28% (10 subjects with 13 adverse reactions).

No serious adverse reactions to ANDRODERM 2 mg/day and 4 mg/day were reported during the clinical trial.

Table 2 shows the adverse reactions that were reported in > 3% of 122 patients in clinical studies with ANDRODERM dosage strengths of 2.5 mg/day, 5 mg/day, and 7.5 mg/day. The most common adverse reactions reported were application site reactions. Transient mild to moderate erythema was observed at the site of application in the majority of patients at some time during treatment. The overall incidence of application site reactions of any kind was 48% (59 subjects with 107 adverse reactions).

Table 2. Adverse Reactions Seen With the Use of ANDRODERM 2.5 mg/day, 5 mg/day, or 7.5 mg/day (> 3%).

Adverse Reaction	Overall N = 122 %
Application site pruritus	37
Application site blistering	12
Application site erythema	7
Application site vesicles	6
Prostate abnormalities	5
Headache	4
Contact dermatitis to system	4
Application site burning	3
Application site induration	3
Depression	3

The following reactions occurred in less than 3% of patients: rash, gastrointestinal bleeding, fatigue, body pain, pelvic pain, hypertension, peripheral vascular disease, increased appetite, accelerated growth, anxiety, confusion, decreased libido, paresthesia, thinking abnormalities, vertigo, acne, bullae at application site, mechanical irritation at application site, rash at application site, contamination of application site, prostate carcinoma, dysuria, hematuria, impotence, urinary incontinence, urinary tract infection, and testicular abnormalities.

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirement.

7.2 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored, particularly in patients with cardiac, renal or hepatic disease.

7.4 Triamcinolone

- The topical administration of 0.1% triamcinolone cream to the skin under the central drug reservoir prior to the application of the ANDRODERM system did not significantly alter transdermal absorption of testosterone; however, the rate of complete adherence was lower.

- Pretreatment with triamcinolone ointment formulation significantly reduced testosterone absorption from the ANDRODERM system.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4)]* — ANDRODERM is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, ANDRODERM is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation *[see Contraindications (4)]*.

8.4 Pediatric Use

Safety and efficacy of ANDRODERM have not been established in males <18 years of age. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing ANDRODERM to determine whether efficacy in those over 65 years of age differs from younger patients. Additionally, there are insufficient long-term safety data in geriatric patients utilizing ANDRODERM to assess a potential incremental risk of cardiovascular disease and prostate cancer.

8.6 Renal Impairment

No studies were conducted in patients with renal impairment.

8.7 Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ANDRODERM contains testosterone, a Schedule III controlled substance under the Anabolic Steroids Control Act.

9.2 Abuse

Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

9.3 Dependence

Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

- Taking more drug than intended

- Continued drug use despite medical and social problems
- Significant time spent in obtaining adequate amounts of drug
- Desire for anabolic steroids when supplies of the drug are interrupted
- Difficulty in discontinuing use of the drug despite desires and attempts to do so
- Experience of withdrawal syndrome upon discontinuation of anabolic steroid use

10 OVERDOSAGE

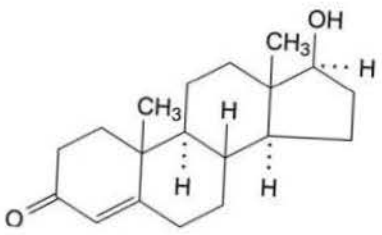
No cases of overdose with ANDRODERM have been reported in clinical trials. There is one report of acute overdosage by injection of testosterone enanthate: testosterone concentrations of up to 11,400 ng/dL were implicated in a cerebrovascular accident. Treatment of overdosage would consist of discontinuation of ANDRODERM together with appropriate symptomatic and supportive care.

11 DESCRIPTION

ANDRODERM (testosterone transdermal system) is designed to deliver testosterone continuously for 24 hours following application to intact, non-scrotal skin (e.g., back, abdomen, thighs, upper arms).

Four strengths of ANDRODERM are available that deliver approximately 2 mg, 2.5 mg, 4 mg, or 5 mg of testosterone per day.

ANDRODERM has a central drug delivery reservoir surrounded by a peripheral adhesive area. The ANDRODERM 2 mg/day system has a total contact surface area of 32 cm^2 with a 6.0 cm^2 central drug delivery reservoir containing 9.7 mg testosterone USP, dissolved in an alcohol-based gel. The ANDRODERM 2.5 mg/day system has a total contact surface area of 37 cm^2 with a 7.5 cm^2 central drug delivery reservoir containing 12.2 mg testosterone USP, dissolved in an alcohol-based gel. The ANDRODERM 4 mg/day system has a total contact surface area of 39 cm^2 with a 12.0 cm^2 central drug delivery reservoir containing 19.5 mg testosterone USP, dissolved in an alcohol-based gel. The ANDRODERM 5 mg/day system has a total contact surface area of 44 cm^2 with a 15 cm^2 central drug delivery reservoir containing 24.3 mg testosterone USP, dissolved in an alcohol-based gel. Testosterone USP is a white, or creamy white crystalline powder or crystals chemically described as 17ß-hydroxyandrost-4-en-3-one.



Testosterone
$C_{19}H_{28}O_2$ mw 288.42

The ANDRODERM systems have six components as shown in Figure 1. Proceeding from the top toward the surface attached to the skin, the system is composed of (1) metallized polyester (ethylene-methacrylic acid copolymer)/ethylene vinyl acetate backing film with alcohol resistant ink, (2) a drug reservoir of testosterone USP, alcohol USP, glycerin USP, glycerol monooleate, methyl laurate, sodium hydroxide NF, to adjust pH, and purified water USP, gelled with carbomer copolymer Type B NF, (3) a permeable polyethylene microporous membrane, and (4) a peripheral layer of acrylic adhesive surrounding the central, active drug delivery area of the system. Prior to opening of the system and application to the skin, the central delivery surface of the system is sealed with a peelable laminate disc (5) composed of a five-layer laminate containing polyester/polyesterurethane adhesive/aluminum foil/polyester-urethane adhesive/polyethylene. The disc is attached to and removed with the release liner (6), a silicone-coated polyester film, which is removed before the system can be used.

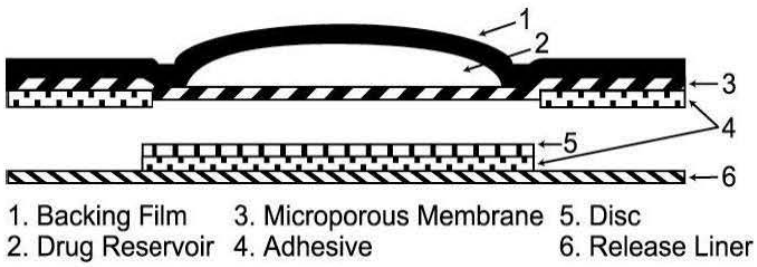


Figure 1: System Schematic

The active ingredient in the system is testosterone. The remaining components of the system are pharmacologically inactive.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement; vocal cord thickening; and alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics, and osteoporosis.

Male hypogonadism has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter Syndrome or Leydig cell aplasia, whereas secondary

hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted using ANDRODERM.

12.3 Pharmacokinetics

Absorption

ANDRODERM delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate the normal concentration range (300 – 1030 ng/dL) seen in healthy men. ANDRODERM provides a continuous daily dose of testosterone in a self-contained transdermal system. Following ANDRODERM application, testosterone is continuously absorbed during the 24-hour dosing period with a median (range) T_{max} of 8 (4-12) hours.

In a group of 34 hypogonadal men, application of two ANDRODERM 2.5 mg/day systems to the abdomen, back, thighs, or upper arms resulted in average testosterone absorption of 4 to 5 mgs over 24 hours. The serum testosterone concentration profiles during application were similar for these sites (Table 3). Applications to the chest and shins resulted in greater inter-individual variability and average 24 hour absorption of 3 to 4 mgs.

Table 3: Mean serum testosterone concentrations (ng/dL) measured during single-dose applications of two ANDRODERM 2.5 mg/day systems applied at night to different sites in 34 hypogonadal men.

Sample Time (hr)	Abdomen		Back		Thigh		Upper Arm	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	90	82	80	74	85	76	81	69
3	286	201	429	252	271	201	308	226
6	476	236	608	250	489	254	468	245
9	570	234	613	214	592	251	534	204
12	575	244	588	233	594	247	527	199
24	352	164	403	174	367	161	332	124

In a steady-state study of 12 hypogonadal men, nightly application of 1, 2, or 3 ANDRODERM 2.5 mg/day systems resulted in increases in the mean morning serum testosterone concentrations. These concentrations averaged 424 ng/dL, 584 ng/dL, and 766 ng/dL with the application of 1, 2, and 3 systems, respectively. The mean baseline serum testosterone concentration was 76 ng/dL.

In a study of 20 hypogonadal patients, two ANDRODERM 2.5 mg/day systems and a single ANDRODERM 5 mg/day system produced equivalent serum testosterone concentration

profiles. Average steady-state concentrations over 24 hours (Css_{avg}) were 613 ± 169 ng/dL and 621 ± 176 ng/dL for the two 2.5 mg/day and single 5 mg/day systems, respectively. C_{max} values were 925 ± 340 ng/dL for the two 2.5 mg/day systems and 905 ± 254 ng/dL for the single 5 mg/day system.

Distribution

Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.

Metabolism

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT).

During steady-state pharmacokinetic studies in hypogonadal men treated with ANDRODERM, the average DHT:T and E2:T ratios were approximately 1:10 and 1:200, respectively.

Excretion

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

Upon removal of the ANDRODERM systems, serum testosterone concentrations decrease with an apparent half-life of approximately 70 minutes. Hypogonadal concentrations are reached within 24 hours following system removal. There is no accumulation of testosterone during continuous treatment.

Effect of Showering

In a two-way crossover study, the effects of showering on the pharmacokinetics of total testosterone following a single application of ANDRODERM 4 mg/day were assessed in 16 hypogonadal males. Showering 3 hours after application of ANDRODERM increased C_{avg} by 0.5% and decreased C_{max} by 0.4% respectively, as compared to not showering. The systemic exposure to ANDRODERM was similar following applications with or without showering 3 hours after application.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There

is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays. The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

ANDRODERM 2 mg/day and 4 mg/day were studied in a trial designed to evaluate the use and titration of 2 mg/day and 4 mg/day systems in a clinic setting of 40 men with hypogonadism. Thirty-eight of the 40 subjects (95%) who were enrolled into the study were white and 2 subjects were African American. Ten (25%) subjects were Hispanic and 30 (75%) were Non-Hispanic. Men were between 34 and 76 years of age (mean: 55 years). Patients had previously been on stable therapy of ANDRODERM 5 mg; Androgel® 2.5 g, 5 g, 7.5 g or 10 g; or Testim® 2.5 g or 5 g daily before switching to ANDRODERM 4 mg/day.

Patients applied an ANDRODERM 4 mg/day system around 10 p.m. once daily for 14 days, and then were titrated up to 6 mg/day or down to 2 mg/day according to a morning serum testosterone concentration obtained at 6 a.m. on Day 8. Out of 36 patients who entered the study, 31 (86%) patients remained on the 4 mg/day dose, 4 (11%) were titrated downward to 2 mg/day, and 1 (3%) was titrated upward to 6 mg/day based on the Day 8 testosterone concentrations. The one patient that was titrated to 6 mg/day discontinued from the study for a non-safety related reason. Of the patients who were receiving ANDRODERM 5 mg/day prior to study entry (n = 11), 10 remained at 4 mg/day after titration, and 1 was titrated down to the 2 mg/day dose.

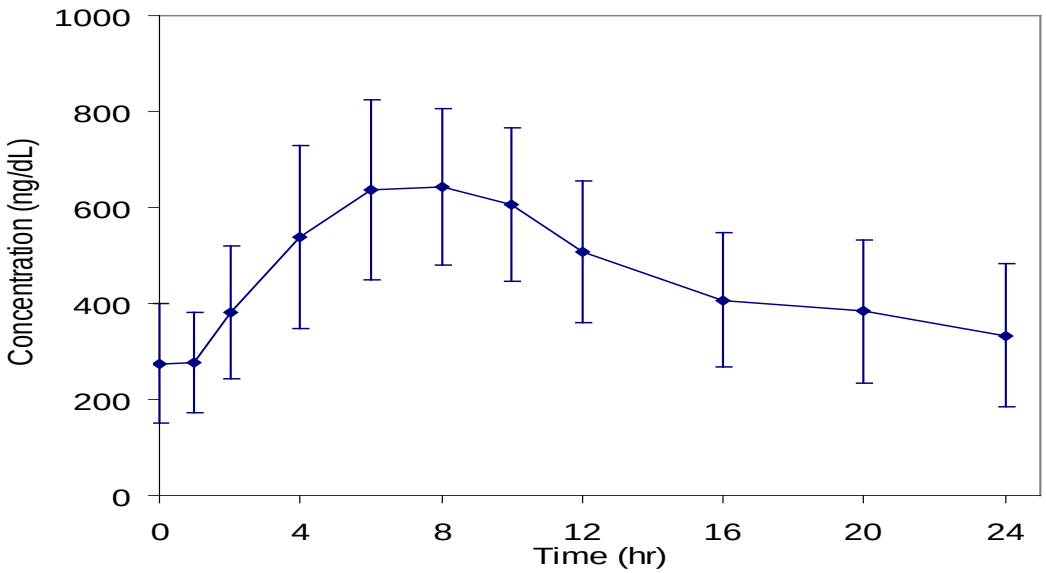
After a total of 28 days of therapy, 34 of the 35 subjects (97%) had serum testosterone C_{avg} within the normal range during the dosing period, with the lower bound of the 95% confidence interval for this estimate being 85% (Table 4). One subject who received ANDRODERM 4 mg/day treatment had serum testosterone C_{avg} below 300 ng/dL and none had C_{avg} concentrations above 1030 ng/dL. The mean (SD) serum testosterone C_{max} following treatment with the 2 mg/day (N = 4) and 4 mg/day (N = 31) systems was 648 (145) ng/dL and 696 (158) ng/dL, respectively. Table 4 summarizes testosterone C_{avg} categories by treatment.

Table 4. Testosterone C_{avg} Categories on Day 28 after One Titration on Day 15

C_{avg} Category	**Current Testosterone User N = 35**
300 - 1030 ng/dL n (%) (95% CI))	34/35 (97%) (85%, 100%)
< 300 ng/dL(n (%))	1/35 (3%)

Figure 2 summarizes the pharmacokinetic profiles of total testosterone in 35 patients completing 28 days of ANDRODERM treatment applied as a starting dose of 4 mg/day for the initial 14 days followed by a possible dose titration.

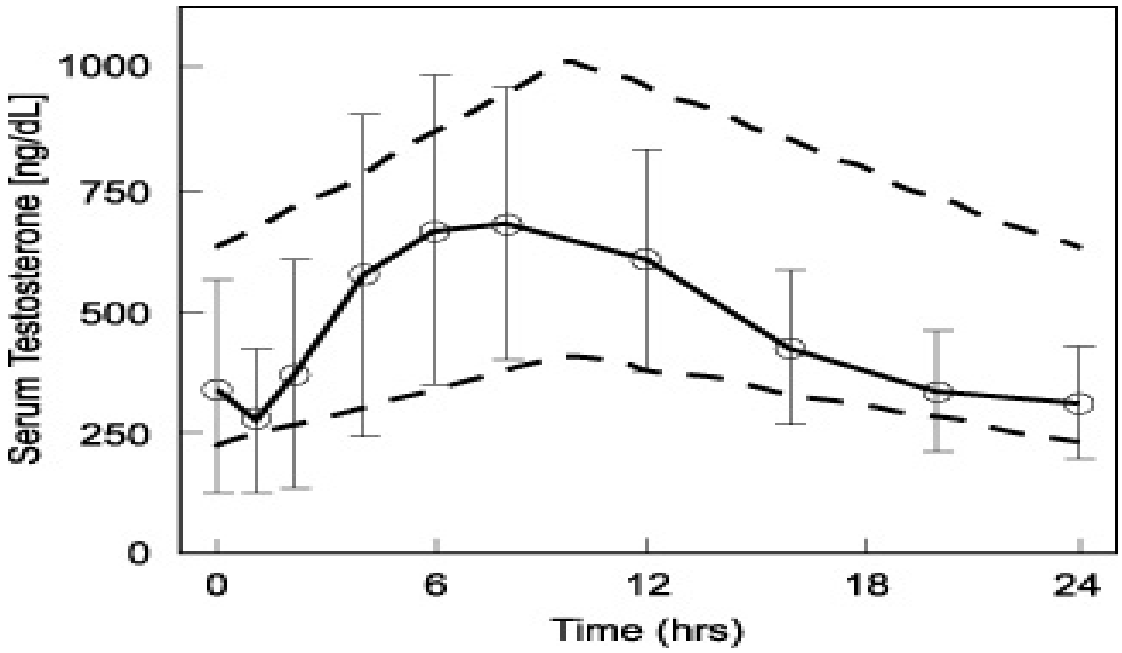
Figure 2. Mean (SD) Steady-State Serum Total Testosterone Concentration (ng/dL) on Day 28



In separate clinical studies using the ANDRODERM 2.5 mg/day system, 1% used 2.5 mg daily, 93% of patients used 5 mg daily, and 6% used 7.5 mg daily. The hormonal effects of ANDRODERM 2.5 mg/day system as a treatment for male hypogonadism was demonstrated in four open-label trials that included 94 hypogonadal men, ages 15 to 65 years. In these trials, ANDRODERM produced average morning serum testosterone concentrations within the normal reference range in 92% of patients.

Figure 3 shows the mean (SD) steady-state serum testosterone concentrations during nightly application of Androderm 2.5 mg/day systems in 29 hypogonadal male patients, 27 patients used 2 systems nightly and 2 patients used 3 systems nightly. Area between the dashed lines shows the 95% confidence interval for the circadian variation observed in healthy men.

Figure 3. Mean (SD) Steady-State Serum Total Testosterone Concentration (ng/dL)



16 HOW SUPPLIED/STORAGE AND HANDLING

ANDRODERM (testosterone transdermal system) 2 mg/day.

Each system contains 9.7 mg testosterone USP for delivery of 2 mg of testosterone per day [*see Description (11)*].

Cartons of 60 systems NDC 52544-076-60

ANDRODERM (testosterone transdermal system) 2.5 mg/day.

Each system contains 12.2 mg testosterone USP for delivery of 2.5 mg of testosterone per day [*see Description (11)*].

Cartons of 60 systems NDC 52544-469-60

ANDRODERM (testosterone transdermal system) 4 mg/day.

Each system contains 19.5 mg testosterone USP for delivery of 4 mg of testosterone per day [*see Description (11)*].

Cartons of 30 systems NDC 52544-077-30

ANDRODERM (testosterone transdermal system) 5 mg/day.

Each system contains 24.3 mg testosterone USP for delivery of 5 mg of testosterone per day [*see Description (11)*].

Cartons of 30 systems NDC 52544-470-30

Store at 20-25°C (68-77°F). [See USP controlled room temperature.] Apply to skin immediately upon removal from the protective pouch. Do not store outside the pouch provided. Damaged systems should not be used. The drug reservoir may be burst by excessive pressure or heat. Discard systems in household trash in a manner that prevents accidental application or ingestion by children, pets or others.

17 PATIENT COUNSELING INFORMATION

See "FDA-approved patient labeling (Patient Information)".

Patients should be informed of the following information:

17.1 Use in Men with Known or Suspected Prostate or Breast Cancer

Men with known or suspected prostate or breast cancer should not use ANDRODERM *[see Contraindications (4)* and *Warnings and Precautions (5.1)]*.

17.2 Potential Adverse Reactions with Androgens

Patients should be informed that treatment with androgens may lead to adverse reactions that include:

- Changes in urinary habits such as increased urination at night, trouble starting your urine stream, passing urine many times during the day, having an urge that you have to go to the bathroom right away, having a urine accident, being unable to pass urine and having a weak urine flow
- Breathing disturbances, including those associated with sleep, or excessive daytime sleepiness
- Too frequent or persistent erections of the penis
- Nausea, vomiting, changes in skin color, or ankle swelling

17.3 Patients Should be Advised of these Application Instructions

- ANDRODERM should not be applied to the scrotum.
- ANDRODERM should not be applied over a bony prominence or on a part of the body that could be subject to prolonged pressure during sleep or sitting. Application to these sites has been associated with burn-like blister reactions.
- ANDRODERM does not have to be removed during sexual intercourse, nor while taking a shower or bath.

- ANDRODERM systems should be applied nightly. The site of application should be rotated, with an interval of 7 days between applications to the same site.

- If the ANDRODERM system becomes loose, smooth it down again by rubbing your finger firmly around the edges. If a patch falls off before noon, replace it with a fresh patch and wear it until you apply a fresh patch(es) that evening. If it falls off later in the day, do not replace it until you apply a fresh patch(es) that evening. If it falls off do not tape ANDRODERM to skin.

- If patients or caregivers experience difficulty separating the patch from the release liner or observe transfer of adhesive to the liner, tearing and/or other damage to the patch during removal from the liner, the patch should be discarded, and a new patch should be applied.

- Androderm should be applied immediately after opening the individual pouch and removing the protective liner. Do not use if the individual pouch seal is broken or if the patch appears to be damaged. Do not cut patches. Only intact patches should be applied.

- Strenuous exercise or excessive perspiration may loosen a patch or cause it to fall off.

- Skin burns have been reported at the application site in patients wearing an aluminized transdermal system during a magnetic resonance imaging scan (MRI). Because ANDRODERM contains aluminum, it is recommended to remove the system before undergoing an MRI.

- Avoid swimming or showering until 3 hours following application of ANDRODERM *[see Dosage and Administration (2) and Clinical Pharmacology (12.3)]*.

For all medical inquiries contact:
WATSON
Medical Communications
Parsippany, NJ 07054
800-272-5525

Watson

Manufactured By:
Watson Laboratories, Inc.
Salt Lake City, UT 84108 USA

Distributed By:
Watson Pharma, Inc.
Parsippany, NJ 07054 USA

PATIENT INFORMATION
ANDRODERM® (an-dro-derm) **CIII**
(testosterone transdermal system)
for topical use

Read this Patient Information before you start taking ANDRODERM and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ANDRODERM?

ANDRODERM is a prescription medicine that contains testosterone. ANDRODERM is used to treat adult males who have low or no testosterone.

Your healthcare provider will test your blood for testosterone before you start and while you are taking ANDRODERM.

It is not known if ANDRODERM is safe and effective in children younger than 18 years old. Improper use of ANDRODERM may affect bone growth in children.

ANDRODERM is a controlled substance (CIII) because it contains testosterone that can be a target for people who abuse prescription medicines. Keep your ANDRODERM in a safe place to protect it. Never give your ANDRODERM to anyone else, even if they have the same symptoms you have. Selling or giving away this medicine may harm others and it is against the law.

ANDRODERM is not meant for use by women.

Who should not use ANDRODERM?

Do not use ANDRODERM if you:

- are a man who has breast cancer
- have or might have prostate cancer
- are pregnant or may become pregnant or are breastfeeding. ANDRODERM may harm your unborn or breastfeeding baby.

Talk to your healthcare provider before taking this medicine if you have any of the above conditions.

What should I tell my healthcare provider before using ANDRODERM?

Before you use ANDRODERM, tell your healthcare provider if you:

- have breast cancer
- have or might have prostate cancer
- have urinary problems due to an enlarged prostate
- have heart problems
- have kidney or liver problems
- have problems breathing while you sleep (sleep apnea)
- have diabetes
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using ANDRODERM with other medicines can affect each other. Especially, tell your healthcare provider if you take:

- insulin
- medicines that decrease blood clotting
- corticosteroids

Know the medicines you take. Ask your healthcare provider or pharmacist for a list of all your medicines if you are not sure. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use ANDRODERM?

- It is important that you apply ANDRODERM exactly as your healthcare provider tells you to.
- ANDRODERM patches come in 4 different doses and different patch sizes.
- Your healthcare provider will tell you how many ANDRODERM patches to apply and when to apply them.
- Your healthcare provider may change your ANDRODERM dose. Do not change your ANDRODERM dose without talking with your healthcare provider.
- ANDRODERM does not need to be removed during sex or while you take a shower or bath.

- Apply ANDRODERM at about the same time each evening.

- You should change your ANDRODERM patch every 24 hours. You should remove the old patch before applying the new one.

- You should change (rotate) your ANDRODERM application site every day.

- Skin redness may happen on the skin where your ANDRODERM patch was removed. If your skin redness does not go away, talk to your healthcare provider. Your healthcare provider may tell you to use an over-the-counter hydrocortisone cream on your red skin.

- Patches that have aluminum in them can cause skin burns at the patch site during a magnetic resonance imaging scan (MRI). Because ANDRODERM contains aluminum, you should take off your ANDRODERM patch before you have an MRI.

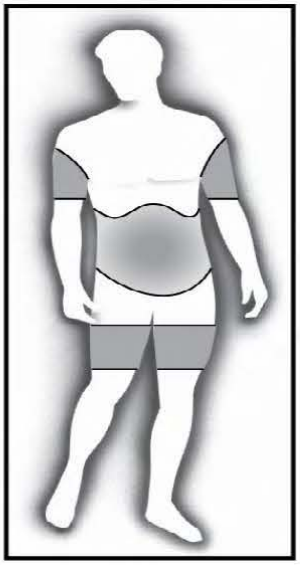
- Do not use an ANDRODERM patch if the pouch seal is broken or the patch is cut, damaged, or changed in anyway. Throw it away and get a new one.

Applying ANDRODERM:

- Before applying ANDRODERM, make sure that the application area is clean, dry, and there is no broken skin.

- Avoid areas of skin that are oily, perspire heavily, or are covered with hair, since ANDRODERM may not stick well to these areas.

- **ANDRODERM is to be applied to your back, stomach area (abdomen), upper arms, or thighs only (See Figure A and Figure B)**. **Do not** apply ANDRODERM to any other parts of your body such as your scrotum, buttocks or over a bony area.



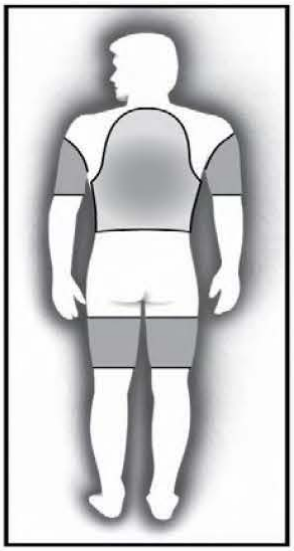


Figure A **Figure B**

- **Maintain Normal Activities:** A patch applied to clean, dry skin will remain in place during normal activities. ANDRODERM may be worn during sex. Also, contact with water, such as showering or swimming, 3 hours after application will not affect the patch. Strenuous exercise or excessive perspiration may loosen a patch or cause it to fall off.

- **What to Do if a Patch Becomes Loose, or Falls Off:** If the patch becomes loose, smooth it down again by rubbing your finger firmly around the edges. If a patch falls off before noon, replace it with a fresh patch and wear it until you apply a fresh patch(es) that evening. If it falls off later in the day, do not replace it until you apply a fresh patch(es) that evening. If a patch falls off do not tape it to skin.

1. Open the foil pouch. Tear along the edge and remove the patch from the pouch **(See Figure C).**

Do not cut the ANDRODERM protective pouch.

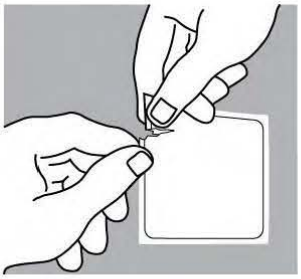


Figure C

2. Remove the protective plastic liner and silver disc from the patch. Hold on to the tabs on the patch and the protective plastic liner and gently pull the two apart to remove the plastic liner and silver disc from the patch **(See Figure D).**

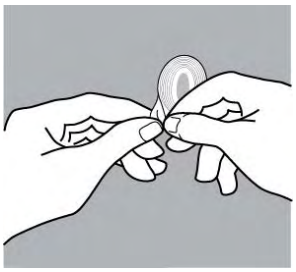


Figure D

This will expose the adhesive and central reservoir area on the patch **(See Figure E)**.

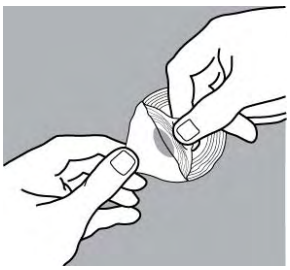


Figure E

The patch should separate easily from the protective liner. Throw away the patch if the liner is hard to remove. There should not be any adhesive (glue) sticking to the liner.

Throw away the clear plastic liner and silver disc.

3. Apply the patch. Apply the patch right away after you remove the patch from the protective pouch and remove the plastic liner.

Place the patch flat on the skin with the sticky side down and firmly press around the edges. Make sure that the patch sticks well to the skin.

What are the possible side effects of ANDRODERM?

ANDRODERM can cause serious side effects including:

- **If you already have an enlargement of your prostate gland your signs and symptoms may get worse while using ANDRODERM. This can include:**
  - increased urination at night
  - trouble starting your urine stream
  - having to pass urine many times during the day
  - having an urge that you have to go to the bathroom right away
  - having a urine accident
  - being unable to pass urine or weak urine flow
- **Possible increased risk of prostate cancer**. Your healthcare provider should check you for prostate cancer or any other prostate problems before you start and while you use ANDRODERM.
- **Blood clots in the legs.** This can include pain, swelling or redness of your legs.
- **In large doses ANDRODERM may lower your sperm count.**
- **Swelling of your ankles, feet, or body, with or without heart failure.**
- **Enlarged or painful breasts.**
- **Problems breathing while you sleep (sleep apnea).**

Call your healthcare provider right away if you have any of the serious side effects listed above.

The most common side effects of ANDRODERM include:

- skin redness, irritation, burning, or blisters where ANDRODERM is applied
- back pain
- depression

- headache

- prostate abnormalities

Other side effects include more erections than are normal for you or erections that last a long time.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ANDRODERM. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ANDRODERM?

- Keep ANDRODERM at room temperature between 68°F to 77°F (20°C to 25°C).

- Keep ANDRODERM in its sealed protective foil pouch until you are ready to use it. Do not remove an ANDRODERM patch from the pouch until you are ready to use it.

- Safely throw away your used ANDRODERM patch. Fold your used ANDRODERM patch in half so that the sticky sides stick together. Throw away your used ANDRODERM patch in the household trash.

- Be careful to prevent accidental exposure of ANDRODERM to children or pets.

General information about the safe and effective use of ANDRODERM

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ANDRODERM for a condition for which it was not prescribed. Do not give ANDRODERM to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about ANDRODERM. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about ANDRODERM that is written for health professionals.

For more information, go to www.androderm.com or call 1-800-272-5525. If you have questions or concerns about your ANDRODERM treatment, ask your pharmacist, healthcare provider or pharmacist.

What are the ingredients in ANDRODERM?

Active ingredient: testosterone

Inactive ingredients:

- **Backing film:** Metallized polyester/Surlyn (ethylene-methacrylic acid copolymer)/ethylene vinyl acetate backing film with alcohol resistant ink
- **Drug Reservoir:** Testosterone USP, alcohol USP, glycerin USP, glycerol monooleate, methyl laurate, sodium hydroxide NF, purified water USP, gelled with carbomer copolymer Type B NF
- **Microporous Membrane:** a permeable polyethylene microporous membrane
- **Adhesive:** a peripheral layer of acrylic adhesive surrounding the central, active drug delivery area of the system.
- **Disc:** a five-layer laminate containing polyester/polyesturethane adhesive/aluminum foil/polyester-urethane adhesive/polyethylene
- **Release Liner:** a silicone-coated polyester film, which is removed before the system can be used

Distributed By:

Watson Pharma, Inc.

Parsippany, NJ 07054 USA

This Patient Information has been approved by the U.S. Food and Drug Administration

Issued: 10/2011

Exhibit

F

ESTRADIOL- estradiol tablet
Mylan Pharmaceuticals Inc.

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than "synthetic" estrogens at equivalent estrogen doses (see WARNINGS: Malignant Neoplasms: Endometrial Cancer).

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease (see WARNINGS: Cardiovascular Disorders).

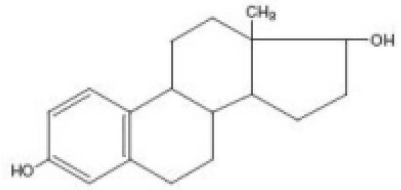
The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo (see CLINICAL PHARMACOLOGY: Clinical Studies).

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy (see CLINICAL PHARMACOLOGY: Clinical Studies).

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Estradiol tablets, USP for oral administration contains 0.5 mg, 1 mg or 2 mg of micronized estradiol per tablet. Estradiol (17β-estradiol) is a white, crystalline solid, chemically described as estra-1,3,5(10)-triene-3,17β-diol. It has a molecular formula of $C_{18}H_{24}O_2$ and molecular weight of 272.39. The structural formula is:



$C_{18}H_{24}O_2$
M.W. 272.39

In addition, each tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The 1 mg tablet also contains FD&C Red No. 40 Aluminum Lake and the 2 mg tablet also contains FD&C Blue No. 1 Aluminum Lake.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 mcg to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to

estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Special Populations

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Clinical Studies

Osteoporosis

Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification by other risk factors, and tend to show a universally salutary effect on bone.

The results of a 2-year, randomized, placebo-controlled, double-blind, dose-ranging study have shown that treatment with 0.5 mg estradiol daily for 23 days (of a 28 day cycle) prevents vertebral bone mass loss in postmenopausal women. When estrogen therapy is discontinued, bone mass declines at a rate comparable to the immediate postmenopausal period. There is no evidence that estrogen replacement therapy restores bone mass to premenopausal levels.

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral 0.625 mg conjugated estrogens (CE) per day alone or the use of oral 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke,

pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 1 below:

Table 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI*

Event†	Relative Risk CE/MPA vs. placebo at 5.2 Years (95% CI‡)	Placebo n = 8,102	CE/MPA n = 8,506
		Absolute Risk per 10,000 Women-Years	
CHD events *Non-fatal MI* *CHD death*	1.29 (1.02 to 1.63) *1.32 (1.02 to 1.72)* *1.18 (0.70 to 1.97)*	30 *23* *6*	37 *30* *7*
Invasive breast cancer§	1.26 (1 to 1.59)	30	38
Stroke	1.41 (1.07 to 1.85)	21	29
Pulmonary embolism	2.13 (1.39 to 3.25)	8	16
Colorectal cancer	0.63 (0.43 to 0.92)	16	10
Endometrial cancer	0.83 (0.47 to 1.47)	6	5
Hip fracture	0.66 (0.45 to 0.98)	15	10
Death due to causes other than the events above	0.92 (0.74 to 1.14)	40	37
Global Index†	1.15 (1.03 to 1.28)	151	170
Deep vein thrombosis¶	2.07 (1.49 to 2.87)	13	26
Vertebral fractures¶	0.66 (0.44 to 0.98)	15	9
Other osteoporotic fractures¶	0.77 (0.69 to 0.86)	170	131

* adapted from JAMA, 2002; 288:321 to 333
† a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture or death due to other causes
‡ nominal confidence intervals unadjusted for multiple looks and multiple comparisons
§ includes metastatic and non-metastatic breast cancer with the exception of *in situ* breast cancer
¶ not included in Global Index

For those outcomes included in the "global index," the absolute excess risks per 10,000 women-years in the group treated with CE/MPA were seven more CHD events, eight more strokes, eight more PEs and eight more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were six fewer colorectal cancers and five fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality (see BOXED WARNINGS, WARNINGS and PRECAUTIONS).

Women's Health Initiative Memory Study

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women (see BOXED WARNINGS and WARNINGS: Dementia).

INDICATIONS AND USAGE

Estradiol tablets are indicated in the:

- Treatment of moderate to severe vasomotor symptoms associated with the menopause.
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
- Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
- Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).
- Prevention of osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate (see CLINICAL PHARMACOLOGY: Clinical Studies). The mainstays for decreasing the risk of postmenopausal osteoporosis are weight bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400 to 800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

- Undiagnosed abnormal genital bleeding.

- Known, suspected or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.
- Known or suspected estrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism or history of these conditions.
- Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
- Liver dysfunction or disease.
- Estradiol tablets should not be used in patients with known hypersensitivity to its ingredients.
- Known or suspected pregnancy. There is no indication for estradiol in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy (see PRECAUTIONS).

WARNINGS

See BOXED WARNINGS.

1. Cardiovascular Disorders

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity and systemic lupus erythematosus) should be managed appropriately.

a. *Coronary Heart Disease and Stroke:* In the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE compared to placebo. These observations are preliminary, and the study is continuing (see CLINICAL PHARMACOLOGY: Clinical Studies).

In the CE/MPA substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs. 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs. 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625 mg/2.5 mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary

heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis.

b*. Venous Thromboembolism (VTE):* In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary, and the study is continuing (see CLINICAL PHARMACOLOGY: Clinical Studies).

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant Neoplasms

a. *Endometrial Cancer:* The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use—with increased risks of 15- to 24-fold for 5 to 10 years or more—and this risk persists for 8 to over 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important (see PRECAUTIONS). Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. *Breast Cancer:* The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see CLINICAL PHARMACOLOGY: Clinical Studies). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about 5 years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01 to 1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors and prior mammogram results.

c. *Ovarian Cancer:* The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24).

The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

3. Dementia

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CE/MPA vs. placebo was 2.05 (95% confidence interval 1.21 to 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA vs. placebo was 45 vs. 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women (see CLINICAL PHARMACOLOGY: Clinical Studies and PRECAUTIONS: Geriatric Use).

It is unknown whether these findings apply to estrogen alone therapy.

4. Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

A. General

1. *Addition of a Progestin when a Woman has not had a Hysterectomy:* Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks which may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

2. *Elevated Blood Pressure:* In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. *Hypertriglyceridemia:* In patients with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. *Impaired Liver Function and Past History of Cholestatic Jaundice:* Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. *Hypothyroidism:* Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. *Fluid Retention:* Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. *Hypocalcemia:* Estrogens should be used with caution in individuals with severe hypocalcemia.

8. *Exacerbation of Endometriosis:* Endometriosis may be exacerbated with administration of estrogens. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

9. *Exacerbation of Other Conditions:* Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

B. Patient Information

Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe estradiol tablets.

C. Laboratory Tests

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH) (see DOSAGE AND ADMINISTRATION).

D. Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and betathromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL_2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer and ovarian cancer (see BOXED WARNINGS, WARNINGS and PRECAUTIONS).

Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver.

F. Pregnancy Category X

Estradiol should not be used during pregnancy (see CONTRAINDICATIONS).

G. Nursing Mothers

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk

of mothers receiving this drug. Caution should be exercised when estradiol is administered to a nursing woman.

H. Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphyseal closure, resulting in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. In patients in whom bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended.

Estrogen treatment of prepubertal children also induces premature breast development and vaginal cornification, and may potentially induce vaginal bleeding in girls. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated with estrogen treatment of adults could potentially occur in the pediatric population, including thromboembolic disorders and growth stimulation of certain tumors. Therefore, estrogens should only be administered to pediatric patients when clearly indicated and the lowest effective dose should always be utilized.

I. Geriatric Use

The safety and efficacy of estradiol tablets in geriatric patients has not been established. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greatest frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a 2-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70 (see WARNINGS: Dementia).

It is unknown whether these findings apply to estrogen alone therapy.

ADVERSE REACTIONS

See BOXED WARNINGS, WARNINGS and PRECAUTIONS.

The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting, dysmenorrhea
Increase in size of uterine leiomyomata
Vaginitis, including vaginal candidiasis

Change in amount of cervical secretion
Changes in cervical ectropion
Ovarian cancer; endometrial hyperplasia; endometrial cancer

2. Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer

3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure

4. Gastrointestinal

Nausea, vomiting
Abdominal cramps, bloating
Cholestatic jaundice
Increased incidence of gallbladder disease
Pancreatitis
Enlargement of hepatic hemangiomas

5. Skin

Chloasma or melasma that may persist when drug is discontinued
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Loss of scalp hair
Hirsutism
Pruritus, rash

6. Eyes

Retinal vascular thrombosis
Steepening of corneal curvature
Intolerance to contact lenses

7. Central Nervous System

Headache, migraine, dizziness
Mental depression
Chorea
Nervousness, mood disturbances, irritability
Exacerbation of epilepsy
Dementia

8. Miscellaneous

Increase or decrease in weight
Reduced carbohydrate tolerance

Aggravation of porphyria
Edema
Arthralgias; leg cramps
Changes in libido
Urticaria
Angioedema
Anaphylactoid/anaphylactic reactions
Hypocalcemia
Exacerbation of asthma
Increased triglycerides

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (see BOXED WARNINGS and WARNINGS). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Patients should be started at the lowest dose for the indication.

1. For treatment of moderate to severe vasomotor symptoms, vulval and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals. The usual initial dosage range is 1 mg to 2 mg daily of estradiol adjusted as necessary to control presenting symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Administration should be cyclic (e.g., 3 weeks on and 1 week off).

2. For treatment of female hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

Treatment is usually initiated with a dose of 1 mg to 2 mg daily of estradiol, adjusted as necessary to control presenting symptoms; the minimal effective dose for maintenance therapy should be determined by titration.

3. For treatment of breast cancer, for palliation only, in appropriately selected women and men with metastatic disease.

Suggested dosage is 10 mg three times daily for a period of at least 3 months.

4. For treatment of advanced androgen-dependent carcinoma of the prostate, for palliation only.

Suggested dosage is 1 mg to 2 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.

5. For prevention of osteoporosis.

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be considered only for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate.

The lowest effective dose of estradiol tablets has not been determined.

HOW SUPPLIED

Estradiol Tablets, USP are available containing 0.5 mg, 1 mg or 2 mg of estradiol, USP.

The 0.5 mg tablets are white to off-white, round, scored tablets debossed with **E** to the left of the score and **3** to the right of the score on one side of the tablet and **M** on the other side. They are available as follows:

NDC 0378-1452-01
bottles of 100 tablets

NDC 0378-1452-05
bottles of 500 tablets

The 1 mg tablets are pink, round, scored tablets debossed with **E** to the left of the score and **4** to the right of the score on one side of the tablet and **M** on the other side. They are available as follows:

NDC 0378-1454-01
bottles of 100 tablets

NDC 0378-1454-05
bottles of 500 tablets

The 2 mg tablets are pale blue, round, scored tablets debossed with **E** to the left of the score and **5** to the right of the score on one side of the tablet and **M** on the other side. They are available as follows:

NDC 0378-1458-77
bottles of 90 tablets

NDC 0378-1458-01
bottles of 100 tablets

NDC 0378-1458-05
bottles of 500 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Patient Information Leaflet with each prescription.

Patient Information
Estradiol Tablets, USP

INTRODUCTION: Read this PATIENT INFORMATION before you start taking estradiol tablets and read what you get each time you refill estradiol tablets. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ESTRADIOL TABLETS (AN ESTROGEN HORMONE)?

- Estrogens increase the chances of getting cancer of the uterus.
  Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogens with or without progestins to prevent heart disease, heart attacks or strokes.
  Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with estradiol tablets.

WHAT IS ESTRADIOL?

Estradiol tablets are a medicine that contains estrogen hormones.

WHAT IS ESTRADIOL USED FOR?

Estradiol is used to:

- **reduce moderate to severe hot flashes**
  Estrogens are hormones made by a woman's ovaries. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the “change of life” or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes “surgical menopause.”
  When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating (“hot flashes” or “hot flushes”). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with estradiol.
  Weight-bearing exercise, like walking or running, and taking calcium with vitamin D

supplements may also lower your chances for getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

- **treat dryness, itching, and burning in or around the vagina, difficulty or burning on urination associated with menopause**
  You and your healthcare provider should talk regularly about whether you still need treatment with estradiol to control these problems. If you use estradiol only to treat your dryness, itching, and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.
- **treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally**
- **treat certain types of abnormal vaginal bleeding due to hormonal imbalance when your doctor has found no serious cause of the bleeding**
- **treat certain cancers in special situations, in men and women**
- **prevent thinning of bones**
  Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use estradiol only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with estradiol.

WHO SHOULD NOT USE ESTRADIOL?

Do not start taking estradiol if you:

- **have unusual vaginal bleeding which has not been evaluated by your doctor (see BOXED WARNINGS)**
  Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.
- **currently have or have had certain cancers**
  Estrogens may increase the risk of certain types of cancer, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take estradiol.
  (For certain patients with breast or prostate cancer, estrogens may help.)
- **had a stroke or heart attack in the past year**
- **currently have or have had blood clots**
- **have or have had liver problems**
- **are allergic to estradiol tablets or any of its ingredients**
  See the end of this leaflet for a list of ingredients in estradiol tablets.
- **think you may be pregnant**

Tell your healthcare provider:

- **if you are breast-feeding**
  The hormone in estradiol tablets can pass into your milk
- **about all of your medical problems**
  Your healthcare provider may need to check you more carefully if you have certain

conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys or have high calcium levels in your blood.
- **about all the medicines you take**
  This includes prescription and nonprescription medicines, vitamins and herbal supplements. Some medicines may affect how estradiol works. Estradiol may also affect how your other medicines work.
- **if you are going to have surgery or will be on bed rest**
  You may need to stop taking estrogens.

HOW SHOULD I TAKE ESTRADIOL TABLETS?

- Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.
- Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with estradiol.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF ESTROGENS?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of the serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain

- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors ("fibroids") of the uterus
- A spotty darkening of the skin, particularly on the face
- Vaginal yeast infection

These are not all the possible side effects of estradiol tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

WHAT CAN I DO TO LOWER MY CHANCES OF A SERIOUS SIDE EFFECT WITH ESTRADIOL?

If you use estrogens, you can reduce your risks by doing these things:

- **Talk with your healthcare provider:**
    - While you are using estrogens, it is important to visit your doctor at least once a year for a check-up.
    - If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you.
    - See your healthcare provider right away if you have vaginal bleeding while taking estradiol.
    - Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.
    - If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.
    - Talk with your healthcare provider regularly about whether you should continue taking estradiol. You and your doctor should reevaluate whether or not you still need estrogens at least every 6 months.

- **Be alert for signs of trouble**
  If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:
  Abnormal bleeding from the vagina (possible uterine cancer)
  Pains in the calves or chest, sudden shortness of breath or coughing blood

(possible clot in the legs, or lungs)
Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)
Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)
Yellowing of the skin or eyes (possible liver problem)
Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

GENERAL INFORMATION ABOUT SAFE AND EFFECTIVE USE OF ESTRADIOL TABLETS

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take estradiol for conditions for which it was not prescribed. Do not give estradiol to other people, even if they have the same symptoms you have. It may harm them.

KEEP ESTRADIOL TABLETS OUT OF THE REACH OF CHILDREN.

This leaflet provides a summary of the most important information about estradiol tablets. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about estradiol that is written for health professionals. You can get more information by calling Mylan at 1-877-446-3679 (1-877-4-INFO-RX).

WHAT ARE THE INGREDIENTS IN ESTRADIOL TABLETS?

Active Ingredient: estradiol

Inactive Ingredients: anhydrous lactose, colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The 1 mg tablet also contains FD&C Red No. 40 Aluminum Lake and the 2 mg tablet also contains FD&C Blue No. 1 Aluminum Lake.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Revised: 8/2018
ESTRT:R6ppt/PL:ESTRT:R3p/PL:ESTRT:R3pt

PRINCIPAL DISPLAY PANEL - 0.5 mg

NDC 0378-1452-01

Estradiol
Tablets, USP
0.5 mg

PHARMACIST: Dispense the accompanying
Patient Information Leaflet to each patient.

Rx only 100 Tablets

Each tablet contains:
Estradiol, USP 0.5 mg

Dispense in a tight, light-resistant
container as defined in the USP

using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM1452A4

PRINCIPAL DISPLAY PANEL - 1 mg

NDC 0378-1454-01

Estradiol
Tablets, USP
1 mg

PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.

Rx only 100 Tablets

Each tablet contains:
Estradiol, USP 1 mg

Dispense in a tight, light-resistant container as defined in the USP

using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM1454A5

PRINCIPAL DISPLAY PANEL - 2 mg

NDC 0378-1458-77

Estradiol
Tablets, USP
2 mg

PHARMACIST: Dispense the accompanying Patient Information Leaflet to each patient.

Rx only 90 Tablets

Each tablet contains:
Estradiol, USP 2 mg

Dispense in a tight, light-resistant container as defined in the USP

using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Usual Dosage: See accompanying prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Mylan.com

RM1458MM3

ESTRADIOL

estradiol tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1452
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.5 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	

Product Characteristics

Color	WHITE (white to off-white)	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	E;3;M
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1452-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/17/1999	05/31/2021
2	NDC:0378-1452-05	500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/17/1999	06/30/2021

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040326	06/17/1999	06/30/2021

ESTRADIOL

estradiol tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1454
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	1 mg

Inactive Ingredients

Ingredient Name	Strength

ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	

Product Characteristics

Color	PINK	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	E;4;M
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1454-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/17/1999	07/31/2021
2	NDC:0378-1454-05	500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/17/1999	07/31/2021

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040326	06/17/1999	07/31/2021

ESTRADIOL

estradiol tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-1458
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	2 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

CROSPOVIDONE (UNII: 2S7830E561)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	

Product Characteristics

Color	BLUE (pale blue)	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	E;5;M
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-1458-77	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/17/1999	07/31/2021
2	NDC:0378-1458-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/17/1999	07/31/2021
3	NDC:0378-1458-05	500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	06/17/1999	09/30/2021

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040326	06/17/1999	09/30/2021

Labeler - Mylan Pharmaceuticals Inc. (059295980)

Revised: 8/2018 Mylan Pharmaceuticals Inc.

Exhibit G

ESTRADIOL VALERATE- estradiol valerate injection
Hikma Pharmaceuticals USA Inc.

ESTRADIOL VALERATE INJECTION, USP
RX ONLY

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, Endometrial cancer.**)

CARDIOVASCULAR AND OTHER RISKS

Estrogens and progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders.**)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

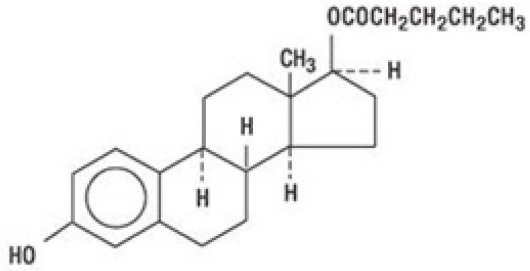
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Estradiol Valerate Injection, USP contains estradiol valerate, a long-acting estrogen in sterile oil solutions for intramuscular use. These solutions are clear, colorless to yellow. Formulations (per mL): 10 mg Estradiol Valerate, USP in a vehicle containing 5 mg Chlorobutanol, NF (chloral derivative/preservative) and Sesame Oil, NF; 20 mg Estradiol Valerate, USP in a vehicle containing 224 mg Benzyl Benzoate, USP, 20 mg Benzyl Alcohol, NF (preservative), and Castor Oil, USP; 40 mg Estradiol Valerate, USP in a vehicle containing 447 mg Benzyl Benzoate, USP, 20 mg Benzyl Alcohol, NF, and Castor Oil, USP.

Estradiol Valerate, USP is designated chemically as estra-1,3,5(10)-triene-3, 17-diol(17β)-, 17-pentanoate. Graphic formula:



$C_{23}H_{32}O_3$ MW 356.50

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

Absorption

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a

circulating reservoir for the formation of more active estrogens.

When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone sulfate, with smaller amounts of other conjugated and unconjugated estrogenic species. This results in limited oral potency. By contrast, synthetic estrogens, such as ethinyl estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other tissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enterohepatic recycling.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Clinical Studies

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of oral 0.625 mg conjugated estrogens (CE) per day alone or the use of oral 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results of the CE/MPA substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in **Table 1** below:

Table 1. RELATIVE AND ABSOLUTE RISK SEEN IN THE CE/MPA SUBSTUDY OF WHI *

Event†	**Relative Risk CE/MPA vs placebo at 5.2 Years (95% CI‡)**	**Placebo n = 8102**	**CE/MPA n = 8506**
		Absolute Risk per 10,000 Person-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer§	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10

Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index†	1.15 (1.03-1.28)	151	170
Deep vein thrombosis¶	2.07 (1.49-2.87)	13	26
Vertebral fractures¶	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures¶	0.77 (0.69-0.86)	170	131

*adapted from JAMA, 2002; 288:321-333
†a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
‡nominal confidence intervals unadjusted for multiple looks and multiple comparisons
§includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
¶not included in Global Index

For those outcomes included in the "global index," the absolute excess risks per 10,000 women-years in the group treated with CE/ MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNING**, **WARNINGS**, and **PRECAUTIONS**.)

Women's Health Initiative Memory Study

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of CE/MPA (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen/progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See **BOXED WARNING** and **WARNINGS, Dementia**.)

INDICATIONS AND USAGE

Estradiol Valerate Injection, USP is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).

CONTRAINDICATIONS

Estradiol Valerate Injection should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.

2. Known, suspected, or history of cancer of the breast.

3. Known or suspected estrogen-dependent neoplasia.

4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.

5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).

6. Liver dysfunction or disease.

7. Estradiol Valerate Injection should not be used in patients with known hypersensitivity to its ingredients.

8. Known or suspected pregnancy. There is no indication for Estradiol Valerate Injection in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**.)

WARNINGS

See **BOXED WARNINGS.**

The use of unopposed estrogens in women who have a uterus is associated with an increased risk of endometrial cancer.

1. Cardiovascular disorders

Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/ or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Coronary heart disease and stroke

In the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA sub-study of WHI, an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs. 30 per 10,000 women-years). The increase in risk was observed in year one and persisted.

In the same sub-study of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs. 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n=2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625mg/2.5mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of

CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. Venous thromboembolism (VTE)

In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CE compared to placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA sub-study of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

a. Endometrial cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2-to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15-to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) sub-study of CE/ MPA (see**CLINICAL PHARMACOLOGY, Clinical Studies**). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA sub-study of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination hormone therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA sub-study, 26% of the women reported prior use of estrogen alone and/or

estrogen/progestin combination therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

c. Ovarian cancer

The CE/MPa sub-study of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77 – 3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years.

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

3. Dementia

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n = 2,229) and 21 women in the placebo group (0.9%, n = 2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21 – 3.48), and was similar for women with and without histories of menopausal hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies** and **PRECAUTIONS, Geriatric Use**.)

It is unknown whether these findings apply to estrogen alone therapy.

4. Gallbladder disease

A 2-to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken

to reduce the serum calcium level.

6. Visual abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

PRECAUTIONS

A. General

1. Addition of a progestin when a woman has not had a hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

2. Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

3. Hypertriglyceridemia

In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. Impaired liver function and past history of cholestatic jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid retention

Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

7. Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

8. Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of estrogens. A few cases of malignant

transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

9. Exacerbation of other conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

10. Hypercoagulability

Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose-and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogens users) report no such increase.

11. Uterine bleeding and mastodynia

Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

B. Patient Information

Physicians are advised to discuss the **PATIENT INFORMATION** leaflet with patients for whom they prescribe Estradiol Valerate Injection

C. Laboratory Tests

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).

D. Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.

3. Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG)) leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

F. Pregnancy

Estradiol Valerate Injection should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

G. Nursing Mothers

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Estradiol Valerate Injection is administered to a nursing woman.

H. Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time may accelerate epiphyseal closure. Therefore, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended in patients in whom bone growth is not complete.

I. Geriatric Use

Clinical studies of estradiol valerate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of the women that were older than 70. (See **WARNINGS, Dementia**.)

It is unknown whether these findings apply to estrogen alone therapy.

ADVERSE REACTIONS

See **BOXED WARNINGS, WARNINGS,** and **PRECAUTIONS**.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea, increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

4. Gastrointestinal

Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.

5. Skin

Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

6. Eyes

Retinal vascular thrombosis; intolerance to contact lenses.

7. Central Nervous System

Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

8. Miscellaneous

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

For medical advice about adverse reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-233-2001 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (See **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Care should be taken to inject deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. By virtue of the low viscosity of the vehicles, the various preparations of Estradiol Valerate Injection, may be administered with a small gauge needle (i.e., 20 Gauge × 1 ½ inches long). Since the 40 mg potency provides a high concentration in a small

volume, particular care should be observed to administer the full dose.

Estradiol Valerate Injection should be visually inspected for particulate matter and color prior to administration; the solution is clear, colorless to pale yellow. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on warming.

Note: A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

Patients should be started at the lowest dose for the indication. The lowest effective dose of Estradiol Valerate Injection has not been determined for any indication. Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding. See **PRECAUTIONS** concerning addition of a progestin.

1. For treatment of moderate to severe vasomotor symptoms, vulvar and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

The usual dosage is 10 mg to 20 mg Estradiol Valerate Injection every four weeks.

Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

2. For treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

The usual dosage is 10 mg to 20 mg Estradiol Valerate Injection every four weeks.

3. For treatment of advanced androgen-dependent carcinoma of the prostate, for palliation only.

The usual dosage is 30 mg or more administered every one or two weeks.

HOW SUPPLIED

Estradiol Valerate Injection, USP

Multiple Dose Vials

Presentation	Carton of	NDC number
10 mg/mL (5 mL)	1 vial	0143-9289-01
20 mg/mL (5 mL)		0143-9290-01
40 mg/mL (5 mL)		0143-9291-01

Storage

Store between 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]

Keep out of reach of children.

Protect from light. Store vial in carton until used.

PATIENT INFORMATION

Estradiol Valerate Injection, USP

Read this **PATIENT INFORMATION** before you start taking Estradiol Valerate Injection and read what you get each time you refill Estradiol Valerate Injection. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ESTRADIOL VALERATE INJECTION (AN ESTROGEN HORMONE)?

- Estrogens increase the chances of getting cancer of the uterus. Report any unusual vaginal bleeding right away while you are taking estrogens. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes. Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. Using estrogens with progestins may increase your risk of dementia. You and your healthcare provider should talk regularly about whether you still need treatment with Estradiol Valerate Injection.

What is Estradiol Valerate Injection?

Estradiol valerate is a medicine that contains estrogen hormones.

What is Estradiol Valerate Injection used for?

Estradiol Valerate Injection is used after menopause to:

- **reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause." When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feeling of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Estradiol Valerate Injection.
- **treat moderate to severe dryness, itching, and burning in and around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with Estradiol Valerate Injection to control these problems. If you use Estradiol Valerate Injection only to treat your dryness, itching, and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

Who should not take Estradiol Valerate Injection?

Do not start taking Estradiol Valerate Injection if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or had cancer, talk with your healthcare provider about whether you should take Estradiol Valerate Injection.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **currently have or have had liver problems.**
- **are allergic to Estradiol Valerate Injection or any of its ingredients.** See the end of this leaflet for a list of ingredients in Estradiol Valerate Injection.
- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breastfeeding.** The hormone in Estradiol Valerate Injection can pass into your milk.
- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine,

endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **about all the medicines you take.** This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Estradiol Valerate Injection works. Estradiol Valerate Injection may also affect how your other medicines work.
- **if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens.

How should I take Estradiol Valerate Injection?

Estradiol Valerate Injection should be injected deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. By virtue of the low viscosity of the vehicles, the various preparations of Estradiol Valerate Injection, may be administered with a small gauge needle (i.e., 20 Gauge x 1 1/2 inches long). Since the 40 mg potency provides a high concentration in a small volume, particular care should be observed to administer the full dose.

Estradiol Valerate Injection should be visually inspected for particulate matter and color prior to administration; the solution is clear, colorless to pale yellow. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on warming.

Note: A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

1. Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you.
2. Estrogens should be used at the lowest dose possible for your treatment only as long as needed. The lowest effective dose of Estradiol Valerate Injection has not been determined. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Estradiol Valerate Injection.

How should I dispose of used syringes and needles?

1. Do not re-use needles or syringes.
2. Do not throw the needles and syringes in household waste. These should be discarded into an appropriate container (such as a sharps container) immediately after use. Refer to state or local laws and regulations for appropriate container requirements.
3. Make sure the container is tightly capped.
4. Strategically place the container so as to minimize handling and keep out of the reach of children.
5. Label the container indicating the presence of used needles/sharps.
6. For disposal of containers containing used needles and syringes refer to the state or local laws and regulations or as instructed by your healthcare provider or pharmacist.
7. Refer to your health care provider or pharmacist for guidance, and for additional information contact the Coalition for Safe Community Needle Disposal online at http://www.safeneedledisposal.org or refer to the FDA website Needles and Other Sharps at http://www.fda.gov/MedicalDevices/ProductsandMedical Procedures/HomeHealthandConsumer/ConsumerProducts/ Sharps/default.htm

How should I dispose of expired or unused Estradiol Valerate Injection?

1. Do not flush unused Estradiol Valerate Injection or pour down the sink or drain.
2. Refer to the state or local laws and regulations for the safest and proper disposal of injectable medications. Contact your city or county government's household trash and recycling service to find out if a drug take-back program is available in your community. You can also refer to your health care provider or pharmacist for guidance.
3. For additional information refer to the following FDA websites: Disposal of Unused Medicines: What You Should Know http://www.fda.gov/drugs/resourcesforyou/consumers/buyng usingmedicinesafely/ensureingsafeuseofmedicine/safedisposal ofmedicines/ucm186187.htm

How to Dispose of Unused Medicines http://www.fda.gov/ downloads/Drugs/ResourcesForYou/Consumers/BuyingUsing MedicineSafely/Understandingover-the-CounterMedicines/ ucm107163.pdf

What are the possible side effects of estrogens? Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:

- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infection

These are not all the possible side effects of Estradiol Valerate Injection. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of a serious side effect with Estradiol Valerate Injection?

Talk with your healthcare provider regularly about whether you should continue taking Estradiol Valerate Injection. If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you. See your healthcare provider right away if you get vaginal bleeding while

taking Estradiol Valerate Injection . Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often. If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Estradiol Valerate Injection

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Estradiol Valerate Injection for conditions for which it was not prescribed. Do not give Estradiol Valerate Injection to other people, even if they have the same symptoms you have. It may harm them.

Keep Estradiol Valerate Injection out of the reach of children.

This leaflet provides a summary of the most important information about Estradiol Valerate Injection. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Estradiol Valerate Injection that is written for health professionals. You can get more information by calling the toll free number 1-877-233-2001.

What are the ingredients in Estradiol Valerate Injection?

Estradiol Valerate Injection is supplied in three 5 mL multiple dose vials; 10 mg/mL, 20 mg/mL, and 40 mg/mL strengths. The 10 mg/mL strength contains 10 mg Estradiol Valerate, USP in a solution of Chlorobutanol, NF and Sesame Oil, NF. The 20 mg/mL strength contains 20 mg Estradiol Valerate, USP in a solution of Benzyl Benzoate, USP, Benzyl Alcohol, NF and Castor Oil, USP. The 40 mg/mL strength contains 40 mg Estradiol Valerate, USP in a solution of Benzyl Benzoate, USP, Benzyl Alcohol, NF and Castor Oil, USP.

How should I store Estradiol Valerate Injection?

Store Estradiol Valerate Injection at room temperature between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.)

Manufactured by:

Hikma Farmacêutica (Portugal) S.A.

Estrada do Rio da Mó, 8, 8A e 8B – Fervença – 2705-906 Terrugem, SNT, Portugal

Distributed by:

Hikma Pharmaceuticals USA Inc.

Eatontown, NJ, 07724 USA

Revised: May 2020

PIN556-WES/2

PRINCIPAL DISPLAY PANEL

NDC 0143-**9289**-01 Rx only
Estradiol Valerate
Injection, USP
50 mg per 5 mL
(10 mg/mL)
For Intramuscular use ONLY

5 mL Multiple Dose Vial **STERILE**

NDC 0143-**9289**-01 Rx only
5 mL Multiple Dose Vial
Estradiol Valerate
Injection, USP
50 mg per 5 mL
(10 mg/mL)
STERILE
For Intramuscular use ONLY

PRINCIPAL DISPLAY PANEL

NDC 0143-**9290**-01 Rx only
Estradiol Valerate
Injection, USP
100 mg per 5 mL
(20 mg/mL)
For Intramuscular use ONLY
5 mL Multiple Dose Vial **STERILE**

NDC 0143-**9290**-01 Rx only
5 mL Multiple Dose Vial
Estradiol Valerate
Injection, USP
100 mg per 5 mL
(20 mg/mL)
STERILE
For Intramuscular use ONLY

PRINCIPAL DISPLAY PANEL

NDC 0143-**9291**-01 Rx only
Estradiol Valerate
Injection, USP
200 mg per 5 mL
(40 mg/mL)
For Intramuscular use ONLY
5 mL Multiple Dose Vial **STERILE**

NDC 0143-**9291**-01 Rx only
5 mL Multiple Dose Vial
Estradiol Valerate
Injection, USP
200 mg per 5 mL
(40 mg/mL)
STERILE
For Intramuscular use ONLY

SERIALIZATION IMAGE

ESTRADIOL VALERATE

estradiol valerate injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-9289
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL VALERATE (UNII: OKG364O896) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL VALERATE	10 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
CHLOROBUTANOL (UNII: HM4YQM8WRC)	
SESAME OIL (UNII: QX10HYY4QV)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0143-9289-01	1 in 1 CARTON	04/21/2020	
1		5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203723	04/21/2020	

ESTRADIOL VALERATE

estradiol valerate injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-9290
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL VALERATE (UNII: OKG364O896) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL VALERATE	20 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
BENZYL BENZOATE (UNII: N863NB338G)	

BENZYL ALCOHOL (UNII: LKG8494WBH)	
CASTOR OIL (UNII: D5340Y2I9G)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0143-9290-01	1 in 1 CARTON	04/21/2020	
1		5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203723	04/21/2020	

ESTRADIOL VALERATE

estradiol valerate injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-9291
Route of Administration	INTRAMUSCULAR		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
ESTRADIOL VALERATE (UNII: OKG364O896) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL VALERATE	40 mg in 1 mL

Inactive Ingredients	
Ingredient Name	Strength
BENZYL BENZOATE (UNII: N863NB338G)	
BENZYL ALCOHOL (UNII: LKG8494WBH)	
CASTOR OIL (UNII: D5340Y2I9G)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0143-9291-01	1 in 1 CARTON	04/21/2020	
1		5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203723	04/21/2020	

Labeler - Hikma Pharmaceuticals USA Inc. (001230762)

Revised: 6/2020 Hikma Pharmaceuticals USA Inc.

Exhibit

H

ESTRADIOL TRANSDERMAL SYSTEM- estradiol patch
Sandoz Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ESTRADIOL TRANSDERMAL SYSTEM safely and effectively. See full prescribing information for ESTRADIOL TRANSDERMAL SYSTEM.
ESTRADIOL TRANSDERMAL SYSTEM (estradiol transdermal system)
Initial U.S. Approval: 1975

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

5. **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)**
6. **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
7. **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.1)**
8. **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) (5.1)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

INDICATIONS AND USAGE

The Estradiol Transdermal System is an estrogen indicated for:

- Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause (1.1)
- Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause (1.2)
- Treatment of Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure (1.3)
- Prevention of Postmenopausal Osteoporosis (1.4)

DOSAGE AND ADMINISTRATION

- Start therapy with the Estradiol Transdermal System 0.025 mg per day applied to the skin once-weekly. Dosage adjustment should be guided by the clinical response (2.1)
- The Estradiol Transdermal System should be placed on a clean, dry area of the lower abdomen (below the umbilicus) or upper quadrant of the buttock. The Estradiol Transdermal System should not be applied to the breasts (2.5)

DOSAGE FORMS AND STRENGTHS

- Transdermal system 0.025 mg per day, 0.0375 mg per day, 0.05 mg per day, 0.06 mg per day, 0.075 mg per day and 0.1 mg per day (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.2)

- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema with the Estradiol Transdermal System (4)
- Known liver impairment or disease (4, 5.10)
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogens if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid hormone replacement therapy (5.11, 5.18)

ADVERSE REACTIONS

In a prospective, randomized, placebo-controlled, double-blind study, the most common adverse reactions (≥10 percent) are breast pain, upper respiratory tract infections, headaches, abdominal pain, pain, and edema. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the WHIMS ancillary studies of the WHI (5.3, 8.5, 14.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

1.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

Limitation of Use

When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, topical vaginal products should be considered.

1.3 Treatment of Hypoestrogenism due to Hypogonadism, Castration, or Primary Ovarian Failure

1.4 Prevention of Postmenopausal Osteoporosis

Limitation of Use

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medication should be carefully considered.

2 DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer. A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.2, 5.14)]*.

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2.1 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Start therapy with 0.025 mg per day applied to the skin once weekly. Therapy should be started at the lowest effective dose and the shortest duration consistent with the treatment goals. Attempts to taper or discontinue the medication should be made at 3 to 6 month intervals.

2.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

Start therapy with 0.025 mg per day applied to the skin once weekly. Therapy should be started at the lowest effective dose and the shortest duration consistent with the treatment goals. Attempts to taper or discontinue the medication should be made at 3 to 6 month intervals.

2.3 Treatment of Hypoestrogenism due to Hypogonadism, Castration, or Primary Ovarian Failure

Start therapy with 0.025 mg per day applied to the skin once weekly. The dose should be adjusted as necessary to control symptoms. Clinical responses (relief of symptoms) at the lowest effective dose should be the guide for establishing administration of the Estradiol Transdermal System, especially in women with an intact uterus.

2.4 Prevention of Postmenopausal Osteoporosis

Start therapy with 0.025 mg per day applied to the skin once weekly.

2.5 Application of the Estradiol Transdermal System

Site Selection

- The adhesive side of the Estradiol Transdermal System should be placed on a clean, dry area of the lower abdomen or the upper quadrant of the buttock.
- The Estradiol Transdermal should not be applied to or near the breasts.
- The sites of application must be rotated, with an interval of at least 1-week allowed between applications to the same site.
- The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the transdermal system off.
- Application to areas where sitting would dislodge the Estradiol Transdermal System should also be avoided.

Application

- The Estradiol Transdermal System should be applied immediately after opening the pouch and removing the protective liner.
- The Estradiol Transdermal System should be pressed firmly in place with the fingers for at least 10 seconds, making sure there is good contact, especially around the edges.
- If the system lifts, apply pressure to maintain adhesion.
- In the event that a system should fall off reapply it to a different location. If the system cannot be reapplied, a new system should be applied for the remainder of the 7-day dosing interval.
- Only one system should be worn at any one time during the 7-day dosing interval.
- Swimming, bathing, or using a sauna while using the Estradiol Transdermal System has not been studied, and these activities may decrease the adhesion of the system and the delivery of estradiol.

2.6 Removal of the Estradiol Transdermal System

- Removal of the Estradiol Transdermal System should be done carefully and slowly to avoid irritation of the skin.
- Should any adhesive remain on the skin after removal of the Estradiol Transdermal System, allow the area to dry for 15 minutes. Then gently rubbing the area with an oil-based cream or lotion should remove the adhesive residue.
- Used patches still contain some active hormones. Each patch should be carefully folded in half so that it sticks to itself before throwing it away.

3 DOSAGE FORMS AND STRENGTHS

- Estradiol Transdermal System, 0.025 mg per day—each 6.5 cm^2 system contains 2 mg of estradiol
- Estradiol Transdermal System, 0.0375 mg per day—each 9.375 cm^2 system contains 2.85 mg of estradiol
- Estradiol Transdermal System, 0.05 mg per day—each 12.5 cm^2 system contains 3.8 mg of estradiol
- Estradiol Transdermal System, 0.060 mg per day—each 15 cm^2 system contains 4.55 mg of estradiol
- Estradiol Transdermal System, 0.075 mg per day—each 18.75 cm^2 system contains 5.7 mg of

estradiol

- Estradiol Transdermal System, 0.1 mg per day—each 25.0 cm^2 system contains 7.6 mg of estradiol

4 CONTRAINDICATIONS

The Estradiol Transdermal System is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or a history of these conditions
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions
- Known anaphylactic reaction or angioedema with the Estradiol Transdermal System
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.3)]*. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women years) *[see Clinical Studies (14.3)]*. The increase in risk was demonstrated after the first year and persisted.[1] Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.3)]*.

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.3)]*.

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. A total of 2,321 women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3] *[see Clinical Studies (14.3)]*. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted[4] *[see Clinical Studies (14.3)]*. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

5.2 Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*[5] *[see Clinical Studies (14.3)]*.

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA.

In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years for CE plus MPA compared with placebo *[see Clinical Studies (14.3)]*. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups[6] *[see Clinical Studies (14.3)]*.

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50);

there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years]vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27 to 1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

5.3 Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia.The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

5.4 Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5.5 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

5.7 Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

5.8 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

5.9 Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5.10 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5.11 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

5.12 Fluid Retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal impairment, warrant careful observation when estrogen-alone is prescribed.

5.13 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

5.14 Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

5.15 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema.

5.16 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

5.17 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy.

5.18 Drug-Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased TBG levels leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-l-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, and increased triglyceride levels.

Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning, and Warnings and Precautions (5.1)]*
- Malignant Neoplasms *[see Boxed Warning, and Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect pooled data from 5 clinical trials of the Estradiol Transdermal System. A total of 614 women were exposed to the Estradiol Transdermal System for 3 months (193 women at 0.025 mg per day, 201 women at 0.05 mg per day, 194 women at 0.1 mg per day) in randomized, double-blind trials of clinical efficacy versus placebo and versus active comparator. All women were postmenopausal, had a serum estradiol level of less than 20 pg/mL, and a minimum of five moderate to severe hot flushes per week or a minimum of 15 hot flushes per week of any severity at baseline. Included in this table are an additional 25 postmenopausal hysterectomized women exposed to the Estradiol Transdermal System 0.025 mg per day for 6 to 24 months (N=16 at 24 months) in a randomized, double-blind, placebo-controlled study of the Estradiol Transdermal System for the prevention of osteoporosis.

Table 1: Treatment-Emergent Adverse Reactions Reported at a Frequency of ≥5 Percent and More Frequent in Women Receiving the Estradiol Transdermal System

	The Estradiol Transdermal System			
Body System	**0.025 mg/day[a] (N=219)**	**0.05 mg/day[b] (N=201)**	**0.1 mg/day[b] (N=194)**	**Placebo[c] (N=72)**

Adverse Reactions				
Body as a Whole				
Headache	21%	39%	37%	29%
Pain	5%	18%	13%	10%
Back Pain	1%	8%	11%	7%
Edema	4%	8%	9%	6%
	0.5%	13%	10%	6%
Digestive System				
Abdominal Pain	9%	21%	29%	18%
Nausea	0%	11%	16%	8%
Flatulence	1%	5%	6%	3%
	1%	3%	7%	1%
Musculoskeletal System				
Arthralgia	7%	9%	11%	4%
	1%	5%	5%	3%
Nervous System				
Depression	13%	10%	11%	1%
	1%	5%	8%	0%
Urogenital System				
Breast Pain	12%	18%	41%	11%
Leukorrhea	5%	8%	29%	4%
	1%	6%	7%	1%
Respiratory System				
URTI	15%	26%	29%	14%
Pharyngitis	6%	17%	17%	8%
Sinusitis	0.5%	3%	7%	3%
Rhinitis	4%	4%	5%	3%
	2%	4%	6%	1%
Skin and Appendages				
Pruritus	19%	12%	12%	15%
	0.5%	6%	3%	6%

1. Adverse reactions occurring at rate of ≥5 percent in the Estradiol Transdermal System trials of clinical efficacy versus placebo and versus active comparator; and trial of the Estradiol Transdermal System versus placebo for the prevention of osteoporosis
2. Adverse reactions occurring at rate of ≥5 percent in the Estradiol Transdermal System trials of clinical efficacy versus placebo and versus active comparator
3. Adverse reactions occurring in placebo group in the Estradiol Transdermal System trial of clinical efficacy versus placebo

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of the Estradiol Transdermal System. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System

Changes in bleeding pattern, pelvic pain

Breast

Breast cancer, breast pain, breast tenderness

Cardiovascular

Changes in blood pressure, palpitations, hot flashes

Gastrointestinal

Vomiting, abdominal pain, abdominal distension, nausea

Skin

Alopecia, hyperhidrosis, night sweats, urticaria, rash

Eyes

Visual disturbances, contact lens intolerance,

Central Nervous System

Depression, migraine, paresthesia, dizziness, anxiety, irritability, mood swings, nervousness, insomnia, headache

Miscellaneous

Fatigue, menopausal symptoms, weight increase, application site reaction, anaphylactic reactions

7 DRUG INTERACTIONS

7.1 Metabolic Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort (hypericum perforatum) preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The Estradiol Transdermal System should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as oral contraceptives inadvertently during early pregnancy.

8.3 Nursing Mothers

The Estradiol Transdermal System should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogen therapy. Caution should be exercised when the Estradiol Transdermal System is administered to a nursing woman.

8.4 Pediatric Use

The Estradiol Transdermal System is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing the Estradiol Transdermal System to determine whether those over 65 years of age differ from younger subjects in their response to the Estradiol Transdermal System.

The Women's Health Initiative Studies

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.3)]*.

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age *[see Clinical Studies (14.3)]*.

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo *[see Warnings and Precautions (5.3), and Clinical Studies (14.4)]*.

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women[8] *[see Warnings and Precautions (5.3), and Clinical Studies (14.4)]*.

8.6 Renal Impairment

In postmenopausal women with end stage renal disease (ESRD) receiving maintenance hemodialysis, total estradiol serum levels are higher than in normal subjects at baseline and following oral doses of estradiol. Therefore, conventional transdermal estradiol doses used in individuals with normal renal function may be excessive for postmenopausal women with ESRD receiving maintenance hemodialysis.

8.7 Hepatic Impairment

Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

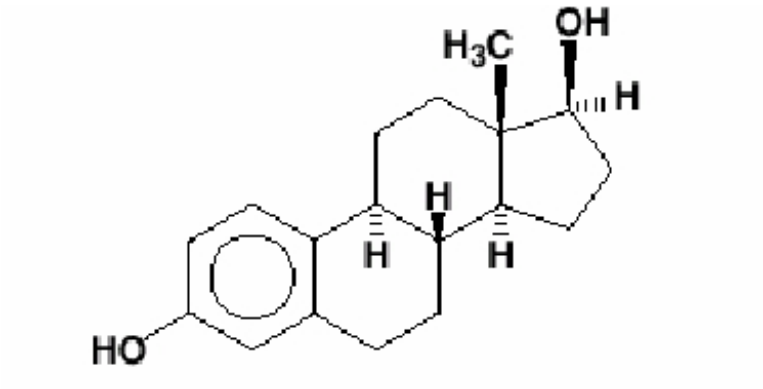
10 OVERDOSAGE

Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding in women. Treatment of overdose consists of discontinuation of the Estradiol Transdermal System therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

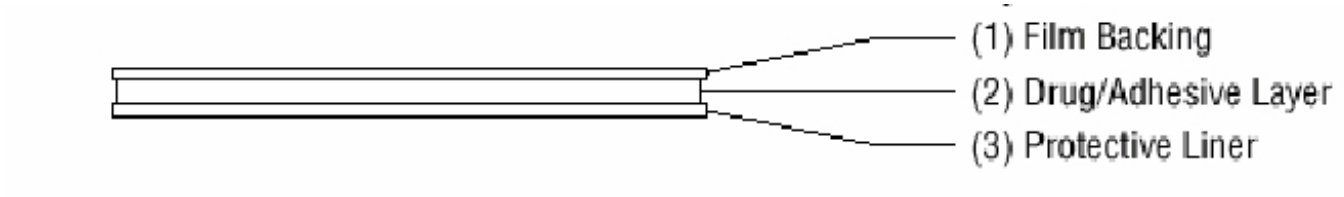
The Estradiol Transdermal System is designed to release estradiol continuously upon application to intact skin. Six (6.5, 9.375, 12.5, 15, 18.75 and 25 cm^2) systems are available to provide nominal *in vivo* delivery of 0.025, 0.0375, 0.05, 0.06, 0.075 or 0.1 mg respectively of estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 9.375, 12.5, 15, 18.75 or 25 cm^2, and contains 2, 2.85, 3.8, 4.55, 5.7 or 7.6 mg of estradiol USP respectively. The composition of the systems per unit area is identical.

Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5(10)-triene-3, 17β-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.38. The structural formula is:



The Estradiol Transdermal System comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are:

1. A translucent polyethylene film.
2. An acrylate adhesive matrix containing estradiol USP.
3. A protective liner of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the system can be used.



The active component of the transdermal system is estradiol. The remaining components of the transdermal system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most

endogenous estrogen is produced by conversion of androstenedione, which is secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

There are no pharmacodynamic data for Estradiol Transdermal System.

12.3 Pharmacokinetics

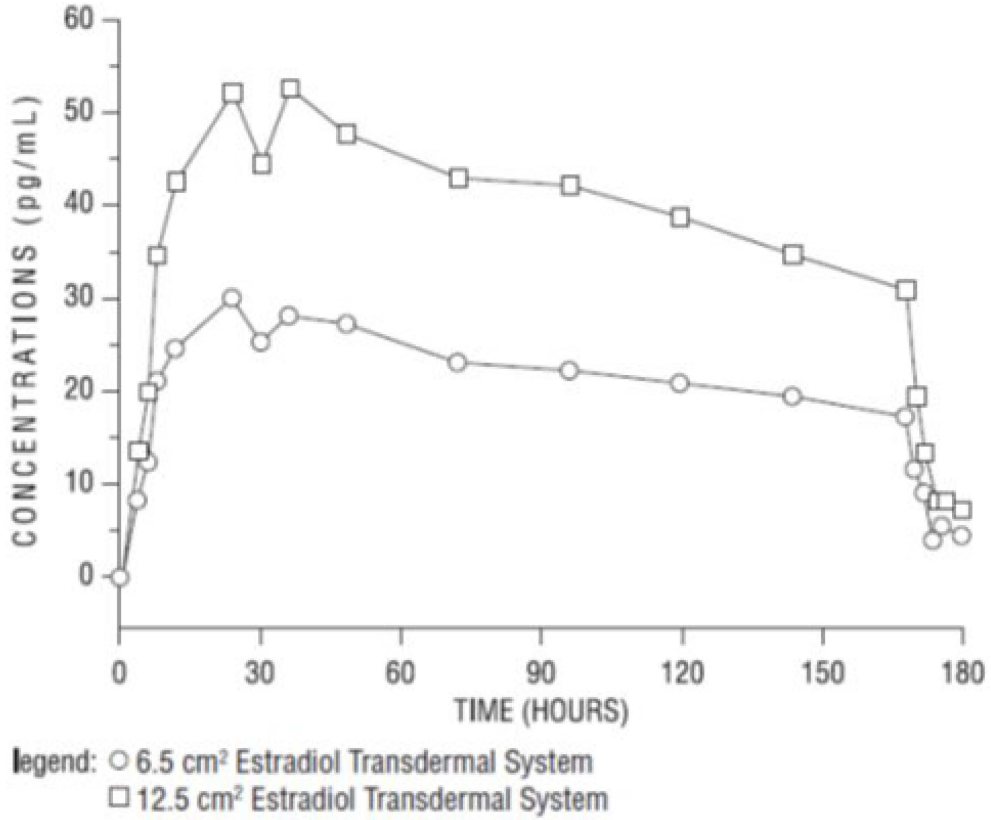
Absorption

Transdermal administration of the Estradiol Transdermal System produces mean serum concentrations of estradiol comparable to those produced by premenopausal women in the early follicular phase of the ovulatory cycle. The pharmacokinetics of estradiol following application of the Estradiol Transdermal System were investigated in 197 healthy postmenopausal women in six studies. In five of the studies, the Estradiol Transdermal System was applied to the abdomen, and in a sixth study, application to the buttocks and abdomen were compared.

The Estradiol Transdermal System continuously releases estradiol which is transported across intact skin leading to sustained circulating levels of estradiol during a 7-day treatment period. The systemic availability of estradiol after transdermal administration is about 20 times higher than that after oral administration. This difference is due to the absence of first pass metabolism when estradiol is given by the transdermal route.

In a bioavailability study, the Estradiol Transdermal System 6.5 cm^2 was studied with the Estradiol Transdermal System 12.5 cm^2 as reference. The mean estradiol levels in serum from the two sizes are shown in **Figure 1**.

Figure 1: Mean Serum 17ß -Estradiol Concentrations versus Time Profile following Application of a 6.5 cm^2 Estradiol Transdermal System and Application of a 12.5 cm^2 Estradiol Transdermal System



Dose proportionality was demonstrated for the 6.5 cm^2 Estradiol Transdermal System as compared to the 12.5 cm^2 Estradiol Transdermal System in a 2-week crossover study with a 1-week washout period between the two-transdermal systems in 24 postmenopausal women.

Dose proportionality was also demonstrated for the Estradiol Transdermal System (12.5 cm^2 and 25 cm^2) in a 1-week study conducted in 54 postmenopausal women. The mean steady state levels (C_{avg}) of the estradiol during the application of the Estradiol Transdermal System 25 cm^2 and 12.5 cm^2 on the abdomen were about 80 and 40 pg/mL, respectively.

In a 3-week multiple application study in 24 postmenopausal women, the 25 cm^2 Estradiol Transdermal System produced average peak estradiol concentrations (C_{max}) of approximately 100 pg/mL. Trough values at the end of each wear interval (C_{min}) were approximately 35 pg/mL. Nearly identical serum curves were seen each week, indicating little or no accumulation of estradiol in the body. Serum estrone peak and trough levels were 60 and 40 pg/mL, respectively.

In a single dose, randomized, crossover study conducted to compare the effect of site of application, 38 postmenopausal women wore a single 25 cm^2 Estradiol Transdermal System for 1 week on the abdomen and buttocks. The estradiol serum concentration profiles are shown in **Figure 2**. Values of C_{max} and C_{avg} were, respectively, 25 percent and 17 percent higher with the buttock application than with the abdomen application.

Figure 2: Observed Mean (± SE) Estradiol Serum Concentrations for a One Week Application of the Estradiol Transdermal System (25 cm^2) to the Abdomen and Buttocks of 38 Postmenopausal Women

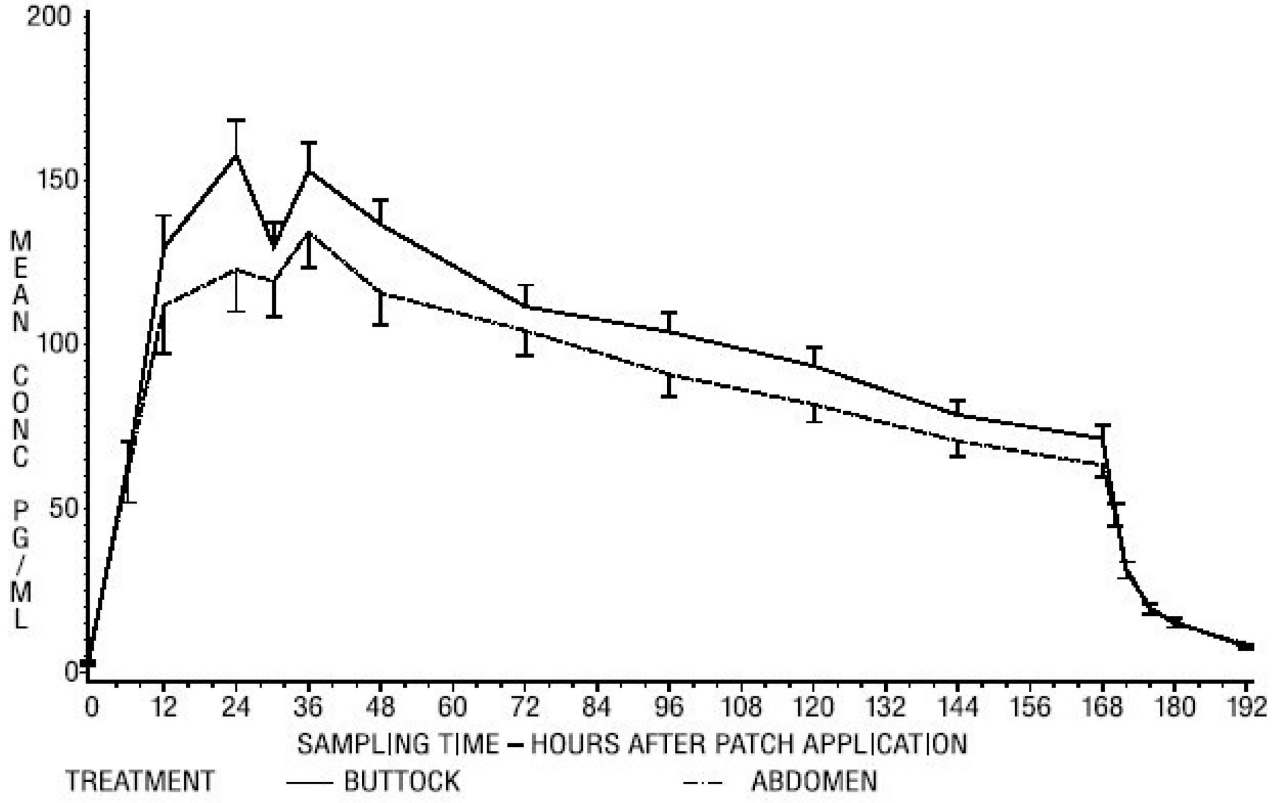


Table 2 provides a summary of estradiol pharmacokinetic parameters determined during evaluation of the Estradiol Transdermal System.

Table 2: Pharmacokinetic Summary (Mean Estradiol Values)

Estradiol Transdermal System Delivery Rate	Surface Area (cm^2)	Application Site	No. of Subjects	Dosing	C_{max} (pg/mL)	C_{min} (pg/mL)	C_{avg} (pg/mL)
0.025	6.5	Abdomen	24	Single	32	17	22
0.05	12.5	Abdomen	102	Single	71	29	41
0.1	25	Abdomen	139	Single	147	60	87
0.1	25	Buttock	38	Single	174	71	106

The relative standard deviation of each pharmacokinetic parameter after application to the abdomen averaged 50 percent, which is indicative of the considerable intersubject variability associated with transdermal drug delivery. The relative standard deviation of each pharmacokinetic parameter after application to the buttock was lower than that after application to the abdomen (for example, for C_{max} 39 percent versus 62 percent, and for C_{avg} 35 percent versus 48 percent).

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to SHBG and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Adhesion

An open-label study of adhesion potentials of placebo transdermal systems that correspond to the 6.5 cm^2 and 12.5 cm^2 sizes of the Estradiol Transdermal System was conducted in 112 healthy women of 45 to 75 years of age. Each woman applied both transdermal systems weekly, on the upper outer abdomen, for 3 consecutive weeks. It should be noted that lower abdomen and upper quadrant of the buttock are the approved sites of application for the Estradiol Transdermal System.

The adhesion assessment was done visually on Days 2, 4, 5, 6, 7 of each week of transdermal system wear. A total of 1,654 adhesion observations were conducted for 333 transdermal systems of each size.

Of these observations, approximately 90 percent showed essentially no lift for both the 6.5 cm^2 and 12.5 cm^2 transdermal systems. Of the total number of transdermal systems applied, approximately 5 percent showed complete detachment for each size. Adhesion potentials of the 18.75 cm^2 and 25 cm^2 sizes of transdermal systems (0.075 mg per day and 0.1 mg per day) have not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms

A study of 214 women 25 to 74 years of age met the qualification criteria and were randomly assigned to one of the three treatment groups: 72 to the 0.05 mg estradiol patch, 70 to the 0.1 mg estradiol patch, and 72 to placebo. Potential subjects were postmenopausal women in good general health who experienced vasomotor symptoms. Natural menopause patients had not menstruated for at least 12 months and surgical menopause patients had undergone bilateral oophorectomy at least 4 weeks before evaluation for study entry. In order to enter the 11-week treatment phase of the study, potential subjects must have experienced a minimum of five moderate to severe hot flushes per week, or a minimum of 15 hot flushes of any severity per week, for 2 consecutive weeks. Women wore the patches in a cyclical fashion (three weeks on and one week off).

During treatment, all subjects used diaries to record the number and severity of hot flushes. Subjects were monitored by clinic visits at the end of weeks 1, 3, 7, and 11 and by telephone at the end of weeks 4, 5, 8, and 9.

Adequate data for the analysis of efficacy was available from 191 subjects. The results are presented as

the mean ± SD number of flushes in each of the 3 treatment weeks of each 4-week cycle. In the 0.05 mg estradiol group, the mean weekly hot flush rate across all treatment cycles decreased from 46 ± 6.5 at baseline to 20 ± 3 (-67 percent). The 0.1 mg estradiol group had a decline in the mean weekly hot flush rate from 52 ± 4.4 at baseline to 16 ± 2.4 (-72 percent). In the placebo group, the mean weekly hot flush rate declined from 53 ± 4.5 at baseline to 46 ± 6.5 (-18.1 percent). Compared with placebo, the 0.05 mg and 0.1 mg estradiol groups showed a statistically significantly larger mean decrease in hot flushes across all treatment cycles ($P<0.05$). When the response to treatment was analyzed for each of the three cycles of therapy, similar statistically significant differences were observed between both estradiol treatment groups and the placebo group during all treatment cycles.

In a double-blind, placebo-controlled, randomized study of 187 women receiving estradiol 0.025 mg per day or placebo continuously for up to three 28-day cycles, the estradiol 0.025 mg per day dosage was shown to be statistically better than placebo at weeks 4 and 12 for relief of both the frequency and severity of moderate to severe vasomotor symptoms.

Table 3: Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms Intent to Treat (ITT)

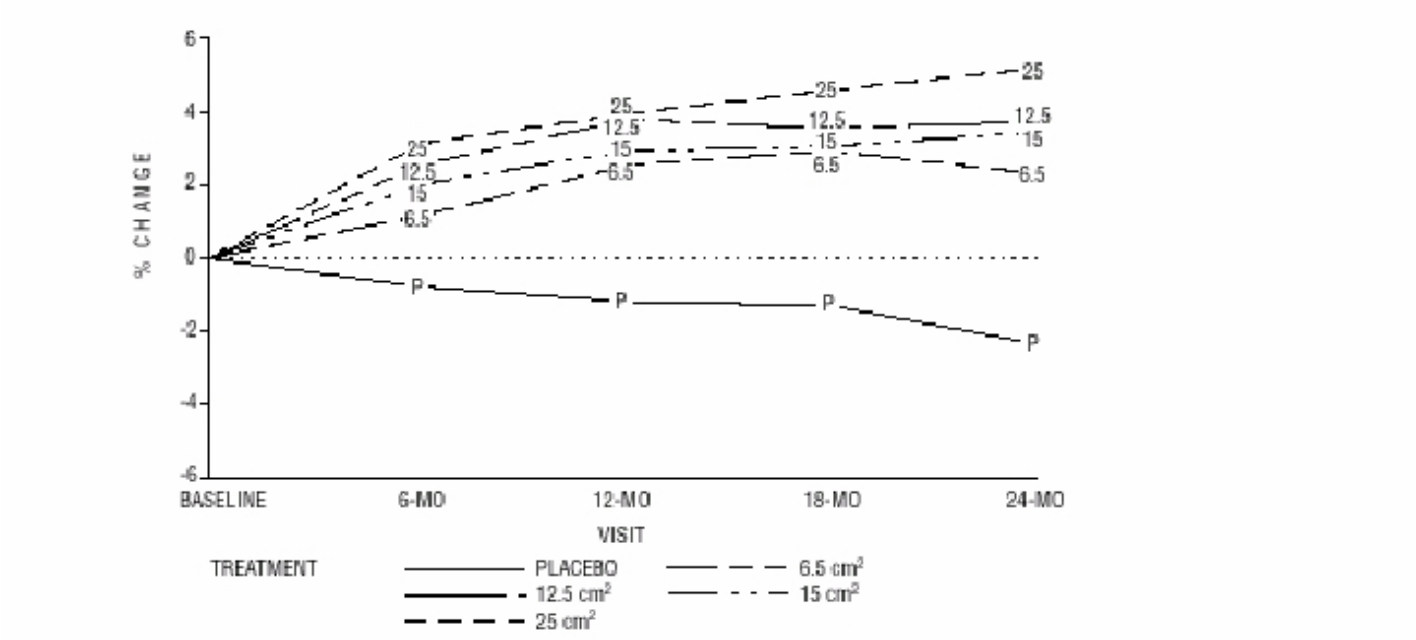
Treatment Group	Statistics	Week 4	Week 8	Week 12
E_2 Transdermal System	N	82	84	68
	Mean	-6.45	-7.69	-7.56
	SD	4.65	4.76	4.64
Placebo	N	83	71	65
	Mean	-5.11	-5.98	-5.98
	SD	7.43	8.63	9.69
	p-Value	<0.002		<0.003

A second active-control trial of 193 randomized subjects was supportive of the placebo-controlled trial.

14.2 Effects on Bone Mineral Density

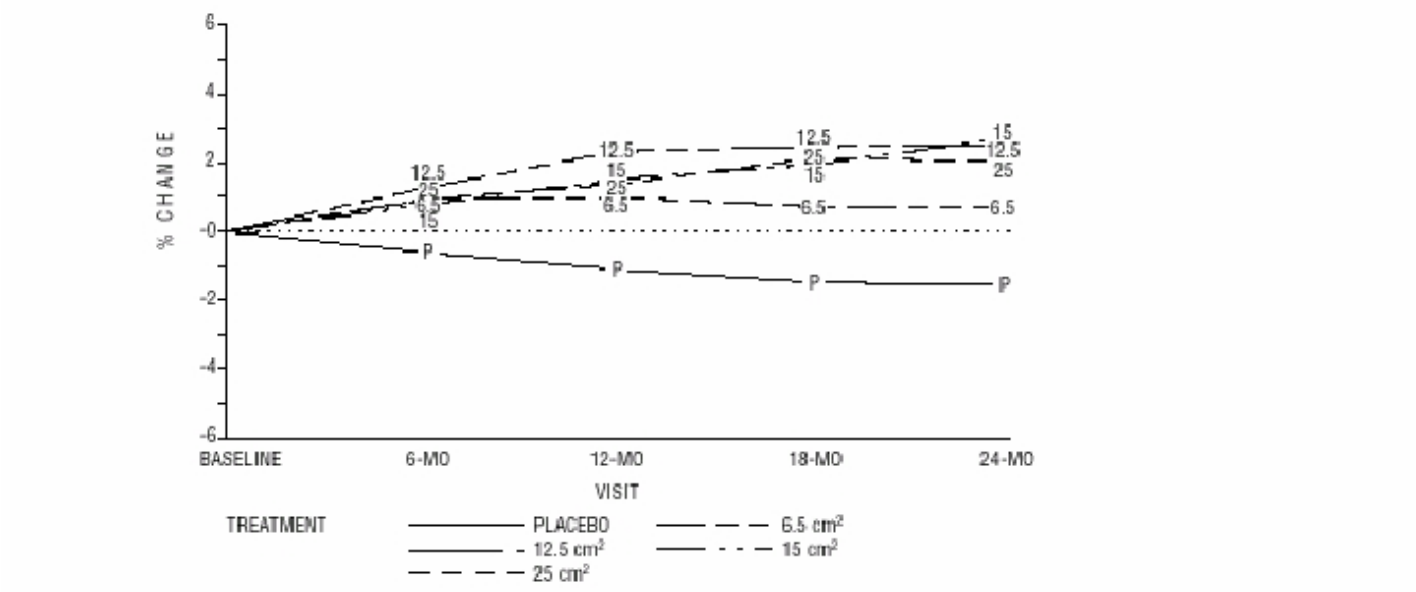
A two-year clinical trial enrolled a total of 175 healthy, hysterectomized, postmenopausal, non-osteoporotic (that is, lumbar spine bone mineral density >0.9 gm/cm^2) women at 10 study centers in the United States. A total of 129 subjects were allocated to receive active treatment with 4 different doses of estradiol patches (6.5, 12.5, 15, 25 cm^2) and 46 subjects were allocated to receive placebo patches. Seventy-seven percent of the randomized subjects (100 on active drug and 34 on placebo) contributed data to the analysis of percent change of anterior-posterior (A-P) spine BMD, the primary efficacy variable (**see Figure 3**). A statistically significant overall treatment effect at each timepoint was noted, implying bone preservation for all active treatment groups at all timepoints, as opposed to bone loss for placebo at all timepoints.

Figure 3: Mean Percent Change from Baseline in Lumbar Spine (A-P View) Bone Mineral Density By Treatment and Time Last Observation Carried Forward



Percent change in BMD of the total hip (see Figure 4) was also statistically significantly different from placebo for all active treatment groups. This figure is based on 74 percent of the randomized subjects (95 on active drug and 34 on placebo).

Figure 4: Mean Percent Change from Baseline in Total Hip by Treatment and Time Last Observation Carried Forward



14.3 Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. These substudies did not evaluate the effects of CE-

alone or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risk and benefits of estrogen-alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79: 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in **Table 4**.

Table 4. Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHIa

Event	**Relative Risk CE vs. Placebo (95% nCI[b])**	**CE n = 5,310**	**Placebo n = 5,429**
		Absolute Risk per 10,000 Women-years	
CHD events[c]	0.95 (0.78-1.16)	54	57
Non-fatal MIc	0.91 (0.73-1.14)	40	43
CHD death[c]	*1.01 (0.71-1.43)*	*16*	*16*
All strokes[c]	1.33 (1.05-1.68)	45	33
Ischemic stroke[c]	*1.55 (1.19-2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06-2.06)	23	15
Pulmonary embolism[c]	1.37 (0.9-2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62-1.04)	28	34
Colorectal cancer[c]	1.08 (0.75-1.55)	17	16
Hip fracture[c]	0.65 (0.45-0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47-0.72)	35	59
Total fractures[c,d]	0.71 (0.64-0.80)	144	197
Death due to causes[e,f]	1.08 (0.88-1.32)	53	50
Overall mortality[c,d]	1.04 (0.88-1.22)	79	75
Global Index[g]	1.02 (0.92-1.13)	206	201

1. Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
2. Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
3. Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
4. Not included in "global index".

5. Results are based on an average follow-up of 6.8 years.
6. All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
7. A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risks per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.[9] The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years. **See Table 4**.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in the distribution of stroke subtype and severity, including fatal strokes, in women receiving estrogen-alone compared to placebo. Estrogen-alone increased the risk of ischemic stroke, and this excess risk was present in all subgroups of women examined.[10] **See Table 4**.

Timing of initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk-benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for CHD *[hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)]* and overall mortality *[HR 0.71 (95 percent CI, 0.46-1.11)]*.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". The absolute excess risk of events included in the “global index” was 19 per 10,000 women-years.

For those outcomes included in the WHI “global index” that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reduction per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.5 percent Black, 5.4 percent Hispanic, 3.9 percent Other), are presented in **Table 5** . These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 5: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a, b]

Event	**Relative Risk CE/MPA vs. placebo (95% nCIc)**	**CE/MPA n = 8,506**	**Placebo n = 8,102**
		Absolute Risk per 10,000 Women-years	
CHD events	1.23 (0.99-1.53)	41	34

Non-fatal MI	*1.28 (1.00-1.63)*	*31*	*25*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All strokes	1.31 (1.03-1.68)	33	25
Ischemic stroke	*1.44 (1.09-1.90)*	*26*	*18*
Deep vein thrombosis[d]	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer[e]	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer[d]	0.81 (0.48-1.36)	6	7
Cervical cancer[d]	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures[d]	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures[d]	0.71 (0.59-0.85)	44	62
Total fractures[d]	0.76 (0.69-0.83)	152	199
Overall mortality[f]	1.00 (0.83-1.19)	52	52
Global Indexg	1.13 (1.02-1.25)	184	165

1. Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
2. Results are based on centrally adjudicated data.
3. Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
4. Not included in “global index”.
5. Includes metastatic and non-metastatic breast cancer, with the exception of *in situ* breast cancer.
6. All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
7. A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

Timing of initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for overall mortality *[HR 0.69 (95 percent CI, 0.44-1.07)]*.

14.4 Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age (45 percent were 65 to 69 years of age;

36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in the study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations(8.5)]*.

The WHIMS estrogen plus progestin ancillary study enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years of age; and 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. Probable dementia as defined in the study included AD, VaD and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.3), and Use in Specific Populations (8.5)]*.

15 REFERENCES

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5. Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy. *JAMA*. 2006;295:1647-1657.
6. Chlebowski RT, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. *JAMA*. 2003;289:3234-3253.
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Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. *J Bone Miner Res.* 2006;21:817-828.
10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation.* 2006;113:2425-2434.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Estradiol Transdermal System, 0.025 mg/day — each 6.5 cm^2 system contains 2 mg of estradiol USP
Individual Carton of 4 systems NDC 0781-7119-54
Estradiol Transdermal System, 0.0375 mg/day — each 9.375 cm^2 system contains 2.85 mg of estradiol USP
Individual Carton of 4 systems NDC 0781-7122-54
Estradiol Transdermal System, 0.05 mg/day — each 12.5 cm^2 system contains 3.8 mg of estradiol USP
Individual Carton of 4 systems ……NDC 0781-7133-54
Estradiol Transdermal System, 0.06 mg/day — each 15 cm^2 system contains 4.55 mg of estradiol USP
Individual Carton of 4 systems NDC 0781-7134-54
Estradiol Transdermal System, 0.075 mg/day — each 18.75 cm^2 system contains 5.7 mg of estradiol USP
Individual Carton of 4 systems…… NDC 0781-7136-54
Estradiol Transdermal System, 0.1 mg/day — each 25 cm^2 system contains 7.6 mg of estradiol USP
Individual Carton of 4 systems ……..NDC 0781-7104-54

16.2 Storage and Handling

Store at 20°C to 25°C (66°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). Do not store above 86°F (30°C).

Do not store unpouched. Apply immediately upon removal from the protective pouch.

Used transdermal systems still contain active hormone. To discard, fold the sticky side of the transdermal system together, place it in a sturdy child-proof container, and place this container in the trash. Used transdermal systems should not be flushed in the toilet.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)

Vaginal Bleeding

Inform postmenopausal women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible *[see Warning and Precautions (5.2)]*.

Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including cardiovascular disorders, malignant neoplasms, and probable dementia *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Possible Less Serious but Common Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.

Patient Package Insert

Patient Information

Estradiol Transdermal System

Read this Patient Information before you start using Estradiol Transdermal System and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about the Estradiol Transdermal System (an estrogen hormone)?

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb). Report any unusual vaginal bleeding right away while you are using the Estradiol Transdermal System. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes, or dementia (decline in brain function).
- Using estrogen-alone may increase your chances of getting strokes or blood clots.
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women age 65 years of age or older.
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia.
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women age 65 years of age or older.
- You and your healthcare provider should talk regularly about whether you still need treatment with the Estradiol Transdermal System.

What is the Estradiol Transdermal System?

The Estradiol Transdermal System is a prescription medicine patch that contains estradiol (an estrogen hormone).

What is the Estradiol Transdermal System used for?

The Estradiol Transdermal System is used after menopause to:

- Reduce moderate to severe hot flashes

  Estrogens are hormones made by a woman’s ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

  When the estrogen levels begin dropping, some women get very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need to use estrogens. In other women, symptoms can be more severe. You and your healthcare provider

should talk regularly about whether you still need treatment with the Estradiol Transdermal System.

- **Treat moderate to severe menopausal changes in and around the vagina**
  You and your healthcare provider should talk regularly about whether you still need treatment with the Estradiol Transdermal System to control these problems. If you use the Estradiol Transdermal System only to treat your menopausal changes in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.
- **Treat certain conditions in women before menopause if their ovaries do not produce enough estrogens naturally**
- **Help reduce your chances of getting osteoporosis (thin weak bones)**
  If you use the Estradiol Transdermal System only to prevent osteoporosis due to menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you still need treatment with the Estradiol Transdermal System.

Who should not use the Estradiol Transdermal System?

Do not start using the Estradiol Transdermal System if you:

- **have unusual vaginal bleeding**
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **currently have or have had certain cancers**
  Estrogens may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use the Estradiol Transdermal System.
- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **have been diagnosed with a bleeding disorder**
- **are allergic to the Estradiol Transdermal System or any of its ingredients**
  See the list of ingredients in the Estradiol Transdermal System at the end of this leaflet.
- **think you may be pregnant**
  The Estradiol Transdermal System is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not use the Estradiol Transdermal System if the test is positive and talk to your healthcare provider.

What should I tell my healthcare provider before I use the Estradiol Transdermal System?

Before you use the Estradiol Transdermal System, tell your healthcare provider if you:

- **have any unusual vaginal bleeding**
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **have any other medical conditions**
  Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face and tongue), or problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **are going to have surgery or will be on bed rest**
  Your healthcare provider will let you know if you need to stop using the Estradiol Transdermal

System.

- **are breastfeeding**

  The hormone in the Estradiol Transdermal System can pass into your breast milk.

  Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how the Estradiol Transdermal System works. The Estradiol Transdermal System may also affect how your other medicines work. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get new medicine.

How should I use the Estradiol Transdermal System? For detailed instructions, see the step-by-step instructions for using the Estradiol Transdermal System at the end of this Patient Information.

- Use the Estradiol Transdermal System exactly as your healthcare provider tells you to use it.
- The Estradiol Transdermal System is for skin use only.
- Change your patch 1 time each week or every 7 days.
- Apply your Estradiol Transdermal patch to a clean, dry area on your lower abdomen or buttocks. This area must be clean, dry, and free of powder, oil or lotion for your patch to stick to your skin.
- Apply your Estradiol Transdermal patch to a different area of your abdomen or your buttocks each time. Do not use the same application site 2 times in the same week.
- Do not apply the Estradiol Transdermal patch to your breasts.
- If you forget to apply a new Estradiol Transdermal patch, you should apply a new patch as soon as possible.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about the dose you are using and whether you still need treatment with the Estradiol Transdermal System.

How to Change the Estradiol Transdermal System

- When changing the Estradiol Transdermal System, peel off the used patch slowly from the skin.
- After removal of the Estradiol Transdermal System, people usually have either no adhesive residue or light adhesive residue. If any adhesive residue remains on your skin after removing the patch, allow the area to dry for 15 minutes. Then, gently rub the area with an oil-based cream or lotion to remove the adhesive from your skin.
- Keep in mind**, the new patch must be applied to a different skin area of your abdomen or buttocks.** This area must be clean, dry, and free of powder, oil or lotion. The same site should not be used again for at least 1 week after removal of the patch.

What are the possible side effects of the Estradiol Transdermal System?

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- heart attack
- stroke
- blood clots
- dementia
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary

- high blood pressure
- high blood sugar
- gallbladder disease
- liver problems
- changes in your thyroid hormone levels
- enlargement of benign tumors of the uterus (“fibroids”)

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- new breast lumps
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue

Less serious, but common side effects include:

- headache
- breast tenderness or pain
- irregular vaginal bleeding or spotting
- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection
- redness or irritation at the patch placement site

These are not all the possible side effects of the Estradiol Transdermal System. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effects that bother you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to Sandoz Inc. at 1-800-525-8747 or to FDA at 1-800-FDA-1088.

What can I do to lower my chances of a serious side effect with the Estradiol Transdermal System?

- Talk with your healthcare provider regularly about whether you should continue using the Estradiol Transdermal System.
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you.
- The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the uterus (womb).
- See your healthcare provider right away if you get vaginal bleeding while using the Estradiol Transdermal System.
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else.
- If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.

- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease.
- Ask your healthcare provider for ways to lower your chances of getting heart disease.

How should I store and throw away used Estradiol Transdermal System?

- Store Estradiol Transdermal System at room temperature 68°F to 77°F (20°C to 25°C).
- Do not store Estradiol Transdermal patches outside of their pouches. Apply immediately upon removal from the protective pouch.
- Used patches still contain estrogen. To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet.

Keep the Estradiol Transdermal System and all medicines out of the reach of children.

General information about the safe and effective use of the Estradiol Transdermal System.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use the Estradiol Transdermal System for conditions for which it was not prescribed. Do not give the Estradiol Transdermal patch to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about the Estradiol Transdermal System. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about the Estradiol Transdermal System that is written for health professionals.

For more information call the toll free number 1-800-525-8747.

What are the ingredients in the Estradiol Transdermal System?

Active ingredient: estradiol

Inactive ingredient: acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

Instructions for Use

The Estradiol Transdermal System

Read this Patient Information before you start using the Estradiol Transdermal System and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

You will need the following supplies: See Figure A.

Figure A

Step 1: Pick the days you will change your Estradiol Transdermal System.

You will need to change your patch 1 time each week or every 7 days.

Step 2. Remove the Estradiol Transdermal System from the pouch.

- Remove patch from its protective pouch by tearing at the notch (do not use scissors). **See Figure B.**
- Do not remove your patch from the protective pouch until you are ready to apply it.

Figure B

Step 3. Remove the adhesive liner. See Figure C.

- You will see that the Estradiol Transdermal System is an oval shaped clear patch that is attached to a thick, hard-plastic adhesive liner and covered by a clear, plastic film. **SeeFigure C**.

- To apply your patch you must first remove the protective, clear plastic film that is attached to the clear thicker plastic backing. **See Figure D.**
- There is a silver foil-sticker attached to the inside of the pouch. Do not remove the silver foil sticker from the pouch. **See Figure E.**

Figure C **Figure D** **Figure E**

Step 4. Placing the patch on your skin.

- Apply the sticky side of the patch to 1 of the areas of skin shown below. **See Figure F andFigure G.**
- **Avoid** touching the sticky side of the patch with your fingers.

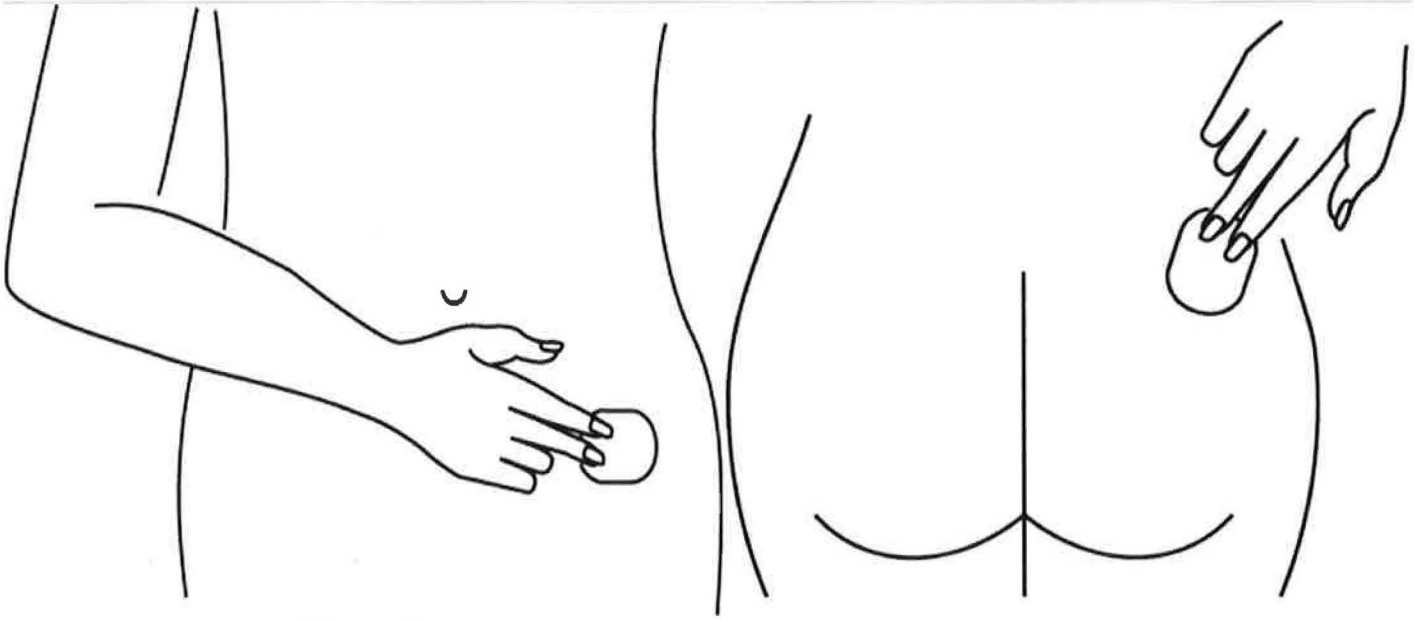


Figure F **Figure G**

Note:

- Avoid the waistline, since clothing and belts may cause the patch to be rubbed off.
- Do not apply the Estradiol Transdermal System to your breasts.
- Only apply the Estradiol Transdermal System to skin that is clean, dry, and free of any powder, oil, or lotion.
- You should not apply the patch to injured, burned, or irritated skin, or areas with skin conditions (such as birth marks, tattoos, or that is very hairy).

Step 5. Press the patch firmly onto your skin.

- Press the patch firmly in place with your fingers for at least 10 seconds
- Rub the edges of the patch to make sure that it will stick to your skin. **See Figure H.**

Figure H

Note:

- Contact with water while you are swimming, using a sauna, bathing, or showering may cause the patch to fall off.
- If your patch falls off reapply it. If you cannot reapply the patch, apply a new patch to another area (**see Figures F and G**), and continue to follow your original application schedule.
- If you stop using your Estradiol Transdermal System patch or forget to apply a new patch as scheduled, you may have spotting, or bleeding, and your symptoms may come back.

Step 6: Throwing away your used patch.

- When it is time to change your patch, remove the old patch before you apply a new patch.
- To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet.

This Patient Information and Instructions for Use have been approved by the U.S Food and Drug Administration.

Rev. Jun 2020

Manufactured by:

Kindeva Drug Delivery L.P.

Northridge, CA 91324

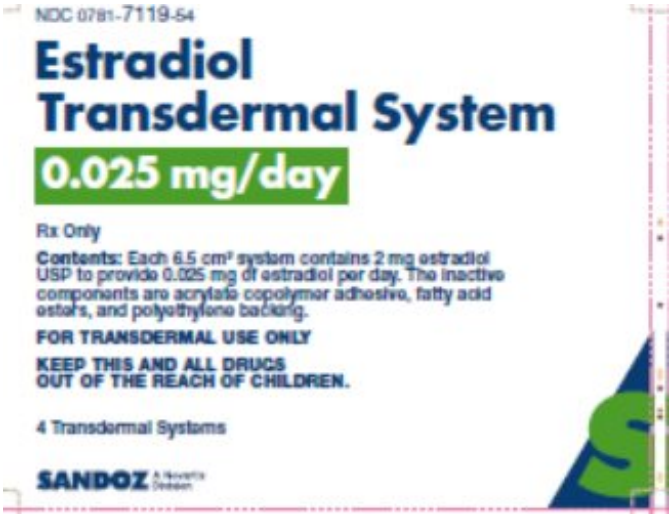
Distributed by:

Sandoz Inc.

Princeton, NJ 08540

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7119-54
  4 transdermal systems
  Estradiol Transdermal System
  0.025 mg/day
  Contents: Each 6.5 cm2 system contains 2 mg estradiol USP to provide 0.025 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.
  For transdermal use only.
  Keep this and all drugs out of the reach of children.
  Rx only



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7122-54
  4 transdermal systems
  Estradiol Transdermal System
  0.0375 mg/day
  Contents: Each 9.375 cm2 system contains 2.85 mg estradiol USP to provide 0.0375 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.
  For transdermal use only.
  Keep this and all drugs out of the reach of children.
  Rx only

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7133-54
  4 transdermal systems
  Estradiol Transdermal System
  0.05 mg/day
  Contents: Each 12.5 cm2 system contains 3.8 mg estradiol USP to provide 0.05 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.
  For transdermal use only.
  Keep this and all drugs out of the reach of children.
  Rx only

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7134-54
  4 transdermal systems
  Estradiol Transdermal System

0.06 mg/day

Contents: Each 15 cm2 system contains 4.55 mg estradiol USP to provide 0.06 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

For transdermal use only.

Keep this and all drugs out of the reach of children.

Rx only

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7136-54

  4 transdermal systems

  Estradiol Transdermal System

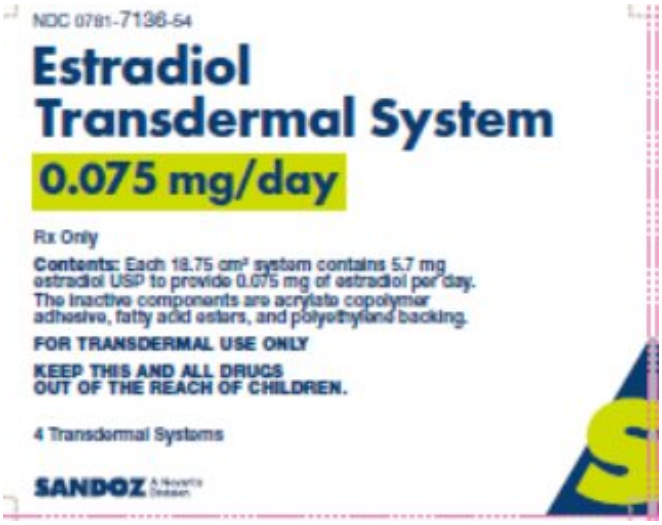
  0.075 mg/day

  Contents: Each 18.75 cm2 system contains 5.7 mg estradiol USP to provide 0.075 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.

  For transdermal use only.

  Keep this and all drugs out of the reach of children.

  Rx only



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

- NDC 0781-7104-54
  4 transdermal systems
  Estradiol Transdermal System
  0.1 mg/day
  Contents: Each 25 cm2 system contains 7.6 mg estradiol USP to provide 0.1 mg of estradiol per day. The inactive components are acrylate copolymer adhesive, fatty acid esters, and polyethylene backing.
  For transdermal use only.
  Keep this and all drugs out of the reach of children.
  Rx only

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0781-7109

Route of Administration	TRANSDERMAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.025 mg in 1 d

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0781-7119-54	4 in 1 CARTON	08/31/2018	
1	NDC:0781-7119-58	7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA020375	03/05/1999	

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-7122
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.0375 mg in 1 d

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0781-7122-54	4 in 1 CARTON	08/31/2018	
1	NDC:0781-7122-58	7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA020375	05/27/2003	

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-7133
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.05 mg in 1 d

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0781-7133-54	4 in 1 CARTON	08/31/2018	
1	NDC:0781-7133-58	7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
NDA authorized generic	NDA020375	12/22/1994	

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-7134
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.06 mg in 1 d

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0781-7134-54	4 in 1 CARTON	08/31/2018	
1	NDC:0781-7134-58	7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**

NDA authorized generic	NDA020375	01/03/2008	

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-7136
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.075 mg in 1 d

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0781-7136-54	4 in 1 CARTON	08/31/2018	
1	NDC:0781-7136-58	7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
NDA authorized generic	NDA020375	03/23/1998	

ESTRADIOL TRANSDERMAL SYSTEM

estradiol patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0781-7104
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	0.1 mg in 1 d

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0781-7104-54	4 in 1 CARTON	08/31/2018	
1	NDC:0781-7104-58	7 d in 1 PATCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA020375	12/22/1994	

Labeler - Sandoz Inc (005387188)

Registrant - Bayer HealthCare Pharmaceuticals Inc. (005436809)

Establishment

Name	Address	ID/FEI	Business Operations
Kindeva Drug Delivery L.P		128688199	ANALYSIS(0781-7119, 0781-7122, 0781-7133, 0781-7134, 0781-7136, 0781-7104) , MANUFACTURE(0781-7119, 0781-7122, 0781-7133, 0781-7134, 0781-7136, 0781-7104)

Revised: 6/2020 Sandoz Inc

Exhibit

I

PROGESTERONE- progesterone capsule
Akorn, Inc.

Progesterone
Capsules 100 mg
Capsules 200 mg

Rx only

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA FOR ESTROGEN PLUS PROGESTIN THERAPY

Cardiovascular Disorders and Probable Dementia

Estrogens plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS**, **Cardiovascular disorders** and **Probable dementia**.)

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders**.)

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable dementia and PRECAUTIONS, Geriatric Use**.)

Breast Cancer

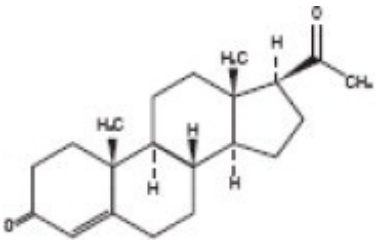
The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. (See **CLINICAL STUDIES** and **WARNINGS, Malignant neoplasms, *Breast Cancer***.)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Progestins with estrogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Progesterone Capsules contain micronized progesterone for oral administration. Progesterone has a molecular weight of 314.47 and a molecular formula of $C_{21}H_{30}O_2$. Progesterone (pregn-4-ene-3, 20-dione) is a white or creamy white, odorless, crystalline powder practically insoluble in water, soluble in alcohol, acetone and dioxane and sparingly soluble in vegetable oils, stable in air, melting between 126° and 131°C. The structural formula is:



Progesterone is synthesized from a starting material from a plant source and is chemically identical to progesterone of human ovarian origin. Progesterone Capsules are available in multiple strengths to afford dosage flexibility for optimum management. Progesterone Capsules contain 100 mg or 200 mg micronized progesterone, USP.

The inactive ingredients for Progesterone Capsules 100 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C Yellow No. 10, and FD&C Red No. 40.

The inactive ingredients for Progesterone Capsules 200 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, and titanium dioxide USP.

CLINICAL PHARMACOLOGY

Progesterone Capsules are an oral dosage form of micronized progesterone which is chemically identical to progesterone of ovarian origin. The oral bioavailability of progesterone is increased through micronization.

Pharmacokinetics

A. Absorption

After oral administration of progesterone as a micronized soft-gelatin capsule formulation, maximum serum concentrations were attained within 3 hours. The absolute bioavailability of micronized progesterone is not known. Table 1 summarizes the mean pharmacokinetic parameters in postmenopausal women after five oral daily doses of Progesterone Capsules 100 mg as a micronized soft-gelatin capsule formulation.

TABLE 1. Pharmacokinetic Parameters of Progesterone

Parameter	Progesterone Capsules Daily Dose		
	100 mg	200 mg	300 mg
C_{max} (ng/mL)	17.3±21.9[a]	38.1±37.8	60.6±72.5
T_{max} (hr)	1.5±0.8	2.3±1.4	1.7±0.6
$AUC_{(0-10)}$ (ng-hr/mL)	43.3±30.8	101.2±66.0	175.7±170.3

[a]Mean±S.D.

Serum progesterone concentrations appeared linear and dose proportional following multiple dose administration of Progesterone Capsules 100 mg over the dose range 100 mg per day to 300 mg per day in postmenopausal women. Although doses greater than 300 mg per day were not studied in females, serum concentrations from a study in male volunteers appeared linear and dose proportional between 100 mg per day and 400 mg per day. The pharmacokinetic parameters in male volunteers were generally consistent with those seen in postmenopausal women.

B. Distribution

Progesterone is approximately 96 percent to 99 percent bound to serum proteins, primarily to serum albumin (50 to 54 percent) and transcortin (43 to 48 percent).

C. Metabolism

Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further metabolized in the intestine via reduction, dehydroxylation, and epimerization.

D. Excretion

The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. Progesterone metabolites are eliminated mainly by the kidneys. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.

E. Special Populations

The pharmacokinetics of Progesterone Capsules have not been assessed in low body weight or obese patients.

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of Progesterone Capsules has not been studied.

Renal Insufficiency: The effect of renal impairment on the pharmacokinetics of Progesterone Capsules has not been studied.

F. Food–Drug Interaction

Concomitant food ingestion increased the bioavailability of Progesterone Capsules relative to a fasting state when administered to postmenopausal women at a dose of 200 mg.

G. Drug Interactions

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC50 <0.1 µM). Ketoconazole is a known inhibitor of cytochrome P450 3A4, hence these data suggest that ketoconazole or other known inhibitors of this enzyme may increase the bioavailability of progesterone. The clinical relevance of the *in vitro* findings is unknown.

Coadministration of conjugated estrogens and Progesterone Capsules to 29 postmenopausal women over a 12-day period resulted in an increase in total estrone concentrations (Cmax 3.68 ng/mL to 4.93 ng/mL) and total equilin concentrations (Cmax 2.27 ng/mL to 3.22 ng/mL) and a decrease in circulating 17ß estradiol concentrations (Cmax 0.037 ng/mL to 0.030 ng/mL). The half-life of the conjugated estrogens was similar with coadministration of Progesterone Capsules. Table 2 summarizes the pharmacokinetic parameters.

TABLE 2. Mean (± S.D.)Pharmacokinetic Parameters for Estradiol, Estrone, and Equilin Following Coadministration of Conjugated Estrogens 0.625 mg and Progesterone Capsules 200 mg for 12 Days to Postmenopausal Women

	Conjugated Estrogens			Conjugated Estrogens plus Progesterone Capsules		
Drug	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0-24h)}$ (ng•h/mL)	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0-24h)}$ (ng•h/mL)
Estradiol	0.037 ± 0.048	12.7 ± 9.1	0.676 ± 0.737	0.030 ± 0.032	17.32 ± 1.21	0.561 ± 0.572
Estrone Total[a]	3.68 ± 1.55	10.6 ± 6.8	61.3 ± 26.36	4.93 ± 2.07	7.5 ± 3.8	85.9 ± 41.2
Equilin Total[a]	2.27 ± 0.95	6.0 ± 4.0	28.8 ± 13.0	3.22 ± 1.13	5.3 ± 2.6	38.1 ± 20.2

[a]Total estrogens is the sum of conjugated and unconjugated estrogen.

Clinical Studies

Effects on the endometrium

In a randomized, double-blind clinical trial, 358 postmenopausal women, each with an intact uterus, received treatment for up to 36 months. The treatment groups were: Progesterone Capsules at the dose of 200 mg per day for 12 days per 28-day cycle in combination with conjugated estrogens 0.625 mg per day (n=120); conjugated estrogens 0.625 mg per day only (n=119); or placebo (n=119). The subjects in all three treatment groups were primarily Caucasian women (87 percent or more of each group). The results for the incidence of endometrial hyperplasia in women receiving up to 3 years of treatment are shown in Table 3. A comparison of the Progesterone Capsules plus conjugated estrogens treatment group to the conjugated estrogens only group showed a significantly lower rate of hyperplasia (6 percent combination product versus 64 percent estrogen alone) in the Progesterone Capsules plus conjugated estrogens treatment group throughout 36 months of treatment.

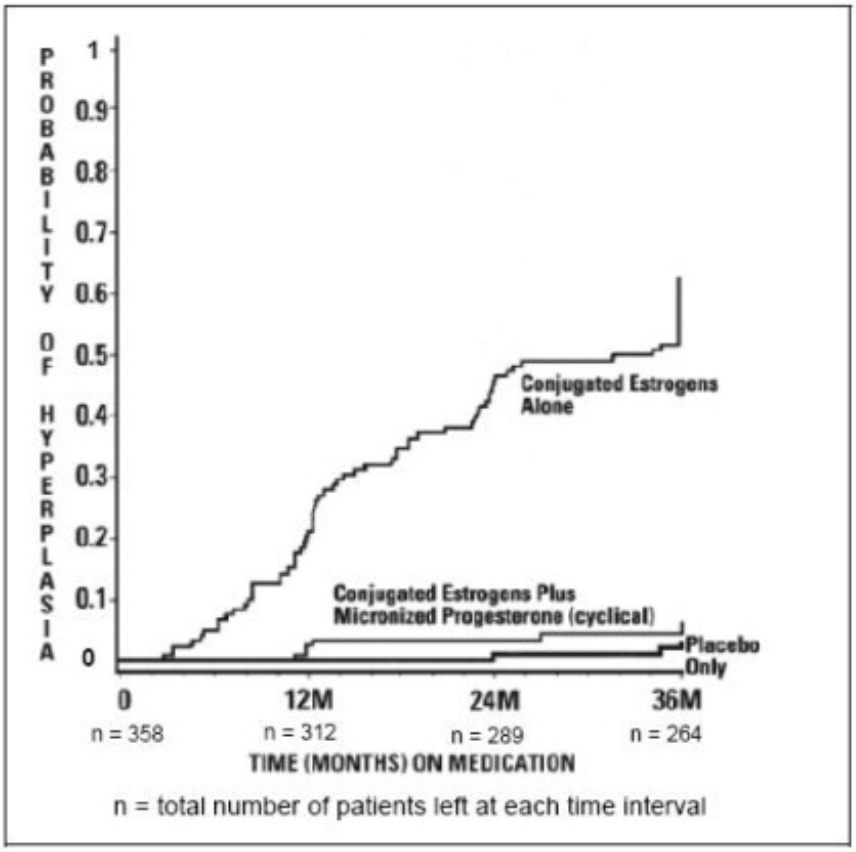
TABLE 3. Incidence of Endometrial Hyperplasia in Women Receiving 3 Years of Treatment

Endometrial Diagnosis	Treatment Group					
	Conjugated Estrogens 0.625 mg +Progesterone Capsules 200 mg (cyclical)		Conjugated Estrogens 0.625 mg (alone)		Placebo	
	Number of patients	% of patients	Number of patients	% of patients	Number of patients	% of patients
	n=117		n=115		n=116	
HYPERPLASIA[a]	7	6	74	64	3	3
Adenocarcinoma	0	0	0	0	1	1
Atypical hyperplasia	1	1	14	12	0	0
Complex hyperplasia	0	0	27	23	1	1
Simple Hyperplasia	6	5	33	29	1	1

[a]Most advanced result to least advanced result:
Adenocarcinoma > atypical hyperplasia > complex hyperplasia > simple hyperplasia

The times to diagnosis of endometrial hyperplasia over 36 months of treatment are shown in Figure 1. This figure illustrates graphically that the proportion of patients with hyperplasia was significantly greater for the conjugated estrogens group (64 percent) compared to the conjugated estrogens plus Progesterone Capsules group (6 percent).

FIGURE 1 Time to Hyperplasia in Women Receiving up to 36 Months of Treatment



The discontinuation rates due to hyperplasia over the 36 months of treatment are as shown in Table 4. For any degree of hyperplasia, the discontinuation rate for patients who received conjugated estrogens plus Progesterone Capsules was similar to that of the placebo only group, while the discontinuation rate for patients who received conjugated estrogens alone was significantly higher. Women who permanently discontinued treatment due to hyperplasia were similar in demographics to the overall study population.

TABLE 4. Discontinuation Rate Due to Hyperplasia Over 36 Months of Treatment

Most Advanced Biopsy Result Through 36 Months of Treatment	Treatment Group					
	Conjugated Estrogens +Progesterone Capsules (cyclical)		Conjugated Estrogens (alone)		Placebo	
	n=120		n=119		n=119	
	Number of patients	% of patients	Number of patients	% of patients	Number of patients	% of patients
Adenocarcinoma	0	0	1	1	1	1
Atypical hyperplasia	1	1	10	8	1	1
Complex hyperplasia	0	0	21	18	1	1
Simple hyperplasia	1	1	13	11	1	1

Effects on secondary amenorrhea

In a single-center, randomized, double-blind clinical study that included premenopausal women with secondary amenorrhea for at least 90 days, administration of 10 days of Progesterone Capsules therapy

resulted in 80 percent of women experiencing withdrawal bleeding within 7 days of the last dose of Progesterone Capsules, 300 mg per day (n=20), compared to 10 percent of women experiencing withdrawal bleeding in the placebo group (n=21).

In a multicenter, parallel-group, open label, postmarketing dosing study that included premenopausal women with secondary amenorrhea for at least 90 days, administration of 10 days of Progesterone Capsules during two 28-day treatment cycles, 300 mg per day (n=107) or 400 mg per day (n=99), resulted in 73.8 percent and 76.8 percent of women, respectively, experiencing withdrawal bleeding.

The rate of secretory transformation was evaluated in a multicenter, randomized, double-blind clinical study in estrogen-primed postmenopausal women. Progesterone Capsules administered orally for 10 days at 400 mg per day (n=22) induced complete secretory changes in the endometrium in 45 percent of women compared to 0 percent in the placebo group (n=23).

A second multicenter, parallel-group, open label postmarketing dosing study in premenopausal women with secondary amenorrhea for at least 90 days also evaluated the rate of secretory transformation. All subjects received daily oral conjugated estrogens over 3 consecutive 28-day treatment cycles and Progesterone Capsules, 300 mg per day (n=107) or 400 mg per day (n=99) for 10 days of each treatment cycle. The rate of complete secretory transformation was 21.5 percent and 28.3 percent, respectively.

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral conjugated estrogens (CE) [0.625 mg] alone or in combination with medroxyprogesterone acetate (MPA) [2.5 mg] compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease [(CHD) defined as nonfatal myocardial infarction (MI), silent MI and CHD death], with invasive breast cancer as the primary adverse outcome. A “global index” included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other cause. These sub studies did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the “global index.” The absolute excess risk of events in the “global index” was 19 per 10,000 women-years.

For those outcomes included in the WHI “global index” that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 5. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

TABLE 5. Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]

Event	Relative Risk CE/MPA versus Placebo (95% nCI [c])	CE/MPA n=8,506	Placebo n=8,102
		Absolute Risk per 10,000 Women-years	
CHD events	1.23 (0.99-1.53)	41	34
Non-fatal MI	*1.28 (1.00-1.63)*	*31*	*25*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All stroke	1.31 (1.03-1.68)	33	25
Ischemic stroke	1.44 (1.09-1.90)	26	18
Deep vein thrombosis [d]	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer [e]	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer [d]	0.81 (0.48-1.36)	6	7
Cervical cancer [d]	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures [d]	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures [d]	0.71 (0.59-0.85)	44	62
Total fractures [d]	0.76 (0.69-0.83)	152	199
Overall mortality [f]	1.00 (0.83-1.19)	52	52
Global Index [g]	1.13 (1.02-1.25)	184	165

a Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
b Results are based on centrally adjudicated data..
c Nominal confidence intervals unadjusted for multiple looks and multiple comparisons..
d Not included in Global Index..
e Includes metastatic and non-metastatic breast cancer with the exception of *in situ* breast cancer..
f All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease..
g A subset of the events was combined in a “global index” defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified for age showed in women 50 to 59 years of age a non-significant trend toward reducing risk of overall mortality [hazard ratio (HR) 0.69 (95 percent CI, 0.44-1.07)].

Women's Health Initiative Memory Study

The estrogen plus progestin Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years of age; and 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21 – 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Probable dementia** and **PRECAUTIONS, Geriatric Use**.)

INDICATIONS AND USAGE

Progesterone Capsules are indicated for use in the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogens tablets. They are also indicated for use in secondary amenorrhea.

CONTRAINDICATIONS

Progesterone Capsules should not be used in women with any of the following conditions:

1. **Progesterone Capsules should not be used in patients with known hypersensitivity to its ingredients. Progesterone Capsules contain peanut oil and should never be used by patients allergic to peanuts.**
2. Undiagnosed abnormal genital bleeding.
3. Known, suspected, or history of breast cancer.
4. Active deep vein thrombosis, pulmonary embolism or history of these conditions.
5. Active arterial thromboembolic disease (for example, stroke and myocardial infarction), or a history of these conditions.
6. Known liver dysfunction or disease.
7. Known or suspected pregnancy.

WARNINGS

See **BOXED WARNING.**

1. Cardiovascular disorders

An increased risk of pulmonary embolism, deep vein thrombosis (DVT), stroke, and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history or family history of venous thromboembolism [VTE], obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Stroke

In the Women's Health Initiative (WHI) estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted. (See **CLINICAL STUDIES**.) Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

b. Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction [MI], silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1 and a trend toward decreasing relative risk was reported in years 2 through 5. (See **CLINICAL STUDIES.**)

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg)

demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one (2,321) women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

c. Venous Thromboembolism (VTE)

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and pulmonary embolism [PE]) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See **CLINICAL STUDIES**.) Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens with progestins should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

a. Breast cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the Women's Health Initiative (WHI) substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24 (95 percent nCI, 1.01-1.54), and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo.

Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups. (See **CLINICAL STUDIES**.)

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare

provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

b. Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

c. Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent nCI, 0.77 – 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies and some report no association.

3. Probable Dementia

In the estrogen plus progestin Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

In the WHIMS estrogen plus progestin ancillary study, after an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestin versus placebo was 2.05 (95 percent CI 1.21– 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

4. Vision abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogen. Discontinue estrogen plus progestin therapy pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, estrogen plus progestin therapy should be permanently discontinued.

PRECAUTIONS

A. General

1. Addition of a progestin when a woman has not had a hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily

with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared with estrogen-alone regimens. These include an increased risk of breast cancer.

2. Fluid Retention

Progesterone may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation.

3. Dizziness and Drowsiness

Progesterone Capsules may cause transient dizziness and drowsiness and should be used with caution when driving a motor vehicle or operating machinery. Progesterone Capsules should be taken as a single daily dose at bedtime.

B. Patient Information

General: This product contains peanut oil and should not be used if you are allergic to peanuts.

Physicians are advised to discuss the contents of the Patient Information leaflet with patients for whom they prescribe Progesterone Capsules.

C. Drug-Laboratory Test Interactions

The following laboratory results may be altered by the use of estrogen plus progestin therapy:

- Increased sulfobromophthalein retention and other hepatic function tests.
- Coagulation tests: increase in prothrombin factors VII, VIII, IX and X.
- Pregnanediol determination.
- Thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T3 uptake values.

D. Carcinogenesis, Mutagenesis, Impairment of Fertility

Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors and endometrial stromal sarcomas. In dogs, long-term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen.

Progesterone did not show evidence of genotoxicity in *in vitro* studies for point mutations or for chromosomal damage. *In vivo* studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg. Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would impair fertility until the cessation of treatment.

E. Pregnancy

Progesterone Capsules should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

Pregnancy Category B: Reproductive studies have been performed in mice at doses up to 9 times the human oral dose, in rats at doses up to 44 times the human oral dose, in rabbits at a dose of 10 mcg/day delivered locally within the uterus by an implanted device, in guinea pigs at doses of approximately one-half the human oral dose and in rhesus monkeys at doses approximately the human dose, all based on body surface area, and have revealed little or no evidence of impaired fertility or harm to the fetus due to progesterone.

F. Nursing Women

Detectable amounts of progestin have been identified in the milk of nursing women receiving progestins. Caution should be exercised when Progesterone Capsules are administered to a nursing woman.

G. Pediatric Use

Progesterone Capsules are not indicated in children. Clinical studies have not been conducted in the pediatric population.

H. Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Progesterone Capsules to determine whether those over 65 years of age differ from younger subjects in their response to Progesterone Capsules.

The Women's Health Initiative Study

In the Women's Health Initiative (WHI) estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders** and **Malignant neoplasms**.)

The Women's Health Initiative Memory Study

In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in the estrogen plus progestin ancillary study when compared to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Probable dementia**.)

ADVERSE REACTIONS

See **BOXED WARNING, WARNINGS** and **PRECAUTIONS.**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a multicenter, randomized, double-blind, placebo-controlled clinical trial, the effects of Progesterone Capsules on the endometrium was studied in a total of 875 postmenopausal women. Table 6 lists adverse reactions greater than or equal to 2 percent of women who received cyclic Progesterone Capsules 200 mg daily (12 days per calendar month cycle) with 0.625 mg conjugated estrogens or placebo.

TABLE 6. Adverse Reactions (≥2%) Reported in an 875 Patient Placebo-Controlled Trial in Postmenopausal Women Over a 3-Year Period [Percentage (%) of Patients Reporting]

	Progesterone Capsules 200 mg with Conjugated Estrogens 0.625 mg	Placebo
	(n=178)	(n=174)
Headache	31	27
Breast Tenderness	27	6
Joint Pain	20	29
Depression	19	12
Dizziness	15	9
Abdominal Bloating	12	5
Hot Flashes	11	35
Urinary Problems	11	9
Abdominal Pain	10	10
Vaginal Discharge	10	3
Nausea/Vomiting	8	7
Worry	8	4
Chest Pain	7	5
Diarrhea	7	4
Night Sweats	7	17
Breast Pain	6	2
Swelling of Hands and Feet	6	9
Vaginal Dryness	6	10
Constipation	3	2
Breast Carcinoma	2	<1
Breast Excisional Biopsy	2	<1
Cholecystectomy	2	<1

Effects on Secondary Amenorrhea

In a multicenter, randomized, double-blind, placebo-controlled clinical trial, the effects of Progesterone on secondary amenorrhea was studied in 49 estrogen-primed postmenopausal women. Table 7 lists adverse reactions greater than or equal to 5 percent of women who received Progesterone capsules or placebo.

TABLE 7. Adverse Reactions (≥5%) Reported in Patients Using 400 mg/day in a Placebo-Controlled Trial in Estrogen-Primed Postmenopausal Women

Adverse Experience	Progesterone Capsules 400 mg	Placebo
	n=25	n=24
	Percentage (%) of Patients	
Fatigue	8	4
Headache	16	8
Dizziness	24	4
Abdominal Distention (Bloating)	8	8
Abdominal Pain (Cramping)	20	13
Diarrhea	8	4
Nausea	8	0
Back Pain	8	8
Musculoskeletal Pain	12	4
Irritability	8	4
Breat Pain	16	8
Infection Viral	12	0
Coughing	8	0

In a multicenter, parallel-group, open label postmarketing dosing study consisting of three consecutive 28 day treatment cycles, 220 premenopausal women with secondary amenorrhea were randomized to receive daily conjugated estrogens therapy (0.625 mg conjugated estrogens) and Progesterone Capsules, 300 mg per day (n=113) or Progesterone Capsules, 400 mg per day (n=107) for 10 days of each treatment cycle. Overall, the most frequently reported treatment-emergent adverse reactions, reported in greater than or equal to 5 percent of subjects, were nausea, fatigue, vaginal mycosis, nasopharyngitis, upper respiratory tract infection, headache, dizziness, breast tenderness, abdominal distension, acne, dysmenorrhea, mood swing, and urinary tract infection.

Postmarketing Experience:

The following additional adverse reactions have been reported with Progesterone Capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Genitourinary System: endometrial carcinoma, hypospadia, intra-uterine death, menorrhagia, menstrual disorder, metrorrhagia, ovarian cyst, spontaneous abortion.

Cardiovascular: circulatory collapse, congenital heart disease (including ventricular septal defect and patent ductus arteriosus), hypertension, hypotension, tachycardia.

Gastrointestinal: acute pancreatitis, cholestasis, cholestatic hepatitis, dysphagia, hepatic failure, hepatic necrosis, hepatitis, increased liver function tests (including alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased), jaundice, swollen tongue.

Skin: alopecia, pruritus, urticaria.

Eyes: blurred vision, diplopia, visual disturbance.

Central Nervous System: aggression, convulsion, depersonalization, depressed consciousness,

disorientation, dysarthria, loss of consciousness, paresthesia, sedation, stupor, syncope (with and without hypotension), transient ischemic attack, suicidal ideation.

During initial therapy, a few women have experienced a constellation of many or all of the following symptoms: extreme dizziness and/or drowsiness, blurred vision, slurred speech, difficulty walking, loss of consciousness, vertigo, confusion, disorientation, feeling drunk, and shortness of breath.

Miscellaneous: abnormal gait, anaphylactic reaction, arthralgia, blood glucose increased, choking, cleft lip, cleft palate, difficulty walking, dyspnea, face edema, feeling abnormal, feeling drunk, hypersensitivity, asthma, muscle cramp, throat tightness, tinnitus, vertigo, weight decreased, weight increased.

OVERDOSAGE

No studies on overdosage have been conducted in humans. In the case of overdosage, Progesterone Capsules should be discontinued and the patient should be treated symptomatically.

DOSAGE AND ADMINISTRATION

Prevention of Endometrial Hyperplasia

Progesterone Capsules should be given as a single daily dose at bedtime, 200 mg orally for 12 days sequentially per 28-day cycle, to a postmenopausal woman with a uterus who is receiving daily conjugated estrogens tablets.

Treatment of Secondary Amenorrhea

Progesterone Capsules may be given as a single daily dose of 400 mg at bedtime for 10 days.

Some women may experience difficulty swallowing Progesterone Capsules. For these women, Progesterone Capsules should be taken with a glass of water while in the standing position.

HOW SUPPLIED

Progesterone Capsules 100 mg are round, pink-colored capsules branded with black imprint “AK”

NDC 17478-766-10 ..... (Bottle of 100)

Progesterone Capsules 200 mg are oval, beige-colored capsules branded with black imprint “AK2”

NDC 17478-767-10 ..... (Bottle of 100)

PATIENT INFORMATION

Read this PATIENT INFORMATION before you start taking Progesterone Capsules and read what you get each time you refill your Progesterone Capsules prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT PROGESTERONE CAPSULES (A Progesterone Hormone)?

- Progestins with estrogens should not be used to prevent heart disease, heart attacks, strokes, or dementia.
- Using progestins with estrogens may increase your chance of getting heart attacks, strokes, breast cancer, and blood clots.
- Using progestins with estrogens may increase your chance of getting dementia, based on a study of women age 65 and older.

- You and your healthcare provider should talk regularly about whether you still need treatment with Progesterone Capsules.

THIS PRODUCT CONTAINS PEANUT OIL AND SHOULD NOT BE USED IF YOU ARE ALLERGIC TO PEANUTS.

What is Progesterone Capsules?

Progesterone Capsules contain the female hormone called progesterone.

What is Progesterone Capsules used for?

Treatment of Menstrual Irregularities

Progesterone Capsules are used for the treatment of secondary amenorrhea (absence of menstrual periods in women who have previously had a menstrual period) due to a decrease in progesterone. When you do not produce enough progesterone, menstrual irregularities can occur. If your healthcare provider has determined your body does not produce enough Progesterone on its own, Progesterone Capsules may be prescribed to provide the progesterone you need.

Protection of the Endometrium (Lining of the Uterus)

Progesterone Capsules are used in combination with estrogen-containing medications in a postmenopausal woman with a uterus (womb). Taking estrogen-alone increases the chance of developing a condition called endometrial hyperplasia that may lead to cancer of the lining of the uterus (womb). The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb).

Who should not take Progesterone Capsules?

Do not start taking Progesterone Capsules if you:

- **Are allergic to peanuts**
- **Have unusual vaginal bleeding**
- **Currently have or have had certain cancers**

Estrogen plus progestin treatment may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should take Progesterone Capsules.

- **Had a stroke or heart attack**
- **Currently have or have had blood clots**
- **Currently have or have had liver problems**
- **Are allergic to Progesterone Capsules or any of its ingredients**

See the list of ingredients in Progesterone Capsules at the end of this leaflet.

- **Think you may be pregnant**

Tell your healthcare provider:

- **If you are breastfeeding.** The hormone in Progesterone Capsules can pass into your breast milk.
- **About all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, problems with your heart, liver, thyroid, or kidneys, or have high calcium levels in your blood.
- **About all the medicines you take.** This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Progesterone Capsules work. Progesterone Capsules may also affect how your other medicines work.

How should I take Progesterone Capsules?

1. Prevention of Endometrial Hyperplasia: A postmenopausal woman with a uterus who is taking estrogens should take a single daily dose of 200 mg Progesterone Capsules at bedtime for 12 continuous days per 28-day cycle.
2. Secondary Amenorrhea: Progesterone Capsules may be given as a single daily dose of 400 mg at bedtime for 10 days.
3. **Progesterone Capsules are to be taken at bedtime as some women become very drowsy and/or dizzy after taking Progesterone Capsules. In a few cases, symptoms may include blurred vision, difficulty speaking, difficulty with walking, and feeling abnormal. If you experience these symptoms, discuss them with your healthcare provider right away.**
4. If you experience difficulty in swallowing Progesterone Capsules, it is recommended that you take your daily dose at bedtime with a glass of water while in the standing position.

What are the possible side effects of Progesterone Capsules?

Side effects are grouped by how serious they are and how often they happen when you are treated:

Serious but less common side effects include:

- ***Risk to the Fetus:*** Cases of cleft palate, cleft lip, hypospadias, ventricular septal defect, patent ductus arteriosus, and other congenital heart defects.
- ***Abnormal Blood Clotting:*** Stroke, heart attack, pulmonary embolus, visual loss or blindness.

Some of the warning signs of serious side effects include:

- Changes in vision or speech
- Sudden new severe headaches
- Severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- Dizziness and faintness
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptoms that concern you.

Less serious, but common side effects include:

- Headaches
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach or abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

These are not all the possible side effects of Progesterone Capsules. For more information, ask your healthcare provider or pharmacist for advice about side effects. You may report side effects to Akorn, Inc. at 1-800-932-5676 or to FDA at 1-800-FDA-1088

What can I do to lower my chances of getting a serious side effect with Progesterone Capsules?

- Talk with your healthcare provider regularly about whether you should continue taking Progesterone Capsules.
- See your healthcare provider right away if you get unusual vaginal bleeding while taking Progesterone Capsules.
- Have a pelvic exam, breast exam, and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.

- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of Progesterone Capsules

- Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Progesterone Capsules for conditions for which it was not prescribed.
- Your healthcare provider has prescribed this drug for you and you alone. Do not give Progesterone Capsules to other people, even if they have the same symptoms you have. It may harm them.
- Progesterone Capsules should be taken as a single daily dose at bedtime. Some women may experience extreme dizziness and/or drowsiness during initial therapy. In a few cases, symptoms may include blurred vision, difficulty speaking, difficulty with walking, and feeling abnormal. If you experience these symptoms, discuss them with your healthcare provider right away.
- Use caution when driving a motor vehicle or operating machinery as dizziness or drowsiness may occur.

Keep Progesterone Capsules out of the reach of children.

This leaflet provides a summary of the most important information about Progesterone Capsules. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Progesterone Capsules that is written for health professionals. You can get more information by calling the toll free number 1-800-932-5676.

What are the ingredients in Progesterone Capsules?

Active ingredient: 100 mg or 200 mg micronized progesterone

The inactive ingredients for Progesterone Capsules 100 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C Yellow No. 10, and FD&C Red No.40.

The inactive ingredients for Progesterone Capsules 200 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, and titanium dioxide USP.

Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Protect from excessive moisture.
Call your doctor for medical advice about side effects. You may report side effects to Akorn, Inc. at 1-800-932-5676 or to FDA at 1-800-FDA-1088.

Dispense in tight, light-resistant container as defined in USP/NF, accompanied by a Patient Insert.

Keep out of reach of children.

Manufactured by USGP,
a division of PROCAPS for Akorn, Inc.
Lake Forest, IL 60045

Made in Columbia.
200014233
PCPR00N
Revision January 2017

Principal Display Panel Text for Container Label:

100 Capsules NDC 17478-766-10

PROGESTERONE

CAPSULES

100 mg

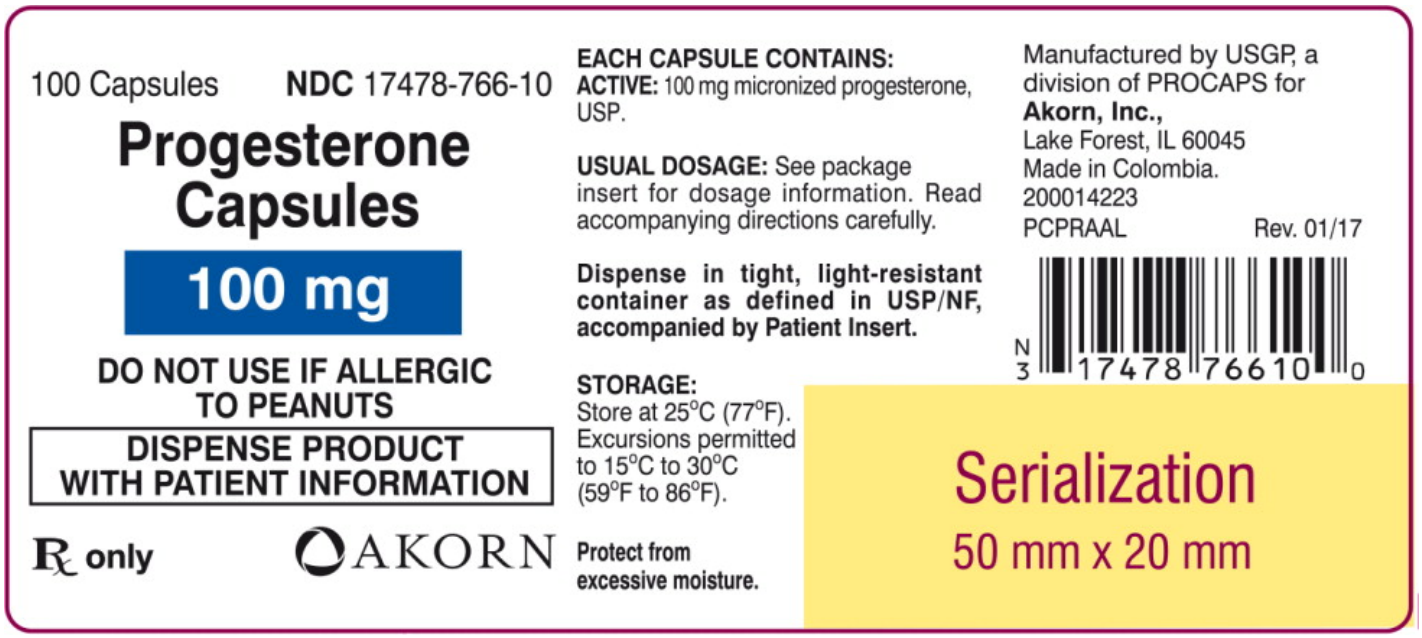
DO NOT USE IF ALLERGIC

TO PEANUTS

DISPENSE PRODUCT

WITH PATIENT INFORMATION

Rx only Akorn Logo



Principal Display Panel Text for Container Label:

100 Capsules NDC 17478-767-10

PROGESTERONE

CAPSULES

200 mg

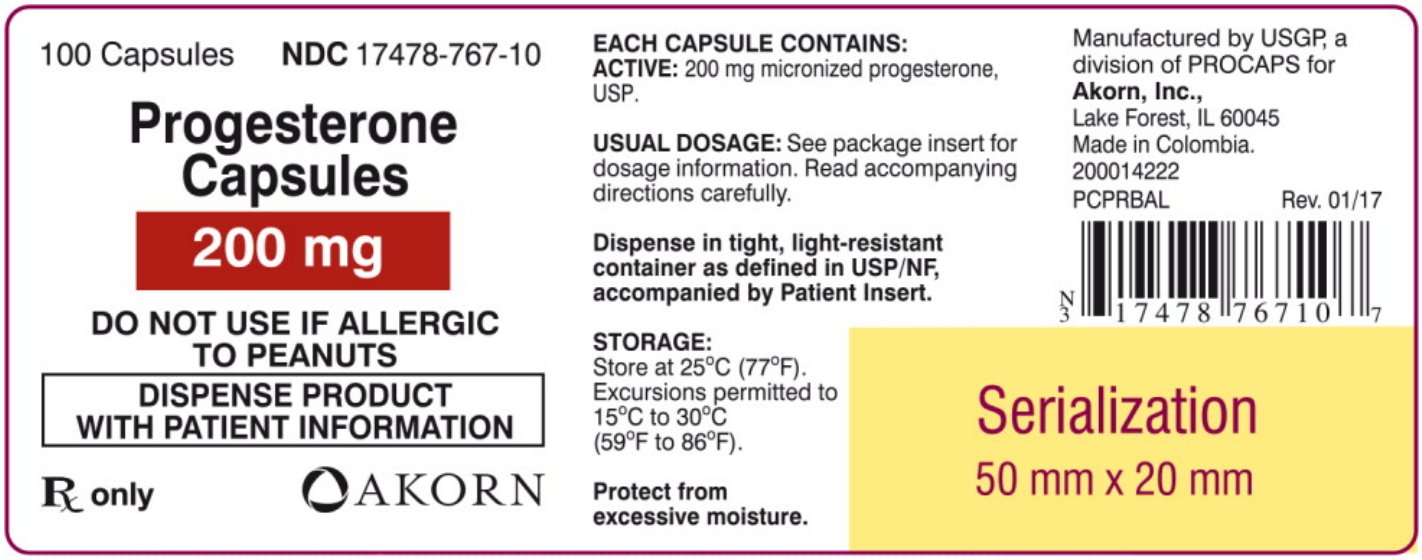
DO NOT USE IF ALLERGIC

TO PEANUTS

DISPENSE PRODUCT

WITH PATIENT INFORMATION

Rx only Akorn Logo



PROGESTERONE

progesterone capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:17478-766
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Progesterone (UNII: 4G7DS2Q64Y) (Progesterone - UNII:4G7DS2Q64Y)	Progesterone	100 mg

Inactive Ingredients	
Ingredient Name	**Strength**
Peanut Oil (UNII: 5TL50QU0W4)	
Gelatin (UNII: 2G86QN327L)	
Glycerin (UNII: PDC6A3C0OX)	
Lecithin, Soybean (UNII: 1DI56QDM62)	
Titanium Dioxide (UNII: 15FIX9V2JP)	
D&C Yellow No. 10 (UNII: 35SW5USQ3G)	
FD&C Red NO. 40 (UNII: WZB9127XOA)	

Product Characteristics			
Color	pink (pink)	**Score**	no score
Shape	ROUND (ROUND)	**Size**	9mm
Flavor		**Imprint Code**	AK
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:17478-766-10	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	10/04/2012	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200456	10/04/2012	

PROGESTERONE

progesterone capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:17478-767
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Progesterone (UNII: 4G7DS2Q64Y) (Progesterone - UNII:4G7DS2Q64Y)	Progesterone	200 mg

Inactive Ingredients

Ingredient Name	Strength
Peanut Oil (UNII: 5TL50QU0W4)	
Gelatin (UNII: 2G86QN327L)	
Glycerin (UNII: PDC6A3C0OX)	
Lecithin, Soybean (UNII: 1DI56QDM62)	
Titanium Dioxide (UNII: 15FIX9V2JP)	

Product Characteristics

Color	brown (beige)	**Score**	no score
Shape	OVAL (OVAL)	**Size**	14mm
Flavor		**Imprint Code**	AK2
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:17478-767-10	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	10/04/2012	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200456	10/04/2012	

Labeler - Akorn, Inc. (117696770)

Registrant - Akorn Operating Company LLC (117693100)

Revised: 10/2020 Akorn, Inc.

Exhibit

J

PROVERA- medroxyprogesterone acetate tablet
Pharmacia and Upjohn Company LLC

PROVERA®
(medroxyprogesterone acetate tablets, USP)

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA FOR ESTROGEN PLUS PROGESTIN THERAPY

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders** and **Probable Dementia.)**

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported an increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders.**)

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**.)

Breast Cancer

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer. (See **CLINICAL STUDIES** and **WARNINGS, Malignant Neoplasm, Breast Cancer.**)

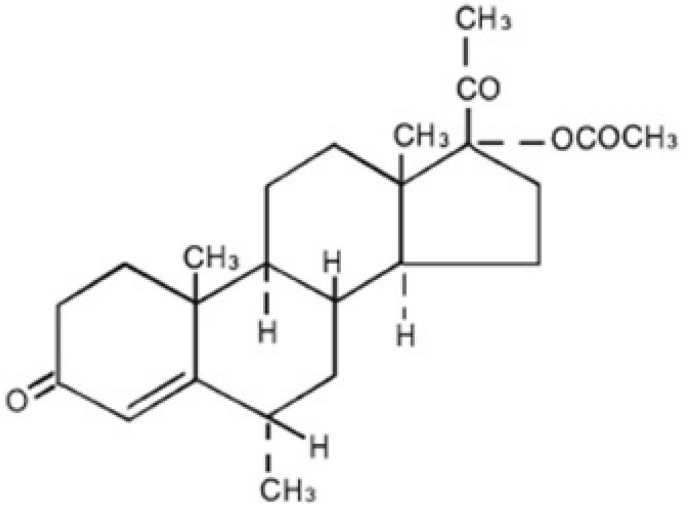
In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Progestins with estrogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

PROVERA® tablets contain medroxyprogesterone acetate, which is a derivative of progesterone. It is a white to off-white, odorless crystalline powder, stable in air, melting between 200 and 210°C. It is freely soluble in chloroform, soluble in acetone and in dioxane, sparingly soluble in alcohol and in methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6α)-. The structural formula is:



Each PROVERA tablet for oral administration contains 2.5 mg, 5 mg or 10 mg of medroxyprogesterone acetate.

Inactive ingredients:

2.5 mg tablets		
calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose, talc, FD&C Yellow No. 6.	OR	calcium stearate, corn starch, lactose, mineral oil, sucrose, talc, FD&C Yellow No. 6.
5 mg tablets		
calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose, talc.	OR	calcium stearate, corn starch, lactose, mineral oil, sucrose, talc, FD&C Blue No.2 – Aluminum Lake.
10 mg tablets		
calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose, talc.	OR	calcium stearate, corn starch, lactose, mineral oil, sucrose, talc.

CLINICAL PHARMACOLOGY

Medroxyprogesterone acetate (MPA) administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, transforms proliferative into secretory endometrium. Androgenic and anabolic effects have been noted, but the drug is apparently devoid of significant estrogenic activity. While parenterally administered MPA inhibits gonadotropin production, which in turn prevents follicular maturation and ovulation, available data indicate that this does not occur when the usually recommended oral dosage is given as single daily doses.

Pharmacokinetics

The pharmacokinetics of MPA were determined in 20 postmenopausal women following a single-dose administration of eight PROVERA 2.5 mg tablets or a single administration of two PROVERA 10 mg tablets under fasting conditions. In another study, the steady-state pharmacokinetics of MPA were determined under fasting conditions in 30 postmenopausal women following daily administration of one PROVERA 10 mg tablet for 7 days. In both studies, MPA was quantified in serum using a validated gas chromatography-mass spectrometry (GC-MS) method. Estimates of the pharmacokinetic parameters of MPA after single and multiple doses of PROVERA tablets were highly variable and are summarized in

Table 1.

Table 1. Mean (SD) Pharmacokinetic Parameters for Medroxyprogesterone Acetate (MPA)

Tablet Strength	C_{max} (ng/mL)	T_{max} (h)	$Auc_{0-(\infty)}$ (ng·h/mL)	$t_{1/2}$ (h)	Vd/f (L)	CL/f (mL/min)
Single Dose						
2 × 10 mg	1.01 (0.599)	2.65 (1.41)	6.95 (3.39)	12.1 (3.49)	78024 (47220)	64110 (42662)
8 × 2.5 mg	0.805 (0.413)	2.22 (1.39)	5.62 (2.79)	11.6 (2.81)	62748 (40146)	74123 (35126)
Multiple Dose						
10 mg *	0.71 (0.35)	2.83 (1.83)	6.01 (3.16)	16.6 (15.0)	40564 (38256)	41963 (38402)

* Following Day 7 dose

A. Absorption

No specific investigation on the absolute bioavailability of MPA in humans has been conducted. MPA is rapidly absorbed from the gastrointestinal tract, and maximum MPA concentrations are obtained between 2 to 4 hours after oral administration.

Administration of PROVERA with food increases the bioavailability of MPA. A 10 mg dose of PROVERA, taken immediately before or after a meal, increased MPA C_{max} (50 to 70%) and AUC (18 to 33%). The half-life of MPA was not changed with food.

B. Distribution

MPA is approximately 90% protein bound, primarily to albumin; no MPA binding occurs with sex hormone binding globulin.

C. Metabolism

Following oral dosing, MPA is extensively metabolized in the liver via hydroxylation, with subsequent conjugation and elimination in the urine.

D. Excretion

Most MPA metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates.

E. Specific Populations

Hepatic Insufficiency

MPA is almost exclusively eliminated via hepatic metabolism. In 14 patients with advanced liver disease, MPA disposition was significantly altered (reduced elimination). In patients with fatty liver, the mean percent dose excreted in the 24-hour urine as intact MPA after a 10 mg or 100 mg dose was 7.3% and 6.4%, respectively.

Renal Insufficiency

The effect of renal impairment on the pharmacokinetics of PROVERA has not been studied.

F. Drug Interactions

Medroxyprogesterone acetate (MPA) is metabolized in vitro primarily by hydroxylation via the

CYP3A4. Specific drug-drug interaction studies evaluating the clinical effects with CYP3A4 inducers or inhibitors on MPA have not been conducted. Inducers and/or inhibitors of CYP3A4 may affect the metabolism of MPA.

CLINICAL STUDIES

Effects on the Endometrium

In a 3-year, double-blind, placebo-controlled study of 356 nonhysterectomized, postmenopausal women between 45 and 64 years of age randomized to receive placebo (n=119), 0.625 mg conjugated estrogen only (n=119), or 0.625 mg conjugated estrogen plus cyclic PROVERA (n=118), results showed a reduced risk of endometrial hyperplasia in the treatment group receiving 10 mg PROVERA plus 0.625 mg conjugated estrogens compared to the group receiving 0.625 mg conjugated estrogens only. See Table 2.

Table 2. Number (%) of Endometrial Biopsy Changes Since Baseline After 3 Years of Treatment [*]

Histological Results	Placebo (n=119)	CEE [†] (n=119)	PROVERA [‡] + CEE (n=118)
Normal/No hyperplasia (%)	116 (97)	45 (38)	112 (95)
Simple (cystic) hyperplasia (%)	1 (1)	33 (28)	4 (3)
Complex (adenomatous) hyperplasia (%)	1 (1)	27 (22)	2 (2)
Atypia (%)	0	14 (12)	0
Adenocarcinoma (%)	1 (1)	0	0

[*] Includes most extreme abnormal result

[†] CEE = conjugated equine estrogens 0.625 mg/day

[‡] PROVERA = medroxyprogesterone acetate tablets 10 mg/day for 12 days

In a second 1-year study, 832 postmenopausal women between 45 and 65 years of age were treated with daily 0.625 mg conjugated estrogen (days 1–28), plus either 5 mg cyclic PROVERA or 10 mg cyclic PROVERA (days 15–28), or daily 0.625 mg conjugated estrogen only. The treatment groups receiving 5 or 10 mg cyclic PROVERA (days 15–28) plus daily conjugated estrogens showed a significantly lower rate of hyperplasia as compared to the conjugated estrogens only group. See Table 3.

Table 3. Number (%) of Women with Endometrial Hyperplasia at 1 Year

	CEE [*]	MPA [†] + CEE [*]	
	(n=283)	MPA 5 mg (n=277)	MPA 10 mg (n=272)
Cystic hyperplasia (%)	55 (19)	3 (1)	0
Adenomatous hyperplasia without atypia	2 (1)	0	0

[*] CEE = conjugated equine estrogen 0.625 mg every day of a 28-day cycle.

[†] Cyclic medroxyprogesterone acetate on days 15 to 28

Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (defined as nonfatal MI, silent MI and CHD death),

with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other cause. These substudies did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reduction per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 4. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 4 : RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN PLUS PROGESTIN SUBSTUDY OF WHI AT AN AVERAGE OF 5.6 YEARS [*,†]

Event	**Relative Risk CE/MPA vs placebo (95% nCI [‡])**	**CE/MPA n = 8,506**	**Placebo n = 8,102**
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99–1.53)	41	34
Non-fatal MI	*1.28 (1.00–1.63)*	*31*	*25*
CHD death	*1.10 (0.70–1.75)*	*8*	*8*
All strokes	1.31 (1.03–1.68)	33	25
Ischemic stroke	*1.44 (1.09–1.90)*	*26*	*18*
Deep vein thrombosis[§]	1.95 (1.43–2.67)	26	13
Pulmonary embolism	2.13 (1.45–3.11)	18	8
Invasive breast cancer[¶]	1.24 (1.01–1.54)	41	33
Colorectal cancer	0.61 (0.42–0.87)	10	16
Endometrial cancer[§]	0.81 (0.48–1.36)	6	7
Cervical cancer[§]	1.44 (0.47–4.42)	2	1
Hip fracture	0.67 (0.47–0.96)	11	16
Vertebral fractures[§]	0.65 (0.46–0.92)	11	17
Lower arm/wrist fractures[§]	0.71 (0.59–0.85)	44	62
Total fractures[§]	0.76 (0.69–0.83)	152	199
Overall mortality[#]	1.00 (0.83–1.19)	52	52
Global Index[Þ]	1.13 (1.02–1.25)	184	165

* Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

† Results are based on centrally adjudicated data.

‡ Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

§ Not included in "global index".

¶ Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.

All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

Þ A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age a nonsignificant trend toward reduced risk in overall mortality [hazard ration (HR) 0.69 (95 percent CI, 0.44–1.07)].

Women's Health Initiative Memory Study

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were aged 65 to 69 years of age, 35 percent were 70 to 74 years of age, and 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21–3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 33 per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use)**.

INDICATIONS AND USAGE

PROVERA tablets are indicated for the treatment of secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. They are also indicated for use in the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving daily oral conjugated estrogens 0.625 mg tablets.

CONTRAINDICATIONS

PROVERA is contraindicated in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of breast cancer.
3. Known or suspected estrogen- or progesterone-dependent neoplasia.
4. Active DVT, PE, or a history of these conditions
5. Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions.
6. Known anaphylactic reaction or angioedema to PROVERA.
7. Known liver impairment or disease.
8. Known or suspected pregnancy.

WARNINGS

See **BOXED WARNINGS.**

1. Cardiovascular Disorders

An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy.

Should any of these events occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Stroke

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years). (See **CLINICAL STUDIES**.) The increase in risk was demonstrated after the first year and persisted. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

b. Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5.

In postmenopausal women with documented heart disease (n = 2,763, average 66.7 years of age), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

c. Venous Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and PE) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See **CLINICAL STUDIES.**) Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens plus progestins should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant Neoplasms

a. Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA.

In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years, for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade, and hormone receptor status did not differ between the groups. (See **CLINICAL STUDIES**.)

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, or routes of administration.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

b. Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen plus progestin therapy is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

c. Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77–3.24). The absolute risk for CE plus MPA was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies and some report no association.

3. Probable Dementia

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women aged 65 to 79 years was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21–3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

4. Visual Abnormalities

Discontinue estrogen plus progestin therapy pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, estrogen plus progestin therapy should be permanently discontinued.

PRECAUTIONS

A. General

1. Addition of a progestin when a woman has not had a hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

2. Unexpected abnormal vaginal bleeding

In cases of unexpected abnormal vaginal bleeding, adequate diagnostic measures are indicated.

3. Elevated blood pressure

Blood pressure should be monitored at regular intervals with estrogen plus progestin therapy.

4. Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen plus progestin therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5. Hepatic Impairment and/or past history of cholestatic jaundice

Estrogens plus progestins may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

6. Fluid Retention

Progestins may cause some degree of fluid retention. Women who have conditions which might be influenced by this factor, such as cardiac or renal impairment, warrant careful observation when estrogen plus progestin are prescribed.

7. Hypocalcemia

Estrogen plus progestin therapy should be used with caution in women with hypoparathyroidism as

estrogen-induced hypocalcemia may occur.

8. Exacerbation of other conditions

Estrogen plus progestin therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

B. Patient Information

Physicians are advised to discuss the Patient Information leaflet with women for whom they prescribe PROVERA.

There may be an increased risk of minor birth defects in children whose mothers are exposed to progestins during the first trimester of pregnancy. The possible risk to the male baby is hypospadias, a condition in which the opening of the penis is on the underside rather than the tip of the penis. This condition occurs naturally in approximately 5 to 8 per 1000 male births. The risk may be increased with exposure to PROVERA. Enlargement of the clitoris and fusion of the labia may occur in female babies. However, a clear association between hypospadias, clitoral enlargement and labial fusion with use of PROVERA has not been established.

Inform the patient of the importance of reporting exposure to PROVERA in early pregnancy.

C. Drug-Laboratory Test Interactions

The following laboratory results may be altered by the use of estrogen plus progestin therapy:

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay, T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone binding globulin (SHBG) leading to increased circulating corticosteroid and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.

D. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Long-term intramuscular administration of medroxyprogesterone acetate has been shown to produce mammary tumors in beagle dogs. There was no evidence of a carcinogenic effect associated with the oral administration of medroxyprogesterone acetate to rats and mice.

Long-term continuous administration of estrogen plus progestin therapy has shown an increased risk of breast cancer and ovarian cancer. (See **WARNINGS** and **PRECAUTIONS**.)

Genotoxicity

Medroxyprogesterone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

Fertility

Medroxyprogesterone acetate at high doses is an antifertility drug and high doses would be expected to impair fertility until the cessation of treatment.

E. Pregnancy

PROVERA should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

There may be increased risks for hypospadias, clitoral enlargement and labial fusion in children whose mothers are exposed to PROVERA during the first trimester of pregnancy. However, a clear association between these conditions with use of PROVERA has not been established.

F. Nursing Mothers

PROVERA should not be used during lactation. Detectable amounts of progestin have been identified in the breast milk of nursing mothers receiving progestins.

G. Pediatric Use

PROVERA tablets are not indicated in children. Clinical studies have not been conducted in the pediatric population.

H. Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing PROVERA alone to determine whether those over 65 years of age differ from younger subjects in their response to PROVERA alone.

The Women's Health Initiative Studies

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age. (See **CLINICAL STUDIES**.)

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo. (See **WARNINGS, Probable Dementia**.)

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Probable Dementia**.)

ADVERSE REACTIONS

See **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following adverse reactions have been reported in women taking PROVERA tablets, without concomitant estrogens treatment:

1. Genitourinary system

Abnormal uterine bleeding (irregular, increase, decrease), change in menstrual flow, breakthrough

bleeding, spotting, amenorrhea, changes in cervical erosion and cervical secretions.

2. Breasts

Breast tenderness, mastodynia or galactorrhea has been reported.

3. Cardiovascular

Thromboembolic disorders including thrombophlebitis and pulmonary embolism have been reported.

4. Gastrointestinal

Nausea, cholestatic jaundice.

5. Skin

Sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash have occurred. Acne, alopecia and hirsutism have been reported.

6. Eyes

Neuro-ocular lesions, for example, retinal thrombosis, and optic neuritis.

7. Central nervous system

Mental depression, insomnia, somnolence, dizziness, headache, nervousness.

8. Miscellaneous

Hypersensitivity reactions (for example, anaphylaxis and anaphylactoid reactions, angioedema), rash (allergic) with and without pruritus, change in weight (increase or decrease), pyrexia, edema/fluid retention, fatigue, decreased glucose tolerance.

The following adverse reactions have been reported with estrogen plus progestin therapy.

1. Genitourinary system

Abnormal uterine bleeding/spotting, or flow; breakthrough bleeding; spotting; dysmenorrheal/pelvic pain; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

4. Gastrointestinal

Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas.

5. Skin

Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

6. Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

7. Central nervous system

Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

8. Miscellaneous

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

OVERDOSAGE

Overdosage of estrogen plus progestin therapy may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of CE plus MPA together with institution of appropriate symptomatic care.

DOSAGE AND ADMINISTRATION

Secondary Amenorrhea

PROVERA tablets may be given in dosages of 5 or 10 mg daily for 5 to 10 days. A dose for inducing an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen is 10 mg of PROVERA daily for 10 days. In cases of secondary amenorrhea, therapy may be started at any time. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing PROVERA therapy.

Abnormal Uterine Bleeding Due to Hormonal Imbalance in the Absence of Organic Pathology

Beginning on the calculated 16th or 21st day of the menstrual cycle, 5 or 10 mg of PROVERA may be given daily for 5 to 10 days. To produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen, 10 mg of PROVERA daily for 10 days beginning on the 16th day of the cycle is suggested. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing therapy with PROVERA. Patients with a past history of recurrent episodes of abnormal uterine bleeding may benefit from planned menstrual cycling with PROVERA.

Reduction of Endometrial Hyperplasia in Postmenopausal Women Receiving Daily 0.625 mg Conjugated Estrogens

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (for example, 3 to 6 month intervals) to determine if treatment is still necessary (see **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

PROVERA tablets may be given in dosages of 5 or 10 mg daily for 12 to 14 consecutive days per month, in postmenopausal women receiving daily 0.625 mg conjugated estrogens, either beginning on the 1st day of the cycle or the 16th day of the cycle.

Patients should be started at the lowest dose.

The lowest effective dose of PROVERA has not been determined.

HOW SUPPLIED

PROVERA Tablets are available in the following strengths and package sizes:

2.5 mg tablets (scored, round, orange, imprinted PROVERA 2.5)

Bottles of 100: NDC 0009-0064-04
Bottles of 100: NDC 0009-0065-01

5 mg tablets

Bottles of 100: NDC 0009-0286-03 (scored, hexagonal, white, imprinted PROVERA 5)
Bottles of 100: NDC 0009-0287-01 (scored, round, blue, imprinted PROVERA 5)

10 mg tablets (scored, round, white, imprinted PROVERA 10)

Bottles of 100: NDC 0009-0050-02
Bottles of 100: NDC 0009-0051-01
Bottles of 500: NDC 0009-0050-11
Bottles of 500: NDC 0009-0051-02

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

"Keep out of reach of children"

Rx only

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PATIENT INFORMATION

PROVERA
(pro-VE-rah**)**
(medroxyprogesterone acetate tablets, USP)

Read this Patient Information before you start taking PROVERA and read what you get each time you refill your PROVERA prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about PROVERA (a progestin hormone)?

- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes, or dementia (decline in brain function).
- Using estrogens with progestins may increase your chance of getting heart attacks, strokes, breast cancer, and blood clots.
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women age 65 years or older.
- You and your healthcare provider should talk regularly about whether you still need treatment with PROVERA.

What is PROVERA?

PROVERA is a medicine that contains medroxyprogesterone acetate, a progestin hormone.

What is PROVERA used for?

PROVERA is used to:

- Treat menstrual periods that have stopped or to treat abnormal uterine bleeding. Women with a uterus who are not pregnant, who stop having regular menstrual periods or who begin to have irregular menstrual periods may have a drop in their progesterone level. Talk with your healthcare provider about whether PROVERA is right for you.
- Reduce your chances of getting cancer of the uterus (womb). In postmenopausal women with a uterus who use estrogens, taking progestin in combination with estrogen will reduce your chance of getting cancer of the uterus (womb).

Who should not take PROVERA?

Do not start taking PROVERA if you:

- **have unusual vaginal bleeding**
- **currently have or have had certain cancers**
  Estrogen plus progestin may increase your chance of getting certain types of cancers, including cancer of the breast. If you have or have had cancer, talk with your healthcare provider about whether you should use PROVERA.
- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **are allergic to PROVERA or any of its ingredients**
  See the list of ingredients in PROVERA at the end of this leaflet.
- **think you may be pregnant**
  PROVERA is not for pregnant women. If you think you may be pregnant, you should have a pregnancy test and know the results. Do not use PROVERA if the test is positive and talk to your healthcare provider. There may be an increased risk of minor birth defects in children whose mothers take PROVERA during the first 4 months of pregnancy.
  PROVERA should not be used as a test for pregnancy.

What should I tell my healthcare provider before taking PROVERA? Before you take PROVERA, tell your healthcare provider if you:

- **have any other medical problems**
  Your healthcare provider may need to check you more carefully if you have certain conditions such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis (severe pelvic pain), lupus, or problems with your heart, liver, thyroid, kidneys, or have high calcium in your blood.
- **are going to have surgery or will be on bed rest**

Your healthcare provider will let you know if you need to stop taking PROVERA.

- **are breast feeding**
  The hormone in PROVERA can pass into your breast milk.

Tell your healthcare provider about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PROVERA works. PROVERA may also affect how other medicines work.

How should I take PROVERA?

Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you. The lowest effective dose of PROVERA has not been determined. You and your healthcare provider should talk regularly (every 3 to 6 months) about the dose you are taking and whether you still need treatment with PROVERA.

1. **Absence of menstrual period:** PROVERA may be given in doses ranging from 5 to 10 mg daily for 5 to 10 days.
2. **Abnormal Uterine Bleeding:** PROVERA may be given in doses ranging from 5 to 10 mg daily for 5 to 10 days.
3. **Overgrowth of the lining of the uterus:** When used in combination with oral conjugated estrogens in postmenopausal women with a uterus, PROVERA may be given in doses ranging from 5 or 10 mg daily for 12 to 14 straight days per month.

What are the possible side effects of PROVERA?

The following side effects have been reported with the use of PROVERA alone:

- breast tenderness
- breast milk secretion
- breakthrough bleeding
- spotting (minor vaginal bleeding)
- irregular periods
- amenorrhea (absence of menstrual periods)
- vaginal secretions
- headaches
- nervousness
- dizziness
- depression
- insomnia, sleepiness, fatigue
- premenstrual syndrome-like symptoms
- thrombophlebitis (inflamed veins)
- blood clot
- itching, hives, skin rash
- acne
- hair loss, hair growth
- abdominal discomfort
- nausea
- bloating
- fever
- increase in weight
- swelling
- changes in vision and sensitivity to contact lenses

Call your healthcare provider right away if you get hives, problems breathing, swelling of the face, mouth, tongue or neck

The following side effects have been reported with the use of PROVERA with an estrogen.

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- heart attack
- stroke
- blood clots
- dementia
- breast cancer
- cancer of the uterus
- cancer of the ovary
- high blood pressure
- high blood sugar
- gallbladder disease
- liver problems
- changes in your thyroid hormone levels
- enlargements of benign tumors ("fibroids")

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- new breast lumps
- unusual vaginal bleeding
- changes in vision and speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- memory loss or confusion

Less serious, but common side effects include:

- headache
- breast pain
- irregular vaginal bleeding or spotting
- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection

These are not all the possible side effects of PROVERA with or without estrogen. For more information, ask your healthcare provider or pharmacist for advice about side effects. Tell your healthcare provider if you have side effect that bothers you or does not go away. You may report side effects to Pfizer at 1-800-438-1985 or FDA at 1-800-FDA-1088.

What can I do to lower my chances of a serious side effect with PROVERA?

- Talk with your healthcare provider regularly about whether you should continue taking PROVERA. The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the uterus (womb).
- See your healthcare provider right away if you get vaginal bleeding while taking PROVERA.
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if

you use tobacco, you may have a higher chance of getting heart disease. Ask your healthcare provider for ways to lower your chance of getting heart disease.

General information about safe and effective use of PROVERA

- Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets.
- Do not take PROVERA for conditions for which it was not prescribed.
- Do not give PROVERA to other people, even if they have the same symptoms you have. It may harm them.

Keep PROVERA out of the reach of children.

This leaflet provides a summary of the most important information about PROVERA. If you would like more information, talk with your health care provider or pharmacist. You can ask for information about PROVERA that is written for health professionals. You can get more information by calling the toll-free number, 1-800-438-1985.

What are the ingredients in PROVERA?

Each PROVERA tablet for oral administration contains 2.5 mg, 5 mg or 10 mg of medroxyprogesterone acetate.

Inactive ingredients:

2.5 mg tablets		
calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose, talc, FD&C Yellow No. 6.	OR	calcium stearate, corn starch, lactose, mineral oil, sucrose, talc, FD&C Yellow No. 6.
5 mg tablets		
calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose, talc.	OR	calcium stearate, corn starch, lactose, mineral oil, sucrose, talc, FD&C Blue No.2 – Aluminum Lake.
10 mg tablets		
calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose, talc.	OR	calcium stearate, corn starch, lactose, mineral oil, sucrose, talc.

This product's label may have been updated. For current full prescribing information, please visit **www.pfizer.com**

Rx only

Distributed by

Pharmacia & Upjohn Co

Division of Pfizer Inc, NY, NY 10017

LAB-0365-8.0
January 2018

PRINCIPAL DISPLAY PANEL - 2.5 mg Tablet Bottle Label - NDC 0064

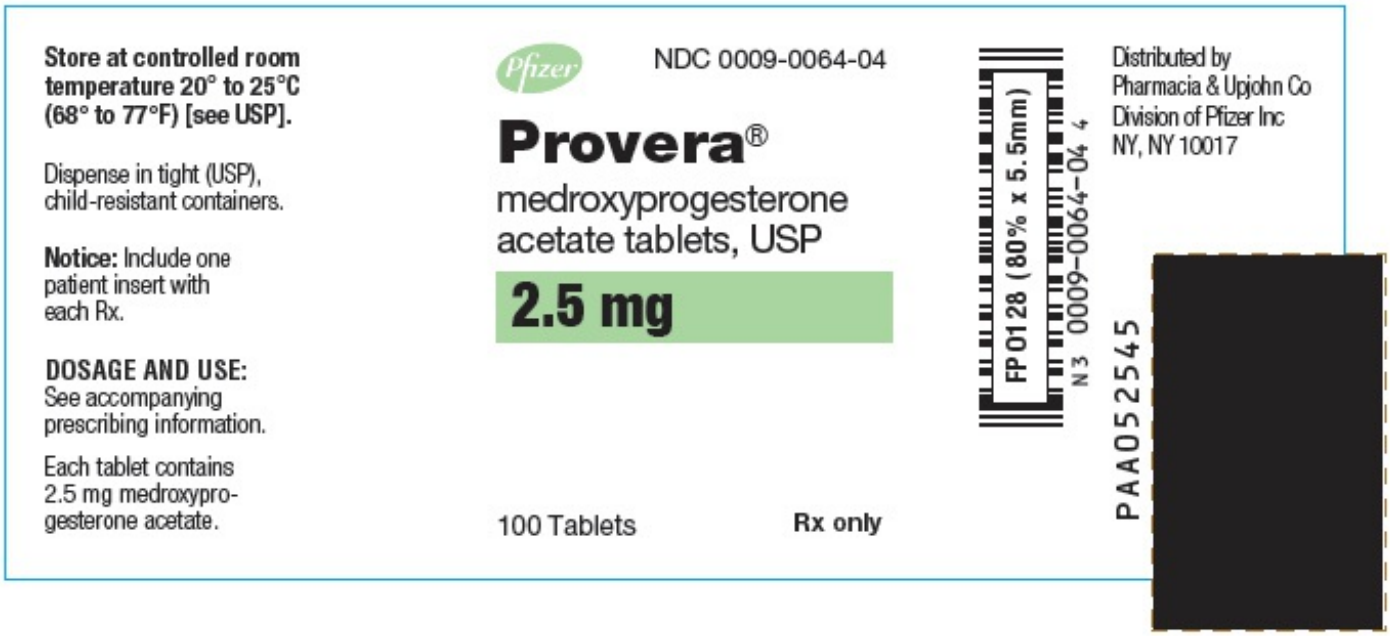
Pfizer

NDC 0009-0064-04

Provera®
medroxyprogesterone
acetate tablets, USP

2.5 mg

100 Tablets
Rx only



PRINCIPAL DISPLAY PANEL - 2.5 mg Tablet Bottle Carton

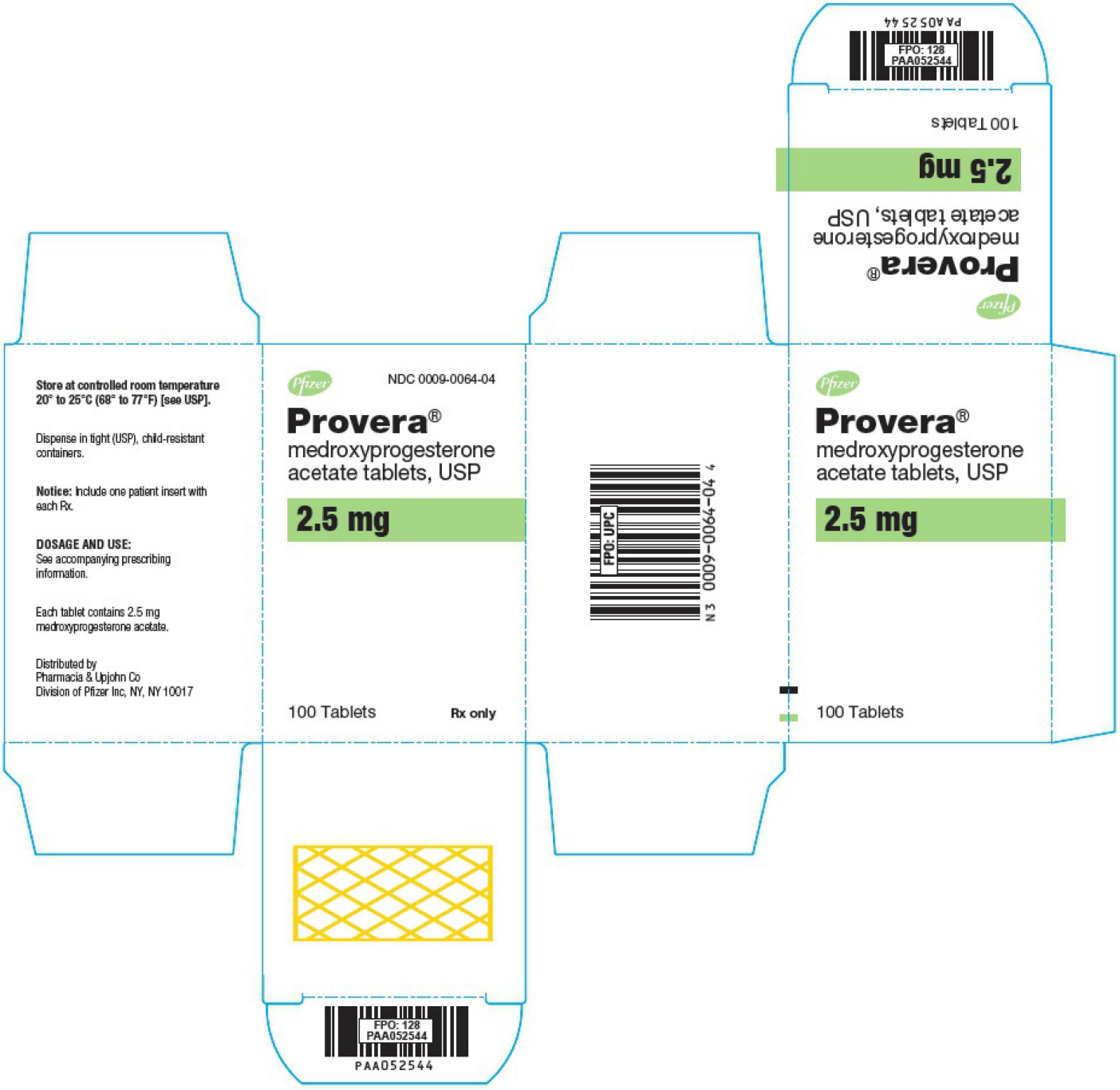
Pfizer

NDC 0009-0064-04

Provera®
medroxyprogesterone
acetate tablets, USP

2.5 mg

100 Tablets
Rx only



PRINCIPAL DISPLAY PANEL - 2.5 mg Tablet Bottle Label - NDC 0065

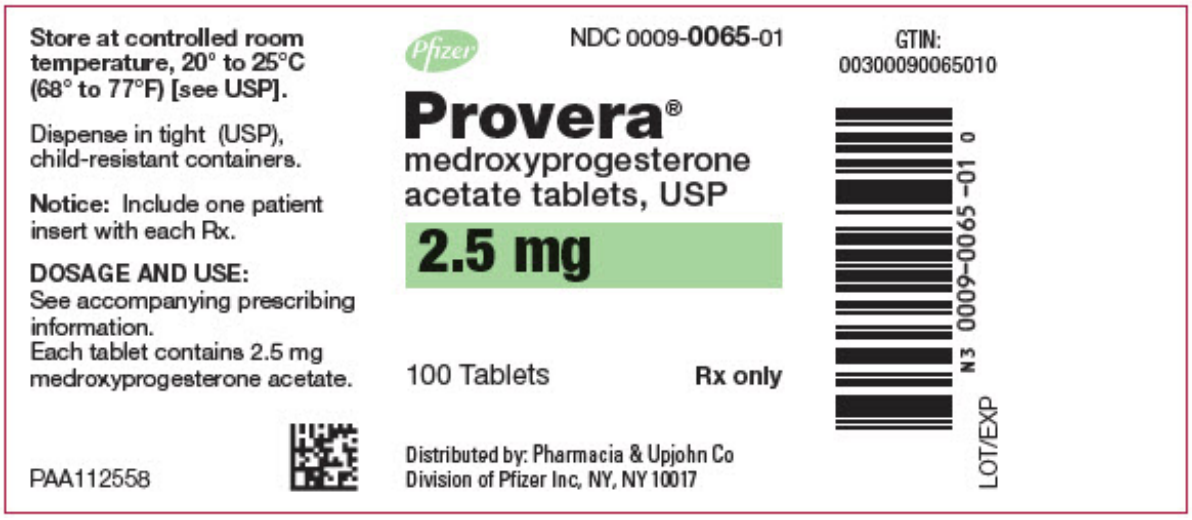
Pfizer
NDC 0009-0065-01

Provera®
medroxyprogesterone
acetate tablets, USP

2.5 mg

100 Tablets
Rx only

Distributed by: Pharmacia & Upjohn Co
Division of Pfizer Inc, NY, NY 10017



PRINCIPAL DISPLAY PANEL - 5 mg Tablet Bottle Label

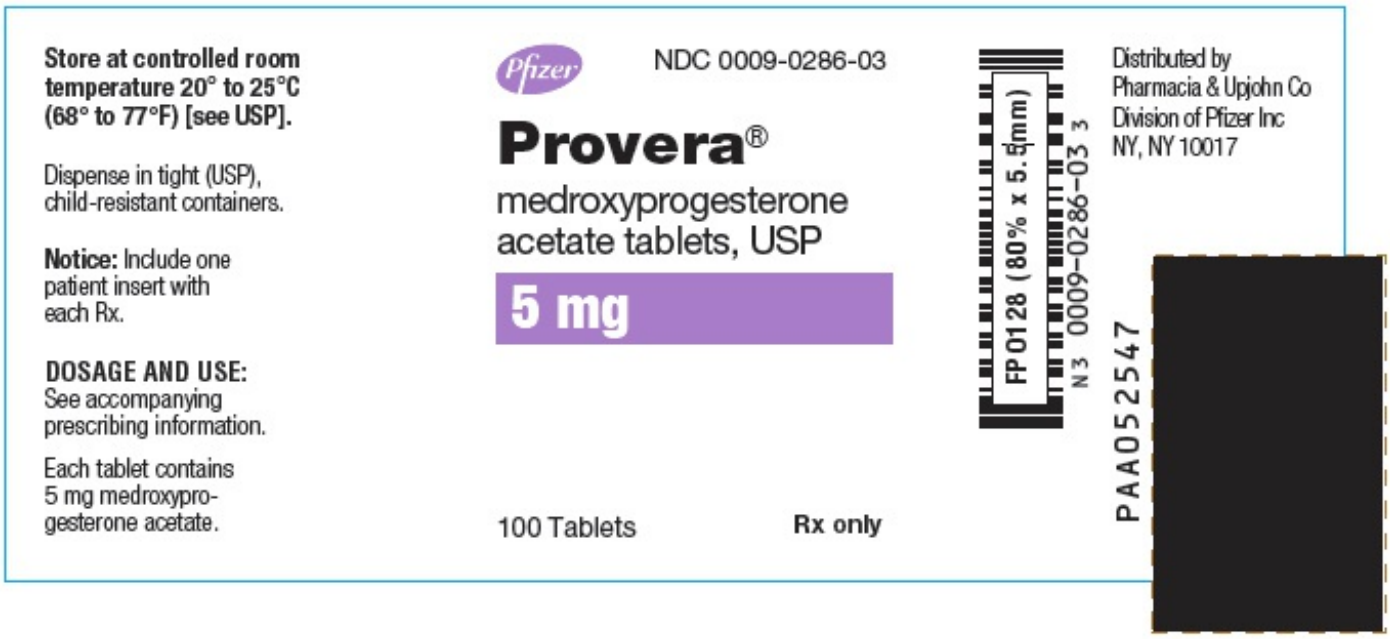
Pfizer

NDC 0009-0286-03

Provera®
medroxyprogesterone
acetate tablets, USP

5 mg

100 Tablets
Rx only



PRINCIPAL DISPLAY PANEL - 5 mg Tablet Bottle Carton

Pfizer

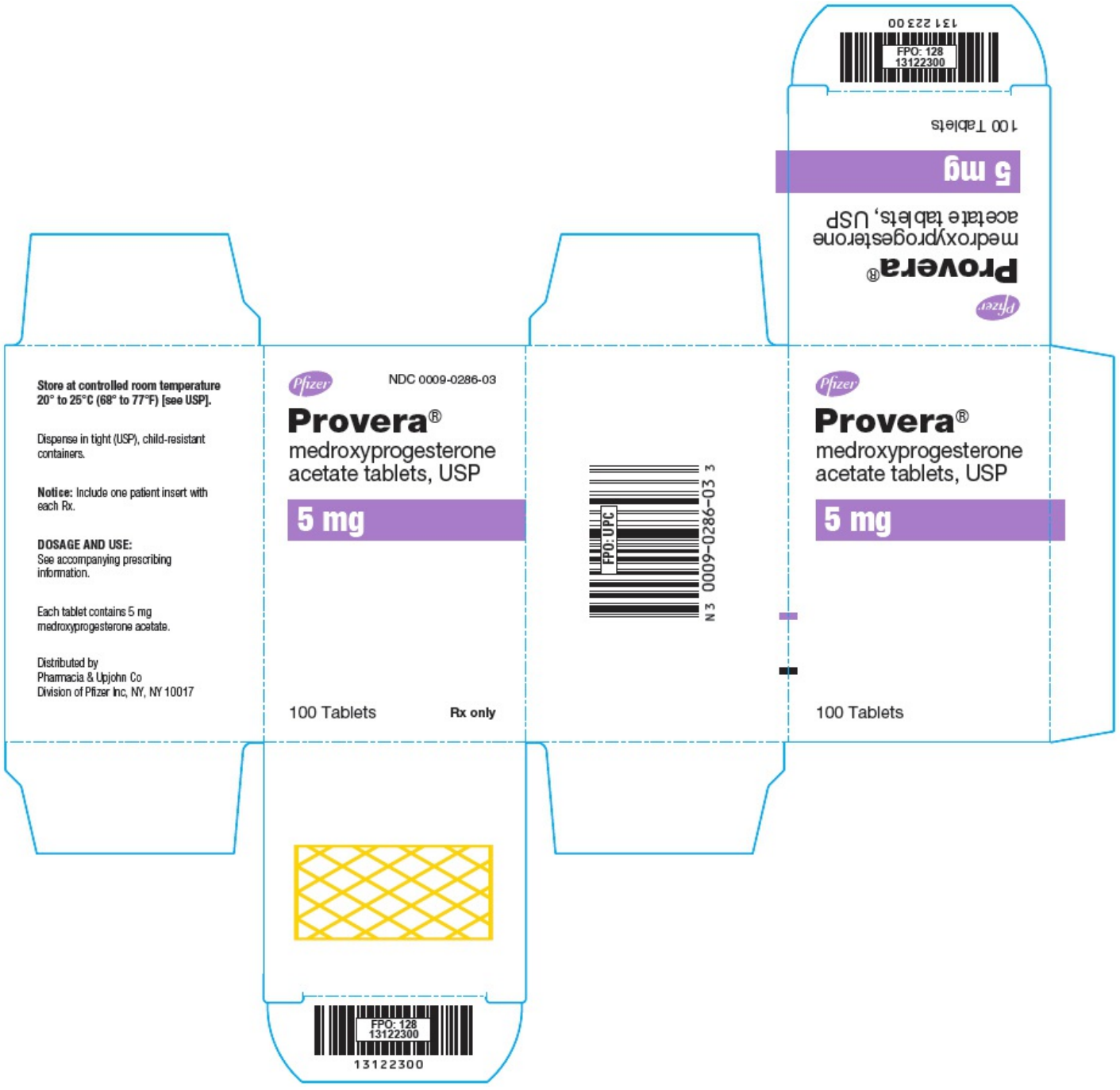
NDC 0009-0286-03

Provera®

medroxyprogesterone
acetate tablets, USP

5 mg

100 Tablets
Rx only



PRINCIPAL DISPLAY PANEL - 5 mg Tablet Bottle Label - 0287

Pfizer

NDC 0009-0287-01

Provera®
medroxyprogesterone

acetate tablets, USP

5 mg

100 Tablets
Rx only

Distributed by: Pharmacia & Upjohn Co
Division of Pfizer Inc, NY, NY 10017

PRINCIPAL DISPLAY PANEL - 10 mg Tablet Bottle Label

Pfizer

NDC 0009-0050-02

Provera®
medroxyprogesterone
acetate tablets, USP

10 mg

100 Tablets
Rx only

PRINCIPAL DISPLAY PANEL - 10 mg Tablet Bottle Carton

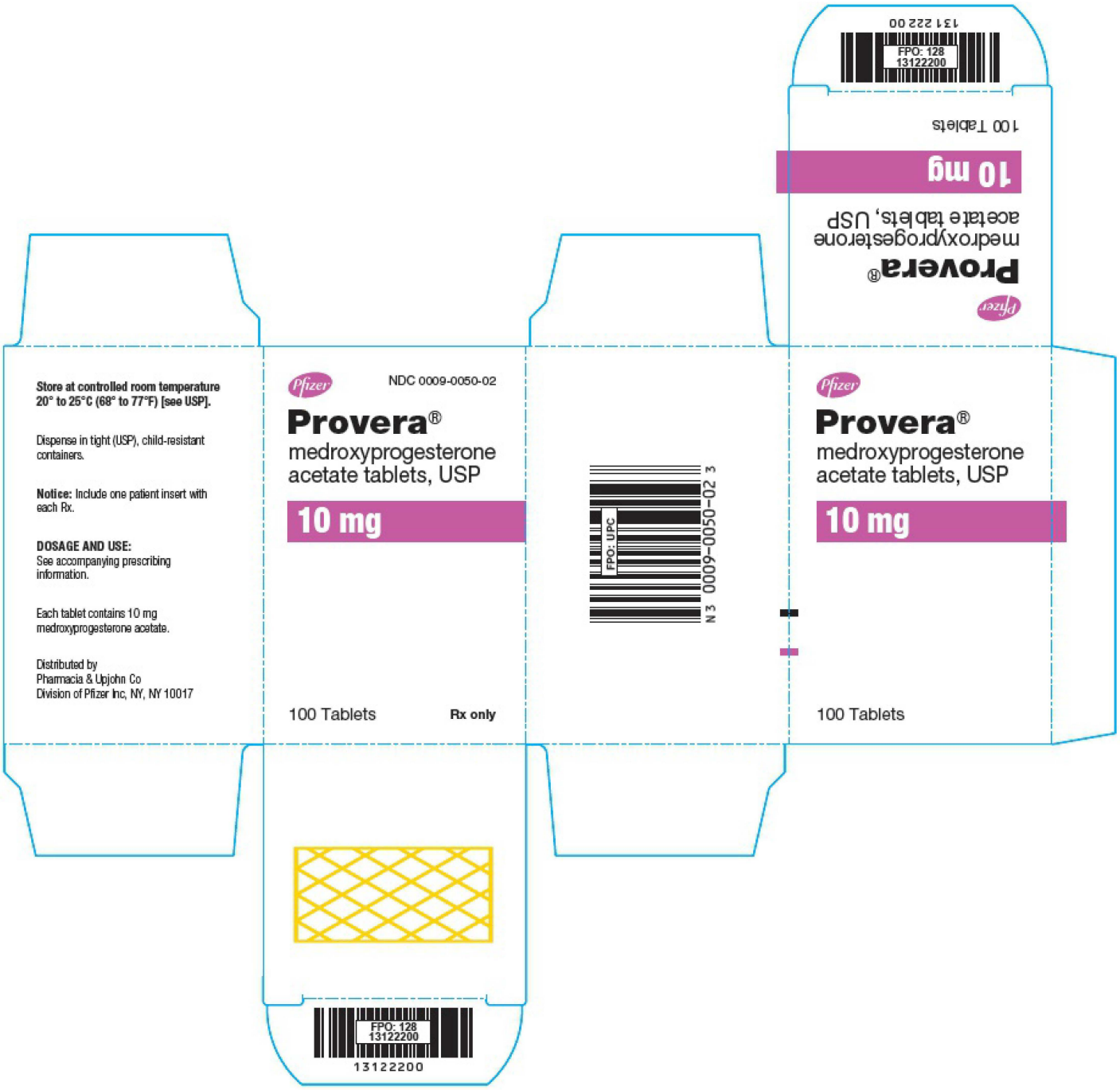
Pfizer

NDC 0009-0050-02

Provera®
medroxyprogesterone
acetate tablets, USP

10 mg

100 Tablets
Rx only



PRINCIPAL DISPLAY PANEL - 10 mg Tablet Bottle Label - 0051

Pfizer

NDC 0009-0051-01

Provera®
medroxyprogesterone
acetate tablets, USP

10 mg

100 Tablets
Rx only

Distributed by: Pharmacia & Upjohn Co
Division of Pfizer Inc, NY, NY 10017

PROVERA

medroxyprogesterone acetate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0009-0064
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
MEDROXYPROGESTERONE ACETATE (UNII: C2QI4IOI2G) (MEDROXYPROGESTERONE - UNII:HSU1C9YRES)	MEDROXYPROGESTERONE ACETATE	2.5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CALCIUM STEARATE (UNII: 776XM7047L)	
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MINERAL OIL (UNII: T5L8T28FGP)	
SORBIC ACID (UNII: X045WJ989B)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics			
Color	ORANGE	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	PROVERA;2;5
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0009-0064-04	1 in 1 CARTON	06/03/1959	04/30/2020
1		100 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA011839	06/03/1959	04/30/2020

PROVERA

medroxyprogesterone acetate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0009-0065
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
MEDROXYPROGESTERONE ACETATE (UNII: C2QI4IOI2G) (MEDROXYPROGESTERONE - UNII:HSU1C9YRES)	MEDROXYPROGESTERONE ACETATE	2.5 mg

Inactive Ingredients	
Ingredient Name	Strength
CALCIUM STEARATE (UNII: 776XM7047L)	
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MINERAL OIL (UNII: T5L8T28FGP)	
SORBIC ACID (UNII: X045WJ989B)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics			
Color	ORANGE	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	PROVERA;2;5
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date

1	NDC:0009-0065-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/03/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA011839	06/03/1959	

PROVERA

medroxyprogesterone acetate tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0009-0286
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEDROXYPROGESTERONE ACETATE (UNII: C2QI4IOI2G) (MEDROXYPROGESTERONE - UNII:HSU1C9YRES)	MEDROXYPROGESTERONE ACETATE	5 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM STEARATE (UNII: 776XM7047L)	
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MINERAL OIL (UNII: T5L8T28FGP)	
SORBIC ACID (UNII: X045WJ989B)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics

Color	WHITE	**Score**	2 pieces
Shape	HEXAGON (6 SIDED)	**Size**	6mm
Flavor		**Imprint Code**	PROVERA;5
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0009-0286-03	1 in 1 CARTON	06/03/1959	06/30/2019
1		100 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA011839	06/03/1959	

PROVERA

medroxyprogesterone acetate tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0009-0287
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEDROXYPROGESTERONE ACETATE (UNII: C2QI4IOI2G) (MEDROXYPROGESTERONE - UNII:HSU1C9YRES)	MEDROXYPROGESTERONE ACETATE	5 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM STEARATE (UNII: 776XM7047L)	
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MINERAL OIL (UNII: T5L8T28FGP)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	BLUE	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	PROVERA;5
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0009-0287-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	11/11/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA011839	06/03/1959	

PROVERA

medroxyprogesterone acetate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0009-0050
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
MEDROXYPROGESTERONE ACETATE (UNII: C2QI4IOI2G) (MEDROXYPROGESTERONE - UNII:HSU1C9YRES)	MEDROXYPROGESTERONE ACETATE	10 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CALCIUM STEARATE (UNII: 776XM7047L)	
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MINERAL OIL (UNII: T5L8T28FGP)	
SORBIC ACID (UNII: X045WJ989B)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	PROVERA;10
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0009-0050-02	1 in 1 CARTON	06/03/1959	11/30/2021
1		100 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:0009-0050-11	500 in 1 BOTTLE; Type 0: Not a Combination Product	06/03/1959	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA011839	06/03/1959	

PROVERA

medroxyprogesterone acetate tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0009-0051
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MEDROXYPROGESTERONE ACETATE (UNII: C2QI4IOI2G) (MEDROXYPROGESTERONE - UNII:HSU1C9YRES)	MEDROXYPROGESTERONE ACETATE	10 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM STEARATE (UNII: 776XM7047L)	
STARCH, CORN (UNII: O8232NY3SJ)	
LACTOSE, UNSPECIFIED FORM (UNII: J2B2A4N98G)	
MINERAL OIL (UNII: T5L8T28FGP)	
SORBIC ACID (UNII: X045WJ989B)	
SUCROSE (UNII: C151H8M554)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics

Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	7mm
Flavor		**Imprint Code**	PROVERA;10
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0009-0051-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	07/20/2020	
2	NDC:0009-0051-02	500 in 1 BOTTLE; Type 0: Not a Combination Product	08/01/2020	08/01/2020

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA011839	06/03/1959	

Labeler - Pharmacia and Upjohn Company LLC (618054084)

Establishment

Name	Address	ID/FEI	Business Operations
Pharmacia and Upjohn		618054084	ANALYSIS(0009-0050, 0009-0051, 0009-0064, 0009-0065, 0009-0286, 0009-0287) , API MANUFACTURE(0009-0050, 0009-0051, 0009-0064, 0009-0065, 0009-0286, 0009-0287) ,

Company LLC			PACK(0009-0050, 0009-0051, 0009-0064, 0009-0065, 0009-0286, 0009-0287)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Italia S.r.l.		458521908	ANALYSIS(0009-0051, 0009-0065, 0009-0287) , MANUFACTURE(0009-0051, 0009-0065, 0009-0287) , PACK(0009-0051, 0009-0065, 0009-0287)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Inc		943955690	ANALYSIS(0009-0050, 0009-0051, 0009-0064, 0009-0065, 0009-0286, 0009-0287)

Revised: 8/2020 Pharmacia and Upjohn Company LLC

Exhibit

K

LUPRON DEPOT- leuprolide acetate
AbbVie Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUPRON DEPOT 11.25 mg safely and effectively. See full prescribing information for LUPRON DEPOT 11.25 mg.

LUPRON DEPOT 11.25 mg (leuprolide acetate for depot suspension) for injection, for intramuscular use
Initial U.S. Approval: 1985

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2)	03/2020
Dosage and Administration (2.1)	03/2020
Warnings and Precautions, Risks Associated with Norethindrone Combination Treatment (5.7)	03/2020

INDICATIONS AND USAGE

LUPRON DEPOT 11.25 mg is a gonadotropin-releasing hormone (GnRH) agonist indicated for:

Endometriosis

- Management of endometriosis, including pain relief and reduction of endometriotic lesions. (1.1)
- In combination with a norethindrone acetate for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms. (1.1)

Limitations of Use:

- The total duration of therapy with LUPRON DEPOT 11.25 mg plus add-back therapy should not exceed 12 months due to concerns about adverse impact on bone mineral density. (1.1, 2.1, 5.1)

Uterine Leiomyomata (Fibroids)

- Concomitant use with iron therapy for preoperative hematologic improvement of women with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary. (1.2)

Limitations of Use:

- LUPRON DEPOT 11.25 mg is not indicated for combination use with norethindrone acetate add-back therapy for the preoperative hematologic improvement of women with anemia caused by heavy menstrual bleeding due to fibroids. (1.2)

DOSAGE AND ADMINISTRATION

LUPRON DEPOT 11.25mg for 3-month administration, given as a single intramuscular injection.
LUPRON DEPOT 11.25 mg has different release characteristics than LUPRON 3.75 mg and is dosed differently. (2.1)

- Do not substitute LUPRON DEPOT 11.25 mg for LUPRON DEPOT 3.75 mg.
- Do not administer LUPRON DEPOT 11.25 mg more frequently than every 3 months.
- Do not give a fractional dose of the LUPRON DEPOT 11.25 mg, as it is not equivalent to the same dose of the LUPRON DEPOT 3.75 mg monthly formulation.

Reconstitute LUPRON DEPOT 11.25 mg prior to use. (2.2)

Endometriosis:

- LUPRON DEPOT 11.25 mg administered as a single intramuscular (IM) injection once every three months for up to two injections (6 months of therapy). LUPRON DEPOT may be administered alone or in combination with daily 5 mg tablet of norethindrone acetate (add-back). (2.1)
- If endometriosis symptoms recur after initial course of therapy, retreatment for no more than six months may be considered but **only** with the addition of norethindrone acetate add-back therapy. Do not re-treat with LUPRON DEPOT 11.25 mg alone. (2.1)

Fibroids:

- Recommended dose of LUPRON DEPOT 11.25 mg is one IM injection. (2.1)

DOSAGE FORMS AND STRENGTHS

- Depot suspension for injection: 11.25 mg lyophilized powder for reconstitution in a dual-chamber syringe. (3)

CONTRAINDICATIONS

- Hypersensitivity to GnRH, GnRH agonist analogs, including leuprolide acetate, or any of the excipients in LUPRON DEPOT 11.25 mg. (4,5.3)
- Undiagnosed abnormal uterine bleeding. (4)
- Pregnancy. (4, 8.1)

If LUPRON DEPOT 11.25 mg is administered with norethindrone acetate, the contraindications for norethindrone acetate also apply. (4)

WARNINGS AND PRECAUTIONS

- Loss of bone mineral density (BMD): Duration of treatment is limited by risk of bone mineral density. When using for management of endometriosis: combination use with norethindrone acetate is effective in reducing loss of BMD; do not retreat without combination norethindrone acetate. Assess BMD before retreatment. (1.1, 1.2, 5.1)
- Embryo-Fetal Toxicity: May cause fetal harm. Exclude pregnancy before initiating treatment if clinically indicated and discontinue use if pregnancy occurs. Use non-hormonal methods of contraception only. (5.2)
- Hypersensitivity reactions, including anaphylaxis, have been reported with LUPRON DEPOT 11.25 mg. (5.3)
- If LUPRON is administered with norethindrone acetate, the warnings and precautions for norethindrone acetate apply to the combination regimen. (5.7)

ADVERSE REACTIONS

Most common adverse reactions (>10%) in clinical trials were hot flashes/sweats, headache/migraine, vaginitis, depression/emotional lability, general pain, weight gain/loss, nausea/vomiting, decreased libido, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Endometriosis

Monotherapy

LUPRON DEPOT 11.25 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions.

In Combination with Norethindrone Acetate

LUPRON DEPOT 11.25 mg in combination with norethindrone acetate is indicated for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.

Use of norethindrone acetate in combination with LUPRON DEPOT 11.25 mg is referred to as add-back therapy, and is intended to reduce the loss of bone mineral density (BMD) and reduce vasomotor symptoms associated with use of LUPRON DEPOT 11.25 mg.

Limitations of Use:

The total duration of therapy with LUPRON DEPOT 11.25 mg plus add-back therapy should not exceed 12 months due to concerns about adverse impact on bone mineral density *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

1.2 Uterine Leiomyomata (Fibroids)

LUPRON DEPOT 11.25 mg, used concomitantly with iron therapy, is indicated for the preoperative hematologic improvement of women with anemia caused by fibroids for whom three months of hormonal suppression is deemed necessary.

Consider a one-month trial period on iron alone, as some women will respond to iron alone *[see Clinical Studies (14.2)]*. LUPRON DEPOT 11.25 mg may be added if the response to iron alone is considered inadequate.

Limitations of Use:

LUPRON DEPOT 11.25 mg is not indicated for combination use with norethindrone acetate add-back therapy for the preoperative hematologic improvement of women with anemia caused by heavy menstrual bleeding due to fibroids *[*see *Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

LUPRON DEPOT 11.25 mg for 3-month administration has different release characteristics than LUPRON 3.75 mg for 1-month administration and is dosed differently.

- Do not substitute LUPRON DEPOT 11.25 mg for LUPRON DEPOT 3.75 mg.
- Do not administer LUPRON DEPOT 11.25 mg more frequently than every 3 months.
- Do not give a fractional dose of the LUPRON DEPOT 11.25 mg, as it is not equivalent to the same dose of the LUPRON DEPOT 3.75 mg monthly formulation.

Endometriosis

The initial and retreatment dosage regimens for LUPRON DEPOT 11.25 mg for the management of women with endometriosis are outlined in Table 1.

Table 1. LUPRON DEPOT 11.25 mg, Management of Endometriosis

Treatment Phase	LUPRON DEPOT 11.25 mg Dosing	Maximum Treatment Duration
Initial Treatment[1]	11.25 mg IM every 3 months for 1 to 2 doses	6 months
Retreatment[2]	11.25 mg IM every 3 months for 1 to 2 doses	6 months
		12 MONTHS[3] TOTAL TREATMENT DURATION

[1]May use LUPRON DEPOT 11.25 mg with or without norethindrone acetate 5 mg tablet taken daily.

[2]Use LUPRON DEPOT 11.25 mg with norethindrone acetate for retreatment 5 mg tablet taken daily *[see Warnings and Precautions (5.1)]* and assess bone mineral density (BMD) prior to retreatment.

[3]Treatment should not exceed 12 months due to concerns about adverse impact on bone mineral density.

Fibroids

The recommended dosage of LUPRON DEPOT 11.25 mg is one IM injection of 11.25 mg which provides a three-month treatment course.

2.2 Reconstitution and Administration for Injection of LUPRON DEPOT

- Reconstitute and administer the lyophilized microsphere as a single IM injection as directed below. Visually inspect the drug product for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Inject the LUPRON DEPOT 11.25 mg suspension immediately or discard if not used within two hours as the suspension does not contain a preservative.
  1. Visually inspect the LUPRON DEPOT 11.25 mg powder. **Do not use** the syringe if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal prior to mixing with the diluent. The diluent should appear clear.
  2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn (see Figure A and Figure B).
     Figure A:

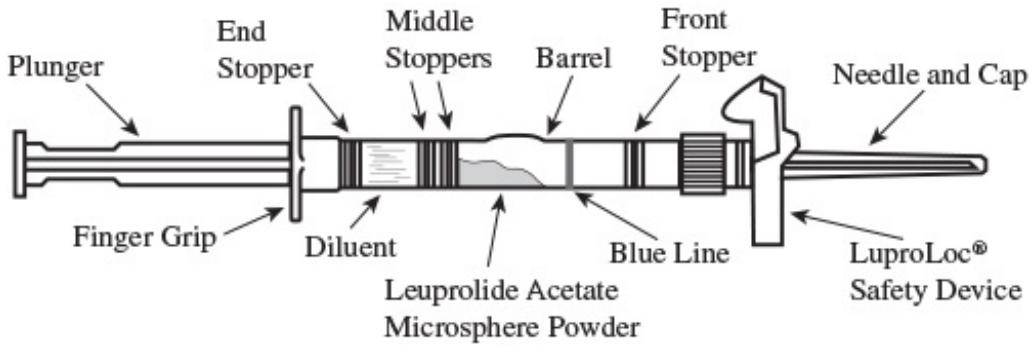
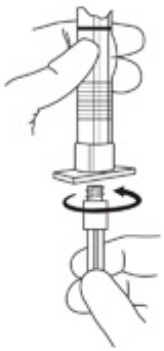
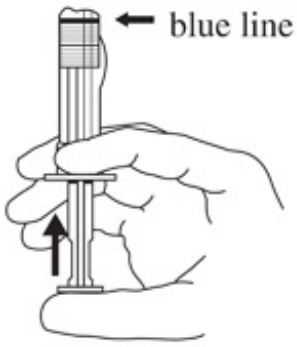


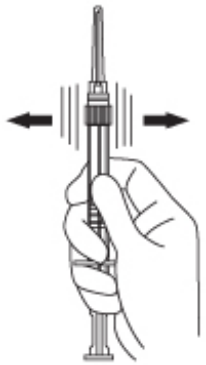
Figure B:



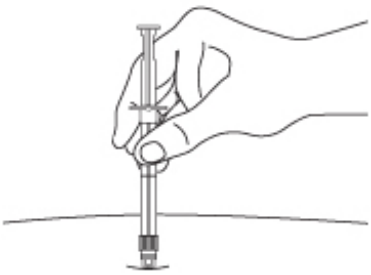
3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING the plunger for 6 to 8 seconds until the first middle stopper is **at the blue line** in the middle of the barrel (see Figure C).
   Figure C:



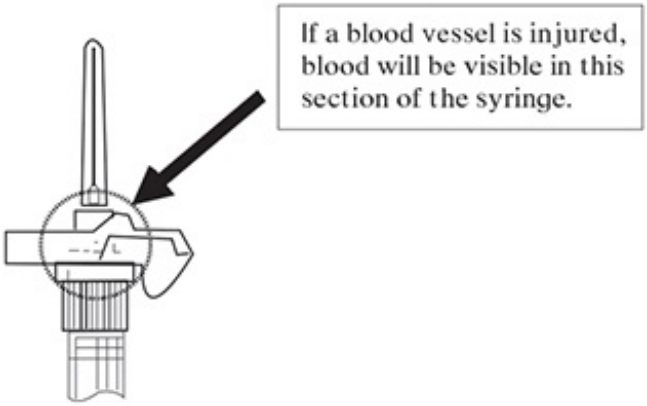
4. Keep the syringe **upright**. Mix the microsphere powder thoroughly by gently shaking the syringe until the powder forms a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. **Do not use** if any of the powder has not gone into suspension (see Figure D).
   Figure D:



5. Keep the syringe **upright**. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe **upright.** Advance the plunger to expel the air from the syringe. The syringe is now ready for injection.
7. After cleaning the injection site with an alcohol swab, administer the IM injection by inserting the needle at a 90-degree angle into the gluteal area, anterior thigh, or deltoid. Injection sites should be alternated (see Figure E).
   Figure E:



Note: If a blood vessel is accidentally penetrated, aspirated blood will be visible just below the luer lock (see Figure F) and can be seen through the transparent LuproLoc® safety device. If blood is present, remove the needle immediately. Do not inject the medication.
Figure F:



8. Inject the entire contents of the syringe intramuscularly.
9. Withdraw the needle. Once the syringe has been withdrawn, immediately activate the LuproLoc® safety device by pushing the arrow on the lock upward towards the needle tip with the thumb or

finger, as illustrated, until the needle cover of the safety device over the needle is fully extended and a **click** is heard or felt (see Figure G).
Figure G:

10. Dispose of the syringe according to local regulations/procedures.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 11.25 mg of leuprolide acetate as a white lyophilized microsphere powder for reconstitution in a single dose prefilled dual chamber syringe; with one chamber containing the lyophilized powder and the other chamber containing the clear diluent.

4 CONTRAINDICATIONS

LUPRON DEPOT 11.25 mg is contraindicated in women with the following:

- Hypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH agonist analogs, including leuprolide acetate, or any of the excipients in LUPRON DEPOT 11.25 mg *[see Warnings and Precautions (5.3) and Adverse Reactions (6.2)]*
- Undiagnosed abnormal uterine bleeding
- Pregnancy *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*

When norethindrone acetate is administered with LUPRON DEPOT 11.25 mg, the contraindications to the use of norethindrone acetate also apply to this combination regimen. Refer to the norethindrone acetate prescribing information for a list of contraindications for norethindrone acetate.

5 WARNINGS AND PRECAUTIONS

5.1 Loss of Bone Mineral Density

LUPRON DEPOT 11.25 mg induces a hypoestrogenic state that results in loss of bone mineral density (BMD), some of which may not be reversible after stopping treatment. In women with major risk factors for decreased BMD such as chronic alcohol use (> 3 units per day), tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of LUPRON DEPOT 11.25 mg may pose an additional risk. Carefully weigh the risks and benefits of LUPRON DEPOT 11.25 mg use in these populations.

The duration of LUPRON DEPOT 11.25 mg treatment is limited by the risk of loss of bone mineral density *[see Dosage and Administration (2.1)]*.

When using LUPRON DEPOT 11.25 mg for the management of endometriosis, combination use of norethindrone acetate (add-back therapy) is effective in reducing the loss of BMD that occurs with leuprolide acetate *[see Clinical Studies (14.2)]*. Do not retreat with LUPRON DEPOT 11.25 mg without combination norethindrone acetate. Assess BMD before retreatment.

5.2 Embryo-Fetal Toxicity

Based on animal reproduction studies and the drug's mechanism of action, LUPRON DEPOT 11.25 mg may cause fetal harm if administered to a pregnant woman and is contraindicated in pregnant women. Exclude pregnancy prior to initiating treatment with LUPRON DEPOT 11.25 mg if clinically indicated. Discontinue LUPRON DEPOT 11.25 mg if the woman becomes pregnant during treatment and inform the woman of potential risk to the fetus *[see Contraindications (4)* and *Use in Specific Populations (8.1)]*. Advise women to notify their healthcare provider if they believe they may be pregnant.

When used at the recommended dose and dosing interval, LUPRON DEPOT 11.25 mg usually inhibits ovulation and stops menstruation. Contraception, however, is not ensured by taking LUPRON DEPOT 11.25 mg. If contraception is indicated, advise women to use non-hormonal methods of contraception while on treatment with LUPRON DEPOT 11.25 mg.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, have been reported with LUPRON DEPOT use. LUPRON DEPOT 11.25 mg is contraindicated in women with a history of hypersensitivity to gonadotropin-releasing hormone (GnRH) or GnRH agonist analogs *[see Adverse Reactions (6.2)]*.

In clinical trials of LUPRON DEPOT 11.25 mg, adverse events of asthma were reported in women with pre-existing histories of asthma, sinusitis, and environmental or drug allergies. Symptoms consistent with an anaphylactoid or asthmatic process have been reported postmarketing.

5.4 Initial Flare of Symptoms

Following the first dose of LUPRON DEPOT 11.25 mg, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in symptoms may be observed during the initial days of therapy, but these should dissipate with continued therapy.

5.5 Convulsions

There have been postmarketing reports of convulsions in women on GnRH agonists, including leuprolide acetate. These included women with and without concurrent medications and comorbid conditions.

5.6 Clinical Depression

Depression may occur or worsen during treatment with GnRH agonists including LUPRON DEPOT 11.25 mg *[see Adverse Reactions (6.1)]*. Carefully observe women for depression, especially those with a history of depression and consider whether the risks of continuing LUPRON DEPOT 11.25 mg outweigh the benefits. Women with new or worsening depression should be referred to a mental health professional, as appropriate.

5.7 Risks Associated with Norethindrone Combination Treatment

If LUPRON DEPOT 11.25 mg is administered with norethindrone acetate, the warnings and precautions for norethindrone acetate apply to this regimen. Refer to the norethindrone acetate prescribing information for a full list of the warnings and precautions for norethindrone acetate.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Loss of Bone Mineral Density *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Initial Flare of Symptoms with Management of Endometriosis *[see Warnings and Precautions (5.4)]*
- Convulsions *[see Warnings and Precautions (5.5)]*
- Clinical Depression *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

LUPRON DEPOT 11.25 mg (Monotherapy)

The safety of LUPRON DEPOT 11.25 mg for the endometriosis and fibroids indications was established based on adequate and well-controlled adult studies of LUPRON DEPOT 3.75 mg for 1-month administration and on a single trial of LUPRON DEPOT 11.25 mg. The safety of LUPRON DEPOT 3.75 mg was evaluated in six clinical studies in which a total of 332 women were treated for up to six months. Women were treated with monthly IM injections of LUPRON DEPOT 3.75 mg. The population age range was 18 to 53 years old.

Adverse Reactions (>1%) Leading to Study Discontinuation

In the six studies 1.8% of women treated with LUPRON DEPOT 3.75 mg discontinued prematurely due to hot flashes.

Common Adverse Reactions

The safety of LUPRON DEPOT 3.75 mg was evaluated in controlled clinical trials in 166 women with endometriosis and 166 women with uterine fibroids. Adverse reactions reported in ≥ 5% of women in either of these populations are noted in Tables 2 and 3, below.

Table 2. Adverse Reactions Reported in ≥ 5% of Women with Endometriosis Taking LUPRON DEPOT 3.75 mg - 2 Studies

	LUPRON DEPOT 3.75 mg N=166	**Danazol N=136**	**Placebo N=31**
	%	**%**	**%**
Hot flashes/sweats*	84	57	29
Headache*	32	22	6
Vaginitis*	28	17	0
Depression/emotional lability*	22	20	3
General pain	19	16	3
Weight gain/loss	13	26	0
Nausea/vomiting	13	13	3
Decreased libido*	11	4	0
Dizziness	11	3	0
Acne	10	20	0
Skin reactions	10	15	3
Joint disorder*	8	8	0
Edema	7	13	3
Paresthesias	7	8	0
GI disturbances*	7	6	3
Neuromuscular disorders*	7	13	0
Breast changes/tenderness/pain*	6	9	0
Nervousness*	5	8	0

In these same studies, symptoms reported in < 5% of women included:

- *Body as a Whole* - Injection site reactions
- *Cardiovascular System* - Palpitations, syncope, tachycardia
- *Digestive System* - Appetite changes, dry mouth, thirst

- *Endocrine System* - Androgen-like effects, lactation
- *Blood and Lymphatic System* - Ecchymosis
- *Nervous/Psychiatric System* - Anxiety*, insomnia/sleep disorders*, delusions, memory disorder, personality disorder
- *Dermal System* - Alopecia, hair disorder
- *Ocular system* - Ophthalmologic disorders*
- *Urogenital System* - Dysuria*.

* = Possible effect of decreased estrogen.

Table 3. Adverse Reactions Reported in ≥ 5% of Women with Uterine Fibroids (4 Studies) Taking LUPRON DEPOT 3.75 mg

	LUPRON DEPOT 3.75 mg N=166	**Placebo N=163**
	%	**%**
Hot flashes/sweats*	73	18
Headache*	26	18
Vaginitis*	11	2
Depression/emotional lability*	11	4
Asthenia	8	5
General pain	8	6
Joint disorder*	8	3
Edema	5	1
Nausea/vomiting	5	4
Nervousness*	5	1

In these same studies, symptoms reported in < 5% of women included:
- *Body as a Whole* - Body odor, flu syndrome, injection site reactions
- *Cardiovascular System* - Tachycardia
- *Digestive System* - Appetite changes, dry mouth, taste perversion
- *Endocrine System* - Androgen-like effects, menstrual disorders
- *Nervous/Psychiatric System* - Anxiety*, insomnia/sleep disorders*
- *Respiratory System* - Rhinitis
- *Dermal System* - Nail disorder
- *Ocular system* - Conjunctivitis

* = Possible effect of decreased estrogen.

In one controlled clinical trial utilizing the monthly formulation of LUPRON DEPOT 3.75 mg and LUPRON DEPOT 7.5 mg in women diagnosed with uterine fibroids received one injection every 4 weeks for a duration of 12 weeks. Adverse reactions of galactorrhea, pyelonephritis, and urinary incontinence were reported in the 7.5 mg dose group but not in the 3.75 mg dose group. Generally, a higher incidence of hypoestrogenic effects was observed at the higher dose.

In a pharmacokinetic trial involving 20 healthy female subjects receiving LUPRON DEPOT 11.25 mg, a few adverse reactions were reported with this formulation that were not reported previously, including face edema.

In a phase 4 study involving women with endometriosis who received LUPRON DEPOT 3.75 mg (N=20) administered monthly or LUPRON DEPOT 11.25 mg (N=21) administered every 3 months, similar adverse reactions were reported by the two groups of women. In general, the safety profiles of the two formulations were comparable in this study.

LUPRON DEPOT 3.75 mg in combination with Norethindrone Acetate 5 mg

The safety of co-administering LUPRON DEPOT 3.75 mg and norethindrone acetate was evaluated in two clinical studies in which a total of 242 women with endometriosis were treated for up to one year. Women were treated with monthly IM injections of LUPRON DEPOT 3.75 mg (13 injections) alone or monthly IM injections of LUPRON DEPOT 3.75 mg (13 injections) plus norethindrone acetate 5 mg daily. The population age range was 17 to 43 years old. The majority of women were Caucasian (87%).

In one study, 106 women were randomized to one year of treatment with LUPRON DEPOT 3.75 mg alone or with LUPRON DEPOT 3.75 mg and norethindrone acetate. The other study was an open-label, single arm clinical study in 136 women on one year of treatment with LUPRON DEPOT 3.75 mg plus norethindrone acetate, with follow-up for up to 12 months after completing treatment.

Adverse Reactions (>1%) Leading to Study Discontinuation

In the controlled study, 18% of women treated monthly with LUPRON DEPOT 3.75 mg and 18% of women treated monthly with LUPRON DEPOT 3.75 mg plus norethindrone acetate discontinued therapy due to adverse reactions, most commonly hot flashes (6%) and insomnia (4%) in the LUPRON DEPOT 3.75 mg alone group and hot flashes and emotional lability (4% each) in the LUPRON DEPOT 3.75 mg plus norethindrone group.

In the open-label study, 13% of women treated monthly with LUPRON DEPOT 3.75 mg plus norethindrone acetate discontinued therapy due to adverse reactions, most commonly depression (4%) and acne (2%).

Common Adverse Reactions

Table 4 lists the adverse reactions observed in at least 5% of women in any treatment group, during the first 6 months of treatment in the two add-back clinical studies, in which women were treated with monthly LUPRON DEPOT 3.75 mg with or without norethindrone acetate 5mg daily co-treatment. The most frequently-occurring adverse reactions observed in these studies were hot flashes and headaches.

Table 4. Adverse Reactions Occurring in the First Six Months of Treatment in ≥ 5% of Women with Endometriosis

	Controlled Study		Open Label Study
	LD-Only*	LD/N†	LD/N†
	N=51	N=55	N=136
Adverse Reactions	%	%	%
Any Adverse Reaction	98	96	93
Hot flashes/Sweats	98	87	57
Headache/Migraine	65	51	46
Depression/Emotional Lability	31	27	34
Insomnia/Sleep Disorder	31	13	15
Nausea/Vomiting	25	29	13
Pain	24	29	21
Vaginitis	20	15	8
Asthenia	18	18	11
Dizziness/Vertigo	16	11	7
Altered Bowel Function (constipation, diarrhea)	14	15	10
Weight Gain	12	13	4
Decreased Libido	10	4	7
Nervousness/Anxiety	8	4	11
Breast Changes/Pain/Tenderness	6	13	8

Memory Disorder	6	2	4
Skin/Mucous Membrane Reaction	4	9	11
GI Disturbance (dyspepsia, flatulence)	4	7	4
Androgen-Like Effects (acne, alopecia)	4	5	18
Changes in Appetite	4	0	6
Injection Site Reaction	2	9	3
Neuromuscular Disorder (leg cramps, paresthesia)	2	9	3
Menstrual Disorders	2	0	5
Edema	0	9	7

* LD-Only = LUPRON DEPOT 3.75 mg
† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg

In the controlled clinical trial, 50 of 51 (98%) women in the LUPRON DEPOT 3.75 mg arm and 48 of 55 (87%) women in the LUPRON DEPOT 3.75 mg plus norethindrone acetate arm reported experiencing hot flashes on one or more occasions during treatment.

Table 5 presents hot flash data in the last month of treatment.

Table 5. Hot Flashes in the Month Prior to the Assessment Visit (Controlled Study)

Assessment Visit	Treatment Group	Number of Women Reporting Hot Flashes		Number of Days with Hot Flashes		Maximum Number Hot Flashes in 24 Hours	
		N	(%)	N[2]	Mean	N[2]	Mean
Week 24	LD-Only*	32/37	86	37	19	36	5.8
	LD/N†	22/38	58[1]	38	7[1]	38	1.9[1]

* LD-Only = LUPRON DEPOT 3.75 mg.
† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg.
[1]Statistically significantly less than the LD-Only group ($p<0.01$).
[2]Number of women assessed.

Serious Adverse Reactions

Urinary tract infection (1.9%), renal calculus (0.7%), depression (0.7%)

Changes in Laboratory Values during Treatment

Liver Enzymes

Three percent of women with uterine fibroids treated with LUPRON DEPOT 3.75 mg for 1-month administration, manifested post-treatment transaminase values that were at least twice the baseline value and above the upper limit of the normal range.

In the two clinical trials of women with endometriosis, 2% (4 of 191) women receiving leuprolide acetate plus norethindrone acetate for up to 12 months developed an elevated (at least twice the upper limit of normal) SGPT and 1% (2 of 136) developed an elevated GGT. Among these six women with increased liver tests, the increases in five were observed beyond 6 months of treatment. None were associated with an elevated bilirubin concentration.

Lipids

Triglycerides were increased above the upper limit of normal in 12% of the women with endometriosis who received LUPRON DEPOT 3.75 mg and in 32% of the women receiving LUPRON DEPOT 11.25 mg.

Of those endometriosis and women with uterine fibroid whose pretreatment cholesterol values were in the normal range, mean change following therapy was +16 mg/dL to +17 mg/dL in women with

endometriosis and +11 mg/dL to +29 mg/dL in women with uterine fibroids. In the women with endometriosis, increases from the pretreatment values were statistically significant ($p<0.03$). There was essentially no increase in the LDL/HDL ratio in women from either population receiving LUPRON DEPOT 3.75 mg.

Percent changes from baseline for serum lipids and percentages of women with serum lipid values outside of the normal range in the two studies of LUPRON DEPOT 3.75 mg and norethindrone acetate are summarized in Table 6 and Table 7 below. The major impact of adding norethindrone acetate to treatment with LUPRON DEPOT 3.75 mg was a decrease in serum HDL cholesterol and an increase in the LDL/HDL ratio.

Table 6. Serum Lipids: Mean Percent Changes from Baseline Values at Treatment Week 24

	LUPRON DEPOT 3.75 mg		**LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily**			
	Controlled Study (n=39)		**Controlled Study (n=41)**		**Open Label Study (n=117)**	
	Baseline Value*	Week 24 % Change	Baseline Value*	Week 24 % Change	Baseline Value*	Week 24 % Change
Total Cholesterol	170.5	9.2%	179.3	0.2%	181.2	2.8%
HDL Cholesterol	52.4	7.4%	51.8	-18.8%	51.0	-14.6%
LDL Cholesterol	96.6	10.9%	101.5	14.1%	109.1	13.1%
LDL/HDL Ratio	2.0†	5.0%	2.1†	43.4%	2.3†	39.4%
Triglycerides	107.8	17.5%	130.2	9.5%	105.4	13.8%
* mg/dL † ratio						

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from women with follow-up data returned to pretreatment values.

Table 7. Percentage of Women with Serum Lipids Values Outside of the Normal Range

	LUPRON DEPOT 3.75 mg		**LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily**			
	Controlled Study (n=39)		**Controlled Study (n=41)**		**Open Label Study (n=117)**	
	Week 0	Week 24*	Week 0	Week 24*	Week 0	Week 24*
Total Cholesterol (>240 mg/dL)	15%	23%	15%	20%	6%	7%
HDL Cholesterol (<40 mg/dL)	15%	10%	15%	44%	15%	41%
LDL Cholesterol (>160 mg/dL)	0%	8%	5%	7%	9%	11%
LDL/HDL Ratio (>4.0)	0%	3%	2%	15%	7%	21%
Triglycerides (>200 mg/dL)	13%	13%	12%	10%	5%	9%
* Includes all women regardless of baseline value.						

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LUPRON DEPOT monotherapy or LUPRON DEPOT with norethindrone acetate add-back therapy. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

During postmarketing surveillance which includes other dosage forms and other populations, the following adverse reactions were reported:

- *Body as a whole:* Hypersensitivity reactions including anaphylaxis, localized reactions including induration and abscess at the site of injection
- *Nervous/Psychiatric System:* Mood swings, including depression; suicidal ideation and attempt; convulsion, peripheral neuropathy, paralysis
- *Hepato-biliary system:* Serious liver injury
- *Injury, poisoning and procedural complications:* Spinal fracture
- *Investigations:* Decreased white blood count
- *Musculoskeletal and connective tissue system:* Tenosynovitis-like symptoms
- *Vascular system:* Hypotension, hypertension, deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, transient ischemic attack
- *Respiratory system:* Symptoms consistent with an asthmatic process
- *Multi-system disorders:* Symptoms consistent with fibromyalgia (e.g., joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath), individually and collectively.

Pituitary apoplexy

During postmarketing surveillance, cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of leuprolide acetate and other GnRH agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with LUPRON DEPOT 11.25 mg.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

LUPRON DEPOT 11.25 mg is contraindicated in pregnancy *[see Contraindications (4)]*.

LUPRON DEPOT 11.25 mg may cause fetal harm based on findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. There are limited human data on the use of LUPRON DEPOT in pregnant women. Based on animal reproduction studies, LUPRON DEPOT 11.25 mg may be associated with an increased risk of pregnancy complications, including early pregnancy loss and fetal harm. In animal reproduction studies, subcutaneous administration of leuprolide acetate to rabbits during the period of organogenesis caused embryo-fetal toxicity, decreased fetal weights and a dose-dependent increase in major fetal abnormalities in animals at doses less than the recommended human dose based on body surface area using an estimated daily dose. A similar rat study also showed increased fetal mortality and decreased fetal weights but no major fetal abnormalities at doses less than the recommended human dose based on body surface area using an estimated daily dose *[see Data]*.

Data

Animal Data

When administered on day 6 of pregnancy at test dosages of 0.00024 mg/kg, 0.0024 mg/kg, and 0.024 mg/kg (1/300 to 1/3 of the human dose) to rabbits, leuprolide acetate produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher

doses of LUPRON DEPOT in rabbits and with the highest dose (0.024 mg/kg) in rats.

8.2 Lactation

Risk Summary

There are no data on the presence of leuprolide acetate in either animal or human milk, the effects on the breastfed infants, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUPRON DEPOT 11.25 mg and any potential adverse effects on the breastfed infant from LUPRON DEPOT 11.25 mg or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Exclude pregnancy in women of reproductive potential prior to initiating LUPRON DEPOT 11.25 mg if clinically indicated *[see Warnings and Precautions (5.2)]*.

Contraception

Females

LUPRON DEPOT 11.25 mg may cause embryo-fetal harm when administered during pregnancy. LUPRON DEPOT 11.25 mg is not a contraceptive. If contraception is indicated, advise females of reproductive potential to use a non-hormonal method of contraception during treatment with LUPRON DEPOT 11.25 mg *[see Warnings and Precautions (5.2)]*.

Infertility

Based on its pharmacodynamic effects of decreasing secretion of gonadal steroids, fertility is expected to be decreased while on treatment with LUPRON DEPOT 11.25 mg. Clinical and pharmacologic studies in adults (>18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks *[see Clinical Pharmacology (12.1)]*.

There is no evidence that pregnancy rates are affected following discontinuation of LUPRON DEPOT 11.25 mg.

Animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery of fertility suppression.

8.4 Pediatric Use

Safety and effectiveness of LUPRON DEPOT 11.25 mg for management of endometriosis and the preoperative hematologic improvement of women with anemia caused by fibroids have been established in females of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. The safety and effectiveness of LUPRON DEPOT 11.25 mg for these indications have not been established in premenarcheal pediatric patients.

8.5 Geriatric Use

LUPRON DEPOT 11.25 mg is not indicated in postmenopausal women and has not been studied in this population.

11 DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of gonadotropin-releasing hormone [GnRH or luteinizing hormone releasing hormone (LH-RH)], a GnRH agonist. The chemical name is 5- oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide

acetate (salt) with the following structural formula:

LUPRON DEPOT 11.25 mg (leuprolide acetate for depot suspension for injection) is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres powder which, when mixed with diluent, become a suspension intended as an IM injection.

The front chamber of LUPRON DEPOT 11.25 mg prefilled dual-chamber syringe contains leuprolide acetate for depot suspension (11.25 mg), polylactic acid (99.3 mg) and D-mannitol (19.45 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT 11.25 mg, acetic acid is lost, leaving the peptide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide acetate is a long-acting GnRH analog. A single injection of LUPRON DEPOT 11.25 mg results in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing of LUPRON DEPOT 11.25 mg at quarterly intervals results in decreased secretion of gonadal steroids. Consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally.

12.2 Pharmacodynamics

In a pharmacokinetic/pharmacodynamic study of LUPRON DEPOT 11.25 mg in healthy female subjects (N=20), the onset of estradiol suppression was observed for individual subjects between day 4 and week 4 after dosing. By the third week following the injection, the mean estradiol concentration (8 pg/mL) was in the menopausal range. Throughout the remainder of the dosing period, mean serum estradiol levels ranged from the menopausal to the early follicular range.

Serum estradiol was suppressed to ≤20 pg/mL in all subjects within four weeks and remained suppressed (≤40 pg/mL) in 80% of subjects until the end of the 12-week dosing interval, at which time two of these subjects had a value between 40 and 50 pg/mL. Four additional subjects had at least two consecutive elevations of estradiol (range 43-240 pg/mL) levels during the 12-week dosing interval, but there was no indication of luteal function for any of the subjects during this period.

Administration of LUPRON DEPOT 11.25 mg in therapeutic doses results in suppression of the pituitary–gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of LUPRON DEPOT 11.25 mg may be affected.

12.3 Pharmacokinetics

Absorption

Following a single injection of the 3-month formulation of LUPRON DEPOT 11.25 mg in female subjects, a mean plasma leuprolide concentration of 36.3 ng/mL was observed at 4 hours. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing and mean levels then declined gradually to near the lower limit of detection by 12 weeks. The mean (± standard deviation) leuprolide concentration from 3 to 12 weeks was 0.23 ± 0.09 ng/mL. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

In a pharmacokinetic/pharmacodynamic study of endometriosis patients, IM LUPRON DEPOT 11.25 mg (n=19) every 12 weeks or IM LUPRON DEPOT 3.75 mg (n=15) every 4 weeks was administered for 24 weeks. There was no statistically significant difference in changes of serum estradiol concentration from baseline between the 2 treatment groups.

Distribution

The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. *In vitro* binding to human plasma proteins ranged from 43% to 49%.

Metabolism

Leuprolide acetate is a peptide that is primarily degraded by peptidase. In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two-compartment model.

Metabolite I, a smaller inactive peptide, plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Excretion

Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Use in Specific Populations

The pharmacokinetics of LUPRON DEPOT have not been evaluated in patients with hepatic and renal impairment.

Drug Interactions

No pharmacokinetic drug-drug interaction studies have been conducted with LUPRON DEPOT 11.25 mg. However, leuprolide acetate is a peptide that is not degraded by cytochrome P-450 enzymes; hence, drug interactions associated with cytochrome P-450 enzymes would not be expected to occur.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years

with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

14 CLINICAL STUDIES

The safety and efficacy of LUPRON DEPOT 11.25 mg for the indicated populations has been established based on adequate and well-controlled studies in adults (See Table 8) of LUPRON DEPOT 3.75 mg and on a single trial of LUPRON DEPOT 11.25 mg *[see Indications and Usage (1)]*.

14.1 Endometriosis

LUPRON DEPOT 11.25 mg Monotherapy

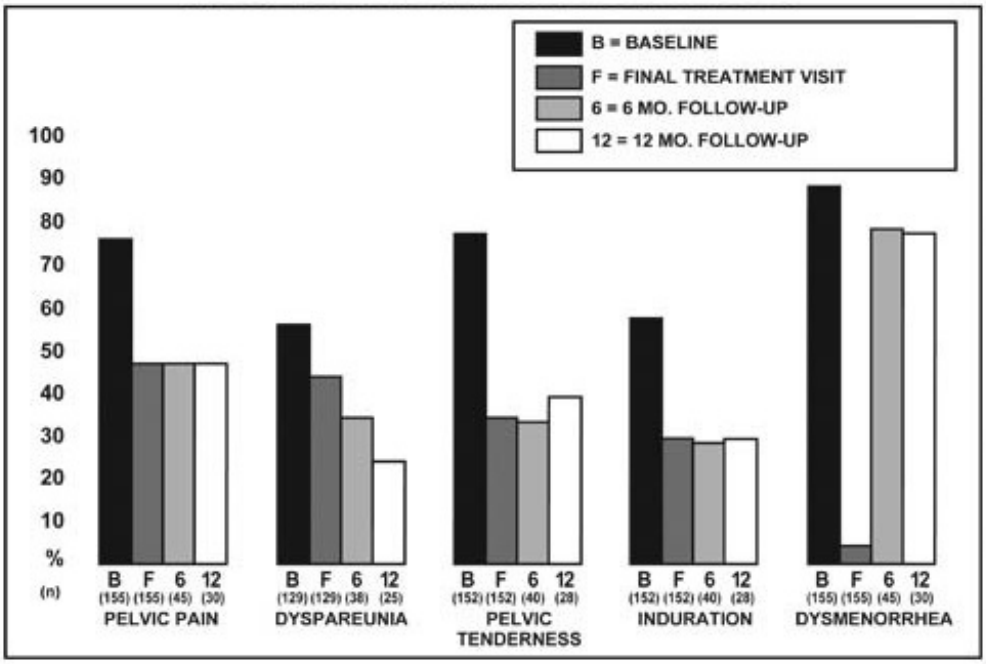
In controlled clinical studies, LUPRON DEPOT 3.75 mg monthly for six months was shown to be comparable to danazol 800 mg/day in relieving the clinical sign/symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants as evidenced by laparoscopy.

The clinical significance of a decrease in endometriotic lesions is not known, and laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.

LUPRON DEPOT 3.75 mg monthly induced amenorrhea in 74% and 98% of the women after the first and second month of treatment, respectively. Most of the remaining women reported episodes of only light bleeding or spotting. In the first, second and third post-treatment months, normal menstrual cycles resumed in 7%, 71% and 95% of women, respectively, excluding those who became pregnant.

Figure 1 illustrates the percent of women with symptoms at baseline, final treatment visit and sustained relief at 6 and 12 months following discontinuation of treatment for the various symptoms evaluated during the two controlled clinical studies. A total of 166 women received LUPRON DEPOT 3.75 mg. Seventy-five percent (N=125) of these elected to participate in the follow-up period. Of these women, 36% and 24% are included in the 6-month and 12-month follow-up analysis, respectively. All the women who had a pain evaluation at baseline and at least of one treatment visit are included in the Baseline (B) and final treatment visit (F) analysis.

Figure 1. Percent of Women with Signs/Symptoms of Endometriosis at Baseline, Final Treatment Visit, and After 6 and 12 Months of Follow-Up, LUPRON DEPOT 3.75 mg Monthly for Six Months



In a pharmacokinetic/pharmacodynamic study of healthy female subjects (N=20) LUPRON DEPOT 11.25 mg induced amenorrhea in 85% (N=17) of subjects during the initial month and 100% during the second month following the injection. All subjects remained amenorrheic through the remainder of the 12-week dosing interval. Episodes of light bleeding and spotting were reported by a majority of subjects during the first month after the injection and in a few subjects at later time-points. Menses resumed on average 12 weeks (range 2.9 to 20.4 weeks) following the end of the 12-week dosing interval.

LUPRON DEPOT 11.25 mg produced similar pharmacodynamic effects in terms of hormonal and menstrual suppression to those achieved with monthly injections of LUPRON DEPOT 3.75 mg during the controlled clinical trials for the management of endometriosis and the anemia caused by uterine fibroids *[see Clinical Pharmacology (12.2)]*.

A six-month pharmacokinetic/pharmacodynamic post-marketing study in 41 women that included both the LUPRON DEPOT 3.75 mg dose (N=20) administered once monthly and the LUPRON DEPOT 11.25 mg dose (N=21) administered once every three months did not reveal clinically significant differences in terms of efficacy in reducing painful symptoms of endometriosis or magnitude of the decrease in bone mineral density (BMD) associated with use of LUPRON DEPOT 3.75 mg and LUPRON DEPOT 11.25 mg. In both treatment groups, suppression of menses (defined as no new menses for at least 60 consecutive days) was achieved in 100% of the women who remained in the study for at least 60 days. Vertebral bone density measured by dual energy x-ray absorptiometry (DEXA) decreased compared with baseline by an average of 3.0% and 2.8% at six months for the two groups, respectively.

LUPRON DEPOT with Norethindrone Acetate Add-Back Therapy

Two clinical studies with treatment duration of 12 months were conducted to evaluate the effect of co-administration of LUPRON DEPOT 3.75 mg and norethindrone acetate on the loss of bone mineral density (BMD) associated with LUPRON DEPOT 3.75 mg and on the efficacy of LUPRON DEPOT in relieving symptoms of endometriosis. All women in these studies received calcium supplementation with 1000 mg elemental calcium. A total of 242 women were treated with monthly administration of LUPRON DEPOT 3.75 mg (13 injections) and 191 of them were co-administered 5 mg norethindrone acetate taken daily. The population age range was 17-43 years old. The majority of women were Caucasian (87%).

One co-administration study was a controlled, randomized and double-blind study included 51 women

treated monthly with LUPRON DEPOT 3.75 mg alone and 55 women treated monthly with LUPRON DEPOT 3.75 mg plus norethindrone acetate daily. Women in this trial were followed for up to 24 months after completing one year of treatment. The other study was an open-label single arm clinical study in 136 women of one year of treatment with LUPRON DEPOT 3.75 mg monthly and daily norethindrone acetate 5 mg, with follow-up for up to 12 months after completing treatment. See Table 8.

The assessment of efficacy was based on the investigator's or the woman's monthly assessment of five signs or symptoms of endometriosis (dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness and pelvic induration).

Table 8 below provides detailed efficacy data regarding relief of symptoms of endometriosis based on the two studies of co-administration of LUPRON DEPOT 3.75 mg monthly and norethindrone acetate 5 mg daily.

Table 8. Effect of LUPRON DEPOT and Norethindrone Acetate on the Symptoms of Endometriosis and Mean Clinical Severity Scores

			Percent of Women with Symptoms			Clinical Pain Severity Score		
			Baseline		Final	Baseline		Final
Variable	Study	Group	N[1]	(%)[2]	(%)	N[1]	Value[3]	Change
Dysmenorrhea	Controlled Study	LD*[4]	51	(100)	(4)	50	3.2	-2.0
		LD/N†	55	(100)	(4)	54	3.1	-2.0
	Open Label Study	LD/N[5]	136	(99)	(9)	134	3.3	-2.1
Pelvic Pain	Controlled Study	LD[4]	51	(100)	(66)	50	2.9	-1.1
		LD/N	55	(96)	(56)	54	3.1	-1.1
	Open Label Study	LD/N[5]	136	(99)	(63)	134	3.2	-1.2
Deep Dyspareunia	Controlled Study	LD	42	(83)	(37)	25	2.4	-1.0
		LD/N	43	(84)	(45)	30	2.7	-0.8
	Open Label Study	LD/N	102	(91)	(53)	94	2.7	-1.0
Pelvic Tenderness	Controlled Study	LD[4]	51	(94)	(34)	50	2.5	-1.0
		LD/N	54	(91)	(34)	52	2.6	-0.9
	Open Label Study	LD/N[5]	136	(99)	(39)	134	2.9	-1.4
Pelvic Induration	Controlled Study	LD[4]	51	(51)	(12)	50	1.9	-0.4
		LD/N	54	(46)	(17)	52	1.6	-0.4
	Open Label Study	LD/N[5]	136	(75)	(21)	134	2.2	-0.9

* LD = LUPRON DEPOT 3.75 mg assessment
† LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg
[1] Number of women that were included in the assessment
[2] Percentage of women with the symptom/sign
[3] Value description: 1=none; 2= mild; 3= moderate; 4= severe
[4] 6-month study duration of treatment
[5] 12-month study duration of treatment with 12 months of follow up

Suppression of menses (menses was defined as three or more consecutive days of menstrual bleeding) was maintained throughout treatment in 84% and 73% of women receiving leuprolide acetate and norethindrone acetate, in the controlled study and open label study, respectively. The median time for menses resumption after treatment with leuprolide acetate and norethindrone acetate was 8 weeks.

Changes in Bone Density

The effect of LUPRON DEPOT 3.75 mg and norethindrone acetate on bone mineral density was evaluated by dual energy x-ray absorptiometry (DEXA) scan in the two clinical trials. For the open-

label study, success in mitigating BMD loss was defined as the lower bound of the 95% confidence interval around the change from baseline at one year of treatment not to exceed -2.2%. The bone mineral density data of the lumbar spine from these two studies are presented in Table 9.

Table 9. Mean Percent Change from Baseline in Bone Mineral Density of Lumbar Spine

	LUPRON DEPOT 3.75 mg (LD only)		LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily (LD/N)			
	Controlled Study		Controlled Study		Open Label Study	
	N	Change Mean (95% CI)#	N	Change Mean (95% CI)#	N	Change Mean (95% CI)#
Week 24*	41	-3.2% (-3.8, -2.6)	42	-0.3% (-0.8, 0.3)	115	-0.2% (-0.6, 0.2)
Week 52†	29	-6.3% (-7.1, -5.4)	32	-1.0% (-1.9, -0.1)	84	-1.1% (-1.6, -0.5)

* Includes on-treatment measurements that fell within 2 to 252 days after the first day of treatment.
† Includes on-treatment measurements >252 days after the first day of treatment.
# 95% CI: 95% Confidence Interval

The change in BMD following discontinuation of treatment is shown in Table 10.

Table 10. Mean Percent Change from Baseline in BMD of Lumbar Spine in Post-Treatment Follow-up Period[1]

Post Treatment Measurement	Controlled Study						Open Label Study		
	LD-Only			LD/N			LD/N		
	N	Mean % Change	95% CI (%)[2]	N	Mean % Change	95% CI (%)	N	Mean % Change	95% CI (%)[2]
Month 8	19	-3.3	(-4.9, -1.8)	23	-0.9	(-2.1, 0.4)	89	-0.6	(-1.2, 0.0)
Month 12	16	-2.2	(-3.3, -1.1)	12	-0.7	(-2.1, 0.6)	65	0.1	(-0.6, 0.7)

[1] Patients with post treatment measurements
[2] 95% CI (2-sided) of percent change in BMD values from baseline

These clinical studies demonstrated that co-administration of leuprolide acetate and norethindrone acetate 5 mg daily is effective in significantly reducing the loss of bone mineral density that occurs with both LUPRON DEPOT 3.75 mg and 11.25 mg treatments, and in relieving symptoms of endometriosis.

14.2 Fibroids

LUPRON DEPOT 3.75 mg monthly for a period of three to six months was studied in four controlled clinical trials.

In one of these clinical studies, enrollment was based on hematocrit ≤ 30% and/or hemoglobin ≤ 10.2 g/dL. Administration of LUPRON DEPOT 3.75 mg monthly, concomitantly with iron, produced an increase of ≥ 6% hematocrit and ≥ 2 g/dL hemoglobin in 77% of women at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of ≥ 36% and hemoglobin of ≥ 12 g/dL, thus allowing for autologous blood donation prior to surgery. At two and three months, respectively, 71% and 75% of women met this criterion (Table 11). These data suggest however, that some women may benefit from iron alone or 1 to 2 months of LUPRON DEPOT 3.75 mg.

Table 11. Percent of Women Achieving Hematocrit ≥ 36% and Hemoglobin ≥ 12 g/dL

Treatment Group	Week 4	Week 8	Week 12

LUPRON DEPOT 3.75 mg with Iron (N=104)	40*	71†	75*
Iron Alone (N=98)	17	39	49
* P-Value < 0.01 † P-Value < 0.001			

Excessive vaginal bleeding (menorrhagia or menometrorrhagia) decreased in 80% of women at three months. Episodes of spotting and menstrual-like bleeding were noted in 16% of women at final visit.

In this same study, a decrease in uterine volume and myoma volume of ≥25% was seen in 60% and 54% of women, respectively. The mean fibroid diameter was 6.3 cm at pretreatment and decreased to 5.6 cm at the end of treatment. LUPRON DEPOT 3.75 mg was found to relieve symptoms of bloating, pelvic pain, and pressure.

In three other controlled clinical trials, enrollment was not based on hematologic status. Mean uterine volume decreased by 41% and myoma volume decreased by 37% at final visit as evidenced by ultrasound or MRI. The mean fibroid diameter was 5.6 cm at pretreatment and decreased to 4.7 cm at the end of treatment. These women also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Ninety-five percent of these women became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively.

In addition, post-treatment follow-up was carried out in one clinical trial for a small percentage of women on LUPRON DEPOT 3.75 mg (N=46) among the 77% who demonstrated a ≥ 25% decrease in uterine volume while on therapy. Menses usually returned within two months of cessation of therapy. Mean time to return to pretreatment uterine size was 8.3 months. Regrowth did not appear to be related to pretreatment uterine volume.

Changes in Bone Density

In one of the studies for fibroids described above, when LUPRON DEPOT 3.75 mg was administered for three months in uterine fibroid women, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2.7% compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each LUPRON DEPOT 11.25 mg kit (NDC 0074-3663-03) contains:

- one prefilled dual-chamber syringe
- one plunger
- two alcohol swabs

Each single-dose dual chamber syringe contains sterile white lyophilized microsphere powder of 11.25 mg of leuprolide acetate incorporated in a biodegradable polymer in one chamber and a colorless diluent (1.5 mL) in the other chamber. When mixed with the diluent, LUPRON DEPOT 11.25 mg for injection, is administered as a single IM injection.

Store between 20° to 25°C (68° to 77°F). Excursions permitted to 15° to 30°C (59° to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Loss of Bone Density

Advise patients about the risk of loss of bone mineral density and that treatment is limited *[see Dosage and Administration (2.1)]*. Advise patients about other factors that can increase and decrease their risk of bone mineral density loss *[see Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the possible risk to a fetus. Advise patients to inform healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.2) and Use in Special Populations (8.1)]*.
- If contraception is indicated, advise females of reproductive potential to use non-hormonal contraception during treatment with LUPRON DEPOT 11.25 mg *[see Use in Special Populations (8.3)]*.

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions, including anaphylaxis, have been reported with LUPRON DEPOT. Advise patients to seek appropriate medical care if symptoms of hypersensitivity reactions occur *[see Warnings and Precautions (5.3) and Adverse Reactions (6.2)]*.

Initial Flare of Symptoms

Advise patients that they may experience an increase in symptoms during the initial days of therapy. Advise patients that these symptoms should dissipate with continued therapy *[see Warnings and Precautions (5.4)]*.

Convulsions

Inform patients that convulsions have been reported in patients who have received LUPRON DEPOT. Advise patients to seek medical attention in the event of a convulsion *[see Warnings and Precautions (5.5)]*.

Clinical Depression

Inform patients that depression may occur or worsen during treatment with GnRH agonists, including LUPRON DEPOT 11.25 mg, especially in patients with a history of depression. Advise patients to immediately report thoughts and behaviors of concern to healthcare providers *[see Warnings and Precautions (5.6)]*.

Manufactured for

AbbVie Inc.

North Chicago, IL 60064

by Takeda Pharmaceutical Company Limited

Osaka, Japan 540-8645

Revised: March 2020

03-B928

NDC 0074-3663-03

FOR ADULT USE 11.25 mg for 3-Month administration

Single Dose Administration Kit with prefilled dual-chamber syringe.

LupronDepot®

(leuprolide acetate for depot suspension)

11.25 mg for 3-Month administration

FOR INTRAMUSCULAR INJECTION

The front chamber contains: leuprolide acetate 11.25 mg, polylactic acid 99.3 mg, D-mannitol 19.45 mg

The second chamber contains: D-mannitol 75.0 mg, carboxymethylcellulose sodium 7.5 mg, polysorbate 80 1.5 mg, water for injection, USP, and glacial acetic acid, USP to control pH

Rx only

LUPRON DEPOT

leuprolide acetate kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0074-3663

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0074-3663-03	1 in 1 CARTON	11/08/2010	

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 SYRINGE	1.5 mL
Part 2	2 PACKET	2 mL

Part 1 of 2

LUPRON DEPOT

leuprolide acetate injection, powder, lyophilized, for suspension

Product Information	
Route of Administration	INTRAMUSCULAR

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LEUPROLIDE ACETATE (UNII: 37JNS02E7V) (LEUPROLIDE - UNII:EFY6W0M8TG)	LEUPROLIDE ACETATE	11.25 mg in 1.5 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1		1.5 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020708	11/08/2010	

Part 2 of 2

ALCOHOL

isopropyl alcohol swab

Product Information	
Route of Administration	TOPICAL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1		1 mL in 1 PACKET; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
OTC monograph final	PART333	07/07/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020708	11/08/2010	

Labeler - AbbVie Inc. (078458370)

Exhibit

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUPPRELIN® LA safely and effectively. See full prescribing information for SUPPRELIN LA.

SUPPRELIN LA (histrelin acetate) subcutaneous implant
Initial U.S. Approval: 1991

----------INDICATIONS AND USAGE----------
SUPPRELIN LA is a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of children with central precocious puberty (CPP) (1).

----------DOSAGE AND ADMINISTRATION----------
The recommended dose of SUPPRELIN LA is one implant every 12 months. The implant is inserted subcutaneously in the inner aspect of the upper arm and provides continuous release of histrelin for 12 months of hormonal therapy (2).

----------DOSAGE FORMS AND STRENGTHS----------
SUPPRELIN LA is available as a 50 mg histrelin acetate subcutaneous implant which delivers approximately 65 mcg histrelin acetate per day over 12 months (3).

----------CONTRAINDICATIONS----------
- History of hypersensitivity to gonadotropin releasing hormone (GnRH) or GnRH analogs (4).
- Pregnancy (4).

----------WARNINGS AND PRECAUTIONS----------
- Initial Agonistic Action: Initial transient increases of estradiol and/or testosterone may cause a temporary worsening of symptoms (5.1).
- Psychiatric Events: Have been reported in patients taking GnRH agonists. Events include emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms (5.3).
- Convulsions have been observed in patients receiving GnRH agonists with or without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions (5.4).

----------ADVERSE REACTIONS----------
- The most common adverse reaction is implant site reaction (51.1%), including complications related to the insertion or removal of the implant (6).
- Adverse events related to suppression of endogenous sex steroid secretion may occur (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals Solutions Inc. at 1-800-462-3636 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

----------USE IN SPECIFIC POPULATIONS----------
Use of SUPPRELIN LA in children less than 2 years of age is not recommended (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SUPPRELIN LA (histrelin acetate) subcutaneous implant is indicated for the treatment of children with central precocious puberty (CPP).

Children with CPP (neurogenic or idiopathic) have an early onset of secondary sexual characteristics (earlier than 8 years of age in females and 9 years of age in males). They also show a significantly advanced bone age that can result in diminished adult height attainment.

Prior to initiation of treatment a clinical diagnosis of CPP should be confirmed by measurement of blood concentrations of total sex steroids, luteinizing hormone (LH) and follicle stimulating hormone (FSH) following stimulation with a GnRH analog, and assessment of bone age versus chronological age. Baseline evaluations should include height and weight measurements, diagnostic imaging of the brain (to rule out intracranial tumor), pelvic/testicular/adrenal ultrasound (to rule out steroid secreting tumors), human chorionic gonadotropin levels (to rule out a chorionic gonadotropin secreting tumor), and adrenal steroids to exclude congenital adrenal hyperplasia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of SUPPRELIN LA is one implant every 12 months. Each implant contains 50 mg histrelin acetate. The implant is inserted subcutaneously in the inner aspect of the upper arm and provides continuous release of histrelin acetate (65 mcg/day) for 12 months of hormonal therapy. SUPPRELIN LA should be removed after 12 months of therapy (the implant has been designed to allow for a few additional weeks of histrelin acetate release, in order to allow flexibility of medical appointments). At the time an implant is removed, another implant may be inserted to continue therapy. Discontinuation of SUPPRELIN LA should be considered at the discretion of the physician and at the appropriate time point for the onset of puberty (approximately 11 years for females and 12 years for males).

2.2 Recommended Procedure for Implant Insertion and Removal

This procedure section is intended to provide guidance for the insertion and removal of SUPPRELIN LA. The actual procedure used, however, is at the discretion of the qualified healthcare provider performing the procedure.

Insertion of a new implant can proceed using the following **Suggested Insertion Procedure**. If a previous SUPPRELIN LA implant must first be removed, please see the **Suggested Removal Procedure** instructions below.

Suggested Insertion Procedure

The supplies necessary to insert the implant, including the Insertion Tool and local anesthetic, are provided in a separate Implantation Kit that is shipped along with the implant. Please note that the implant should be kept refrigerated (2-8°C) in its sealed vial, pouch, and carton, until needed for the procedure. Once removed from refrigeration, the vial containing the implant (still in its unopened pouch and carton) may remain at room temperature for up to 7 days, if necessary, before being used. If not used in that time, the packaged implant may again be properly refrigerated until the expiration date on the carton.

NOTE: The Implantation Kit is to be stored at room temperature and should *not* be refrigerated.

Insertion of the SUPPRELIN LA implant is a surgical procedure. Sterile gloves and aseptic technique must be used to minimize any chance of infection.

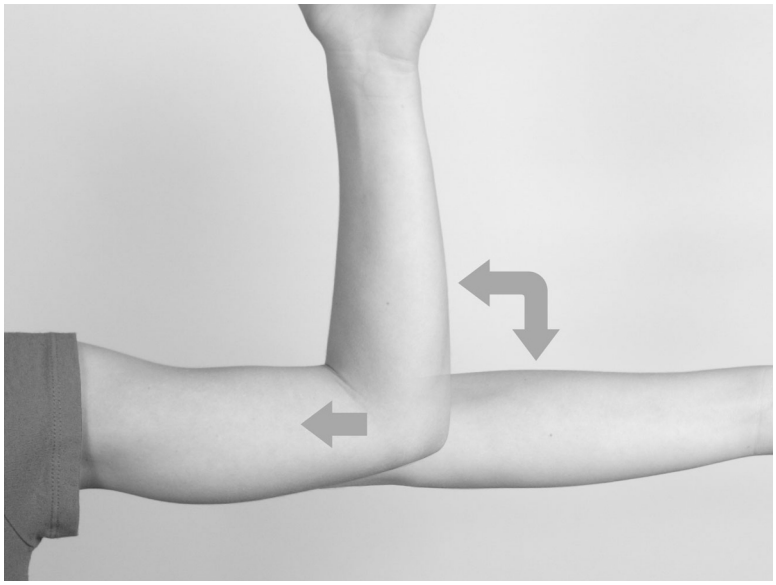
Setting up the Sterile Field

Using proper aseptic technique, the sterilized components of the Implantation Kit needed for the insertion procedure, including the Insertion Tool, are to be carefully dispensed from their packaging onto the Sterile Field drape (*non*-fenestrated) provided. NOTE THAT THE KIT BOX AND ALL PACKAGING ARE NOT STERILE and should be kept off of the Sterile Field drape. DO NOT PLACE THE VIAL OF LOCAL ANESTHETIC OR THE VIAL CONTAINING THE IMPLANT ONTO THE DRAPE as the exterior surface of these vials is not sterile.

The implant vial should not be opened until just before the time of insertion. Open the vial by removing the metal band and carefully pour the sterile contents (implant and sterile saline) onto the Sterile Field drape. The implant can then be handled with sterile gloves or with the sterile mosquito clamp provided. **AVOID bending or pinching the implant.**

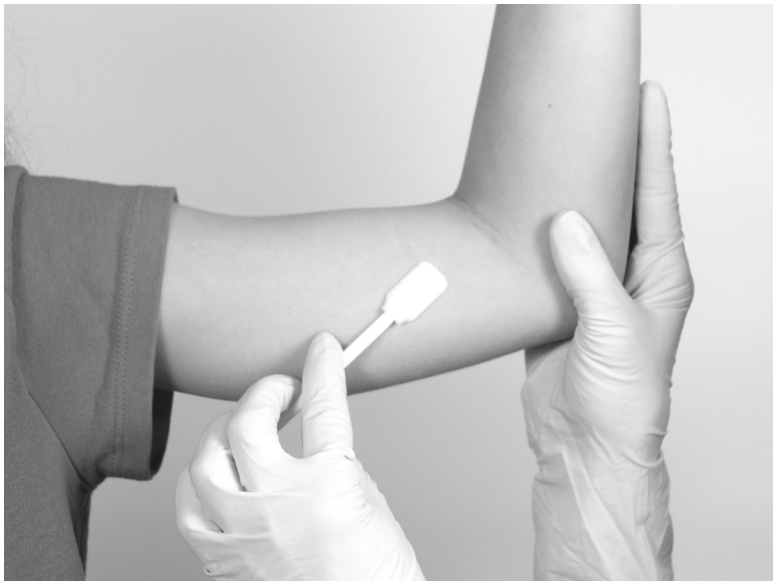
Preparing the Patient and the Insertion Site

The patient should be on his/her back, ideally with the arm least used (e.g., left arm for a right-handed person) positioned, either bent or extended, so that the physician has ready access to the inner aspect of the upper arm. Propping the arm with pillows may help the patient more easily hold the position. The suggested optimum site for subcutaneous insertion is approximately half-way between the shoulder and the elbow, in line with the crease between the biceps and triceps muscles.



Antiseptic

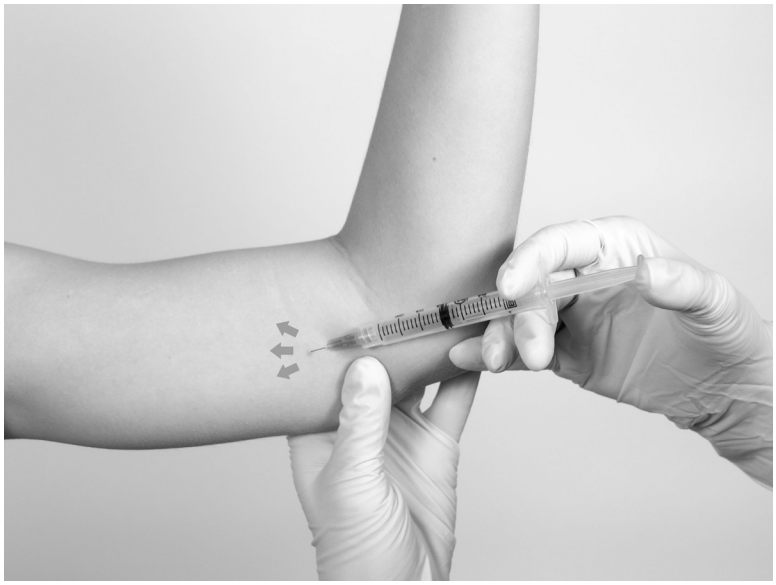
Swab the insertion area with topical antiseptic, then overlay with the *fenestrated* Sterile Field drape provided, so that the opening is over the insertion site (for clarity of illustration, the following images do not show the drape).



Anesthetic

The method of anesthesia utilized (i.e., local, conscious sedation, general) is at the discretion of the healthcare provider.

If local anesthesia is selected: a vial of sterile local anesthetic (note that the exterior of the vial is not sterile) has been provided along with a sterile hypodermic needle for injection. After determining the absence of known allergies to the anesthetic agent, inject anesthetic into the subcutaneous tissue, starting at the planned incision site, then infiltrating along the intended subcutaneous insertion path, up to the length of the implant (a little more than one inch). Local anesthesia may also be supplemented by the use of distraction techniques.



The following sections describe the suggested procedure for insertion of the implant using the Insertion Tool provided. The method of insertion used, however, is at the discretion of the healthcare provider performing the procedure.

Loading the Insertion Tool

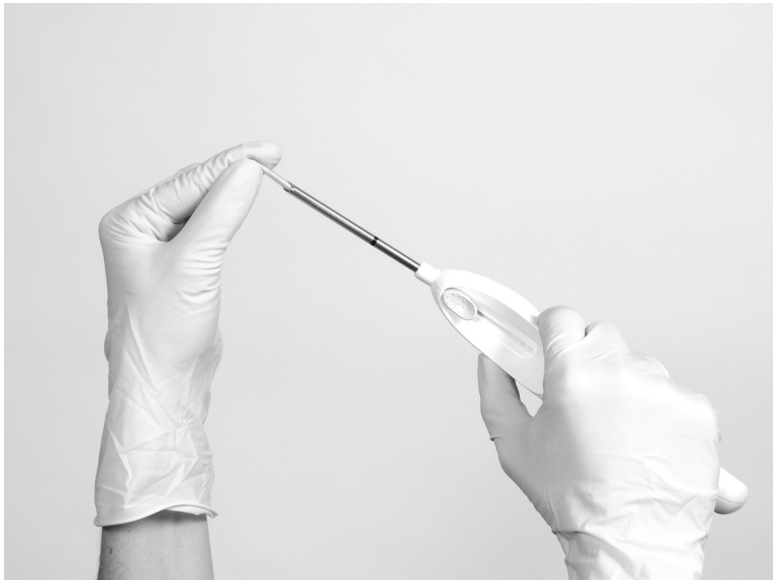
The sterile Insertion Tool is comprised of a fixed handle attached to a retractable, bevel-tipped cannula, into the chamber of which the implant is to be placed for subcutaneous insertion. The cannula can be extended and retracted. The fully extended cannula contains a fixed piston upon which the implant, once inserted, rests. During the final step of the insertion procedure, the cannula will be retracted into the handle using the slide mechanism (green button), thereby exposing and leaving the implant to remain in the subcutaneous tissue.

When first grasping the sterile Insertion Tool, confirm that the cannula is fully extended. Verify this by inspecting the position of the green retraction button. The button should be locked in position all the way forward, towards the cannula, farthest from the handle.

The implant can be picked up using sterile gloves or with the sterile mosquito clamp provided. Avoid bending or pinching the implant. Note that the implant may come out of its vial slightly curved and/or partially flattened after refrigerated storage. To help make the implant more symmetrical prior to loading into the Tool, you can roll the implant a few times (while wearing a sterile glove) between the fingers and thumb.

Insert the implant into the cannula of the Insertion Tool manually or using the mosquito clamp. When inserting the implant into the cannula, DO NOT FORCE the implant. If resistance is felt, the implant should be removed and manually manipulated or rolled as needed, and re-inserted into the cannula.

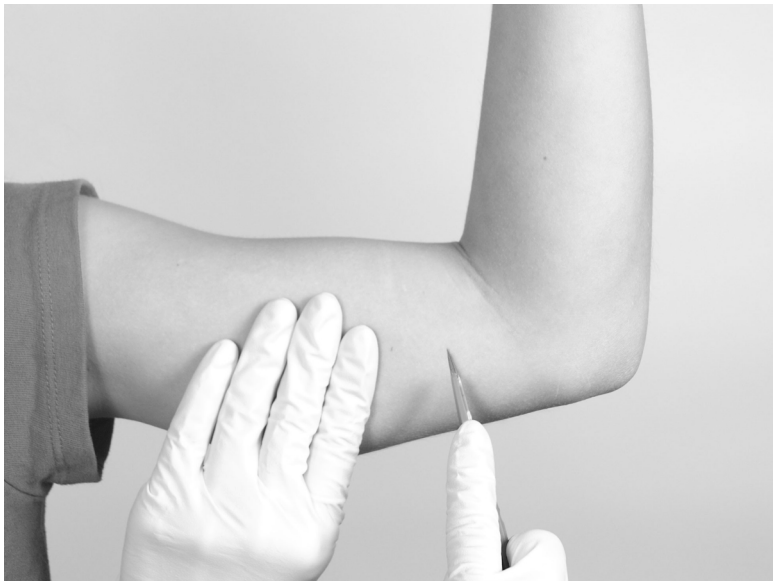
or



When fully inserted, the implant rests inside the cannula so that just the tip of the implant is visible at the beveled end of the cannula.

Making the Incision

Using the sterile scalpel provided, make an incision transverse to the long axis of the arm, and of a size adequate to allow the bore of the cannula to be inserted into the subcutaneous tissue. Be sure that the incision is positioned so that there is sufficient length of upper arm available to fit the implant easily within the intended insertion space.



Inserting the Implant

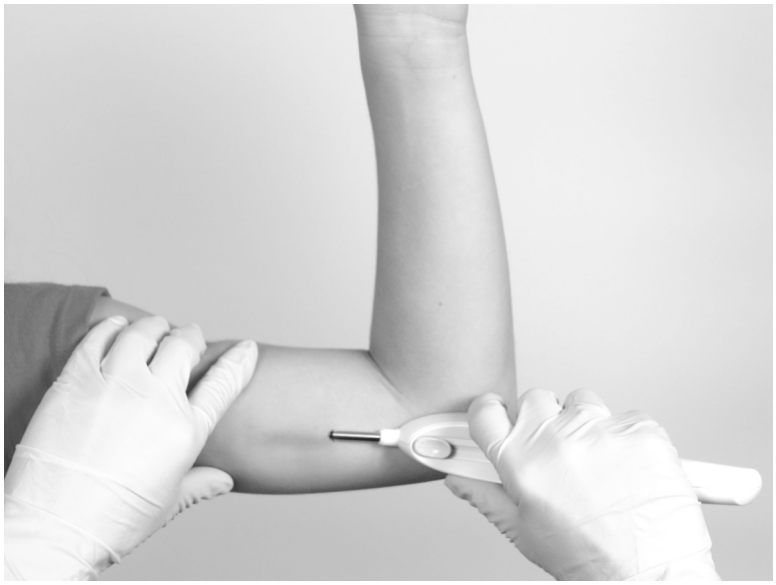
It is suggested that insertion may be easier if a "pocket" for the implant is first created by blunt dissection through the incision, subcutaneously along the path of the anesthetic, using the cannula of the loaded Insertion Tool, or using a sterile hemostatic clamp or equivalent surgical tool.

Be sure to VISIBLY RAISE THE SKIN (known as tenting) at all times during the pocket-making and insertion procedures to ensure correct subcutaneous placement ("just under the skin") of the implant. Note that the cannula of the Insertion Tool, or whatever tool is being used to create the pocket, SHOULD NOT ENTER MUSCLE TISSUE. Deep insertion of the implant will not affect the performance of SUPPRELIN LA, but may cause difficulty in the later removal of the implant.

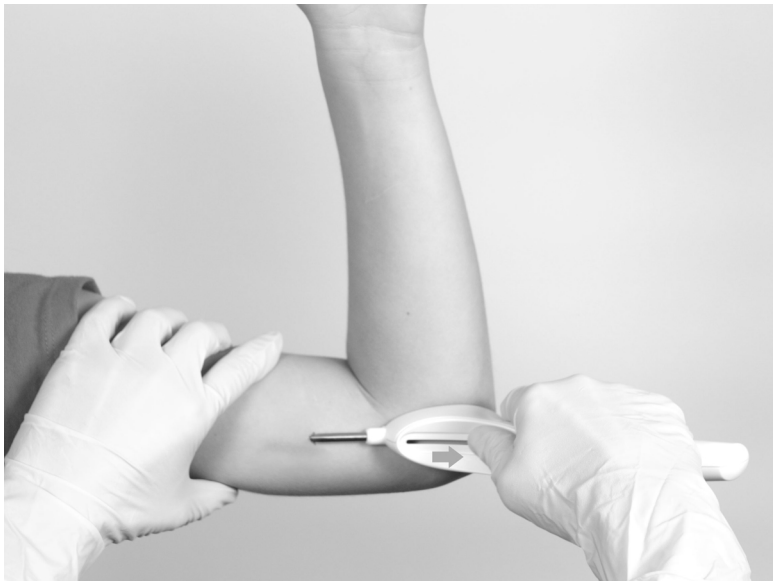
If using the cannula of the loaded Insertion Tool to create the pocket, carefully insert the tip of the cannula into the incision and advance through the subcutaneous tissue, while visibly raising the skin along the length of the cannula up to, but no farther than, the inscribed black line on the cannula. DO NOT DEPRESS THE GREEN RETRACTION BUTTON ON THE TOOL WHILE INSERTING OR ADVANCING THE TOOL INTO THE INCISION.

Pull the Tool back, almost to the beveled tip of the cannula, and advance the Tool forward again, so that the cannula re-enters the pocket completely, but no farther than the inscribed black line. Be sure to keep the insertion path just immediately subcutaneous.

If another tool was used to create the pocket, now insert the loaded cannula of the Insertion Tool containing the implant through the incision, up to the inscribed black line.



Hold the Insertion Tool in place with the base against the patient's arm (if possible) as you carefully move your thumb to the green retraction button. Depress the button to release the locking mechanism, then slide the button back toward the handle until it stops, all the while holding the body of the Insertion Tool in place.



Retracting the button causes the cannula to withdraw from the incision, leaving the implant in the subcutaneous tissue. DO NOT FURTHER ADVANCE THE CANNULA ONCE THE RETRACTION PROCESS HAS STARTED. Likewise, do not withdraw the Insertion Tool until the button is fully retracted or the implant may be pulled partially out of the incision. Once the retraction is complete, the Tool can be fully withdrawn.

NOTE: It may be helpful during the process of retraction and withdrawal of the cannula to apply pressure to the skin over the implant, to help ensure that the implant remains in the subcutaneous pocket.

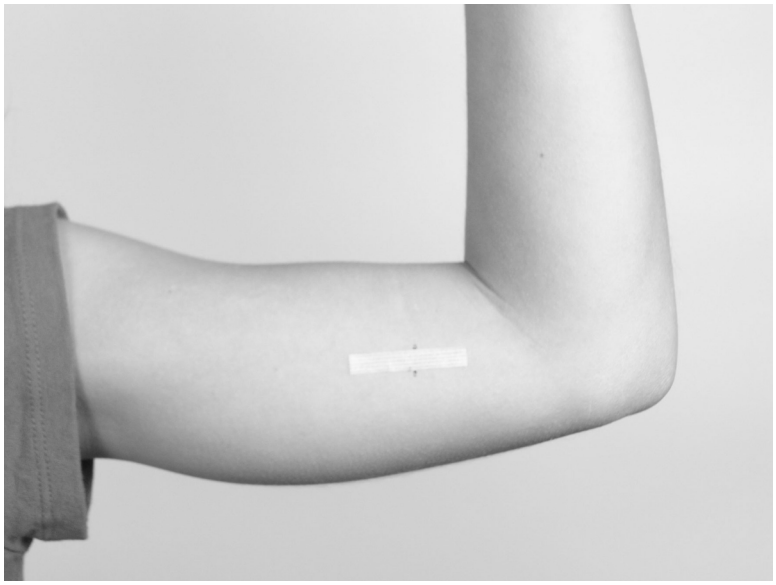
If there is a need to re-start the process at any time during the insertion procedure, withdraw the Insertion Tool, carefully extract the implant from the cannula and reset the retraction button on the Tool to its forward-most position. Examine the implant before reloading the implant into the Insertion Tool, and start again.

Placement of the implant should be confirmed by palpation. Note that the tip of a properly-placed implant may not be visible through the incision.

After implantation, briefly cover the site with a sterile gauze pad and apply pressure to ensure hemostasis.

Closing the Incision

To close the incision, you can use the absorbable sutures and/or the sterile adhesive surgical strips provided. To improve adhesion of the strips, you can apply benzoin tincture antiseptic (provided) to the skin, and let it dry, before applying the adhesive strips.



Once closed, cover the incision site with sterile gauze pads and secure the dressing with the bandage provided.

Please provide the patient's parent or guardian with a Patient Information Leaflet, which includes information about the implant and instructions on proper care of the insertion site.

Suggested Removal Procedure

SUPPRELIN LA should be removed after 12 months of therapy. Most of the supplies necessary to remove the implant, including the local anesthetic and the sterile mosquito clamp, are provided in the Implantation Kit that is shipped along with a new SUPPRELIN LA implant. Note that the Implantation Kit is to be stored at room temperature and must *not* be refrigerated. See the **Suggested Insertion Procedure** above for further instructions.

Removal of the SUPPRELIN LA implant is a surgical procedure. Sterile gloves and aseptic technique must be used to minimize any chance of infection.

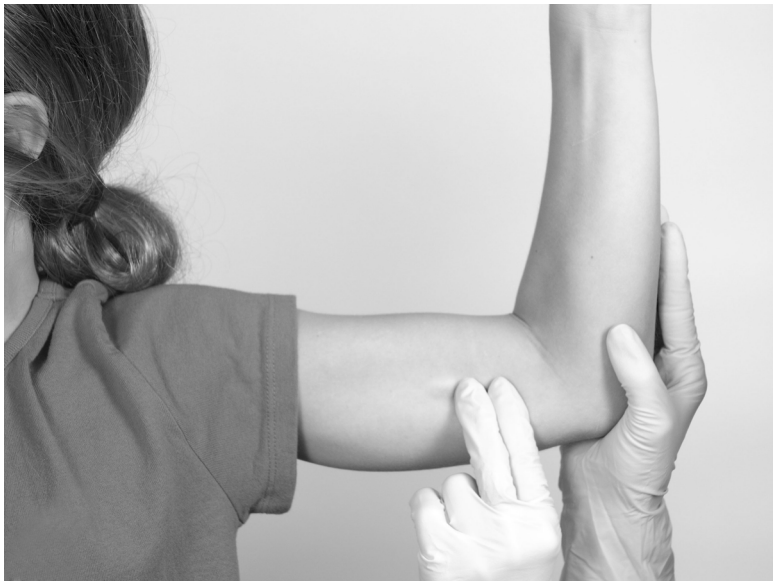
Setting up the Sterile Field

Using proper aseptic technique, the sterilized components of the Implantation Kit needed for the implant removal procedure are to be carefully dispensed from their packaging out onto the Sterile Field drape (*non*-fenestrated) provided. NOTE THAT THE KIT BOX AND ALL PACKAGING ARE NOT STERILE and should be kept off of the Sterile Field drape. DO NOT PLACE THE VIAL OF LOCAL ANESTHETIC ONTO THE DRAPE as the exterior surface of the vial is not sterile.

Preparing the Patient and the Site

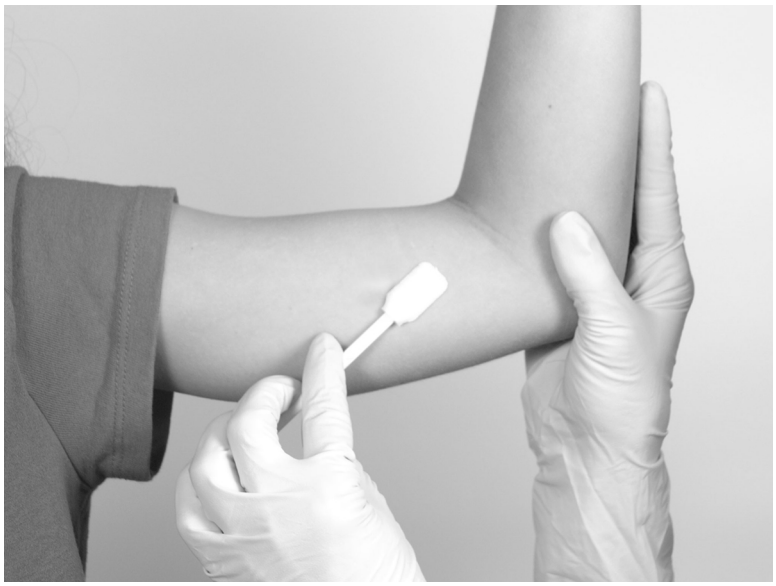
The patient should be on his/her back, with the arm containing the implant positioned, either bent or extended, so that the physician has ready access to the inner aspect of the upper arm. Propping the arm with pillows may help the patient more easily hold the position.

The implant to be removed should first be located by palpating the inner aspect of the upper arm, near the incision from the prior year.



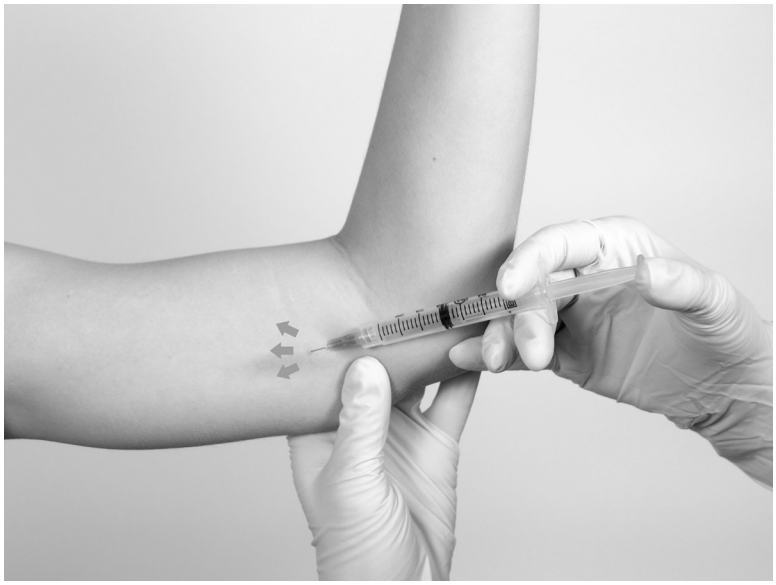
Generally, the previous implant is readily palpated. In the event the implant is difficult to locate, ultrasound may be used. If ultrasound fails to locate the implant, other imaging techniques such as CT or MRI may be used to locate it **(**plain films are not recommended as **the implant is not radiopaque**).

Antiseptic
Swab the area above and around the previous implant with topical antiseptic. Overlay the area with the *fenestrated* Sterile Field drape provided, so that the hole is over the previous insertion site (for clarity of illustration, the following images do not show the drape).



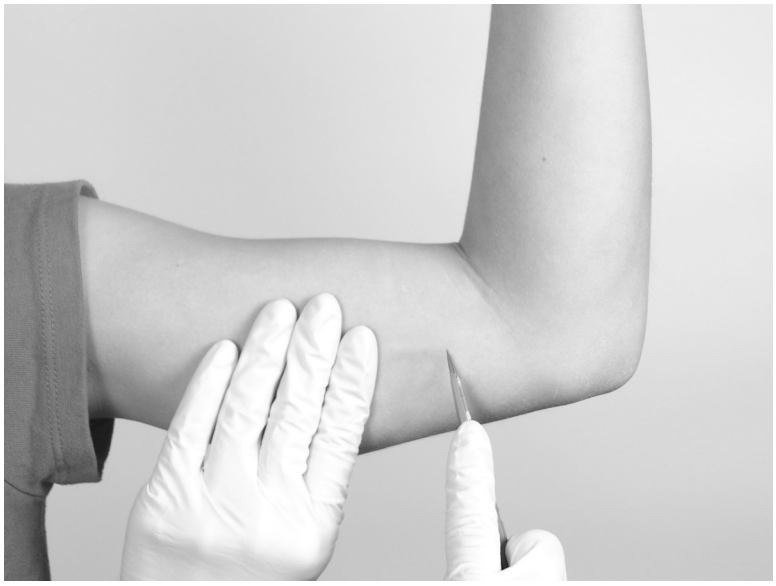
Anesthetic
The method of anesthesia utilized (i.e., local, conscious sedation, general) is at the discretion of the healthcare provider.

If local anesthesia is selected: a vial of sterile local anesthetic (note that the exterior of the vial is not sterile) has been provided along with a sterile hypodermic needle for injection. After determining the absence of known allergies to the anesthetic agent, inject anesthetic into the subcutaneous tissue at and around the site of the intended incision (the site of the previous implant). Local anesthesia may also be supplemented by the use of distraction techniques.



Making the Incision and Removing the Implant

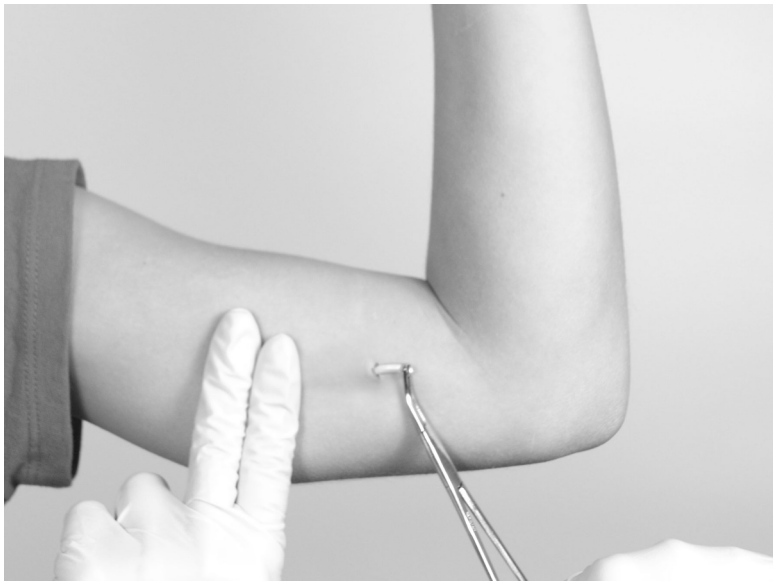
Using the sterile scalpel provided, make an incision of a size adequate to allow the implant to be easily removed and, if a new implant will be inserted, large enough for the bore of the cannula of the Insertion Tool provided.



Generally, the tip of the implant will be visible through the incision, possibly covered by a pseudocapsule of tissue. In order to facilitate the removal of the implant, it may be necessary to palpate the head of the implant through the incision using your smallest finger, especially if the head of the implant is not readily visible. In addition, you may need to push down on the distal end of the implant and "massage it forward" towards the incision.

Carefully nick the pseudocapsule to reveal the polymer tip of the implant. It may be beneficial to insert the sterile mosquito clamp provided into the hole created in the pseudocapsule and expand by opening the clamp. Widening the opening of the pseudocapsule may ease the extraction of the implant.

Gently but securely grasp the implant with the sterile mosquito clamp and extract the implant.



Dispose of the implant in a proper manner, treating it like any other bio-waste.

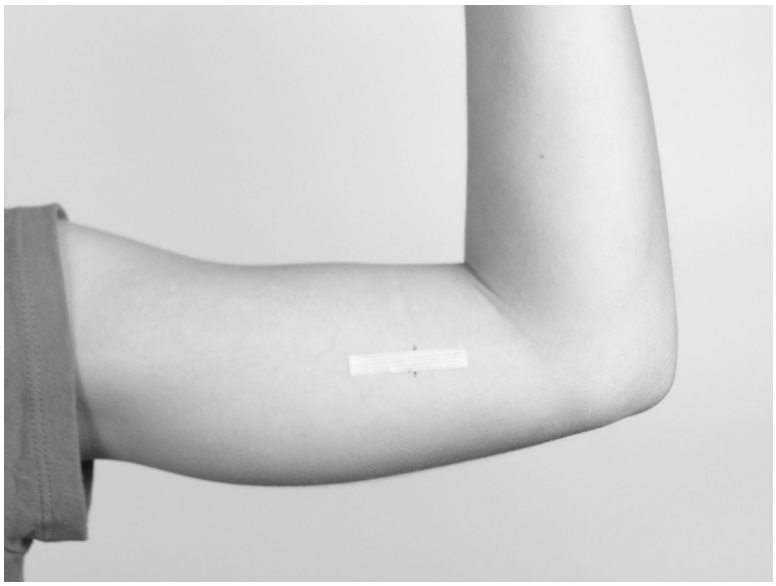
Briefly cover the site with a sterile gauze pad and apply pressure to ensure hemostasis.

If inserting a new implant, see the **Suggested Insertion Procedure** instructions provided above. Note that you can insert the new implant into the same "pocket" as the removed implant, or make a new incision at a different site in the same arm or in the contralateral arm.

If a new implant is not to be inserted, proceed to close the incision.

Closing the Incision

To close the incision, you can use the absorbable sutures and/or the sterile adhesive surgical strips provided. To improve adhesion of the strips, you can apply benzoin tincture antiseptic (provided) to the skin, and let it dry, before applying the adhesive strips.



Once closed, cover the incision site with sterile gauze pads and secure the dressing with the bandage provided.

3 DOSAGE FORMS AND STRENGTHS

SUPPRELIN LA is a sterile, nonbiodegradable, diffusion-controlled, hydrogel polymer reservoir drug delivery system designed to deliver histrelin acetate continuously for 12 months after subcutaneous implantation. The sterile implant contains 50 mg histrelin acetate and delivers approximately 65 mcg histrelin acetate per day over 12 months.

4 CONTRAINDICATIONS

SUPPRELIN LA is contraindicated in:

- Patients who are hypersensitive to gonadotropin releasing hormone (GnRH) or GnRH agonist analogs
- Pregnancy *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Initial Agonistic Action

SUPPRELIN LA, like other GnRH agonists, initially causes a transient increase in serum concentrations of estradiol in females and testosterone in both sexes during the first week of treatment. Patients may experience worsening of symptoms or onset of new symptoms during this period. However, within 4 weeks of histrelin therapy, suppression of gonadal steroids occurs and manifestations of puberty decrease.

5.2 Implant Insertion/Removal Procedure

Implant insertion is a surgical procedure and it is important that the insertion instructions are followed to avoid potential complications. The insertion and removal of the implant should be done aseptically. Proper surgical technique is critical in minimizing adverse events related to the insertion and the removal of the histrelin implant. On occasion, localizing and/or removal of implant products have been difficult and imaging techniques were used, including ultrasound, CT, or MRI (note: the histrelin implant is not radiopaque). In some cases the implant broke during removal and multiple pieces were recovered. Confirm that the entire implant has been removed. If the implant was not retrieved completely, the remaining pieces should be removed following the instructions in the Suggested Removal Procedure section *[see Dosage and Administration (2.2)]*. Rare events of spontaneous extrusion of the implant have been observed in clinical trials. During SUPPRELIN LA treatment, patients should be evaluated for evidence of clinical and biochemical suppression of CPP manifestations (see Section 5.5, Monitoring and Laboratory tests). Detailed instructions on the insertion and removal procedures of the implant are provided above *[see Dosage and Administration (2.2)]*.

5.3 Psychiatric Events

Psychiatric events have been reported in patients taking GnRH agonists, including SUPPRELIN LA. Postmarketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with SUPPRELIN LA *[see Adverse Reactions (6)]*.

5.4 Convulsions

Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists, including SUPPRELIN LA. Reports with GnRH agonists have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

5.5 Monitoring and Laboratory Tests

LH, FSH and estradiol or testosterone should be monitored at 1 month post implantation then every 6 months thereafter. Additionally, height (for calculation of height velocity) and bone age should be assessed every 6-12 months.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

The most common adverse reactions with SUPPRELIN LA involved the implant site. Local reactions after implant insertion include bruising, pain, soreness, erythema and swelling.

During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the natural stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed *[see Warnings and Precautions (5.1)]*.

6.2 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of SUPPRELIN LA in children with CPP was evaluated in two single-arm clinical trials conducted in a total of 47 patients (44 females and 3 males) over a period of time ranging from 9 to 18 months. The most commonly reported adverse reaction was implant site reaction, which was reported by 24 of 47 (51.1%) patients. Implant site reaction includes discomfort, bruising, soreness, pain, tingling, itching, implant area protrusion and swelling. Two subjects experienced a serious adverse reaction: 1 subject who coincidentally had Stargardt's Disease experienced amblyopia and 1 subject had a benign pituitary tumor (pituitary adenoma). One subject discontinued the study due to an adverse reaction of infection at the implant site. There were no clinically meaningful findings in standard clinical hematology and chemistry tests and/or in vital signs. The incidence of implantation adverse events reported by more than 2 patients are summarized in Table 1.

Table 1: Incidence of implantation adverse reactions reported by ≥ 2 patients treated with SUPPRELIN LA in both clinical trials

Adverse Reactions	**N=47** **N (%)**
Implant site reaction	24 (51.1)
Keloid scar	3 (6.4)
Scar	3 (6.4)
Suture related complication	3 (6.4)
Application site pain	2 (4.3)
Post procedural pain	2 (4.3)

The following adverse reactions were reported as possibly related or related in 1 patient each: wound infection, breast tenderness, dysmenorrhea, epistaxis, erythema, feeling cold, gynecomastia, headache, menorrhagia, migraine, mood swings, pituitary tumor benign, pruritus, weight increased, disease progression and influenza-like illness. The adverse reaction metrorrhagia was reported as possibly related or related in 2 patients.

6.3 Post-marketing Experience

The following adverse reactions have been identified during post approval use of SUPPRELIN LA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General Disorders and Administration Site Conditions: implant breakage

Psychiatric Disorders: Emotional lability, such as crying, irritability, impatience, anger, and aggression, has been observed with GnRH agonists, including SUPPRELIN LA *[see Warnings and Precautions (5.3)]*; Depression, including rare reports of suicidal ideation and attempt, has been reported for GnRH agonists, including SUPPRELIN LA, in children treated for central precocious puberty. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities with an increased risk of depression.

Nervous System Disorders: seizures *[see Warnings and Precautions (5.4)]*

7 DRUG INTERACTIONS

Overview: No formal drug-drug, drug-food, or drug-herb interaction studies were performed with SUPPRELIN LA.

Drug-Laboratory Interactions: Therapy with SUPPRELIN LA results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after SUPPRELIN LA therapy may be affected. SUPPRELIN LA decreased mean serum insulin-like growth factor-1 (IGF-1) levels by approximately 11% in one study (Study 1). SUPPRELIN LA increased the serum concentration of dehydroepiandrosterone (DHEA) in 8 of 36 patients in another study (Study 2).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

SUPPRELIN LA is contraindicated during pregnancy *[see Contraindications (4)]* since expected hormonal changes that occur with SUPPRELIN LA treatment increase the risk for pregnancy loss. The limited data with histrelin use in pregnant women are insufficient to determine a drug-associated risk for major birth defects or adverse developmental outcomes. Consistent with mechanism of action for SUPPRELIN LA *[see Clinical Pharmacology (12.1)]*, animal reproduction studies showed an increase in fetal loss at clinically relevant exposures.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Histrelin acetate administered to pregnant rats during the period of organogenesis increased fetal mortality and post-implantation loss at doses of 1, 3, 5 or 15 mcg/kg/day, approximating clinical exposure based on body surface area. These dosages also reduced maternal body weight gain, stimulated ovarian follicular development, increased placental weight and caused abnormal morphology and an increase in fetal size. Histrelin acetate administered to pregnant rabbits during the period of organogenesis increased fetal mortality and abortion/early termination at the two highest doses and caused total litter loss at all doses of 20, 50 or 80 mcg/kg/day (approximately 3- to 12-times clinical exposures based on body surface area).

8.2 Lactation

Risk Summary

There are no data on the presence of SUPPRELIN LA in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Absorption and systemic activity are not expected from potential exposure to the peptide, histrelin, in the breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUPPRELIN LA and any potential adverse effects on the breastfed child from SUPPRELIN LA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established. The use of SUPPRELIN LA in children under 2 years is not recommended.

10 OVERDOSAGE

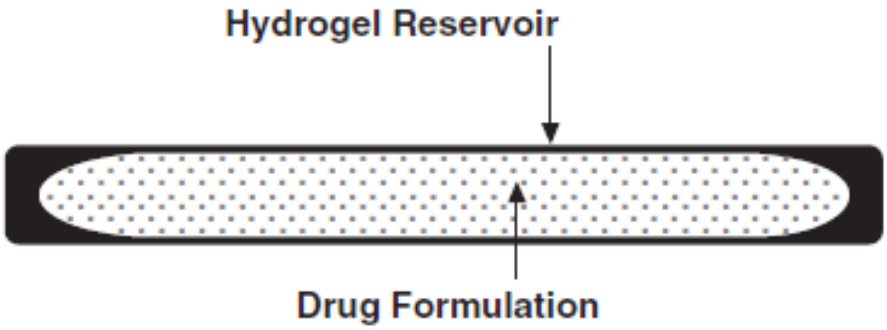
There have been no reports of overdose in SUPPRELIN LA clinical trials. High doses of histrelin acetate injection in animal studies were generally associated only with effects attributed to the expected pharmacology. The method of drug delivery makes accidental or intentional overdosage unlikely.

11 DESCRIPTION

SUPPRELIN LA is a sterile, non-biodegradable, diffusion-controlled, hydrogel polymer reservoir containing histrelin acetate, a synthetic nonapeptide analog of the naturally occurring gonadotropin releasing hormone (GnRH) possessing a greater potency than the natural sequence hormone. SUPPRELIN LA is designed to deliver approximately 65 mcg histrelin acetate per day over 12 months.

The SUPPRELIN LA implant looks like a small thin flexible tube and consists of a 50-mg histrelin acetate drug core inside a 3.5 cm by 3 mm, cylindrical, hydrogel polymer reservoir (Figure 1). The implant may appear partially to completely full with variation in color from off-white to light brown. The color may be uneven within the core.

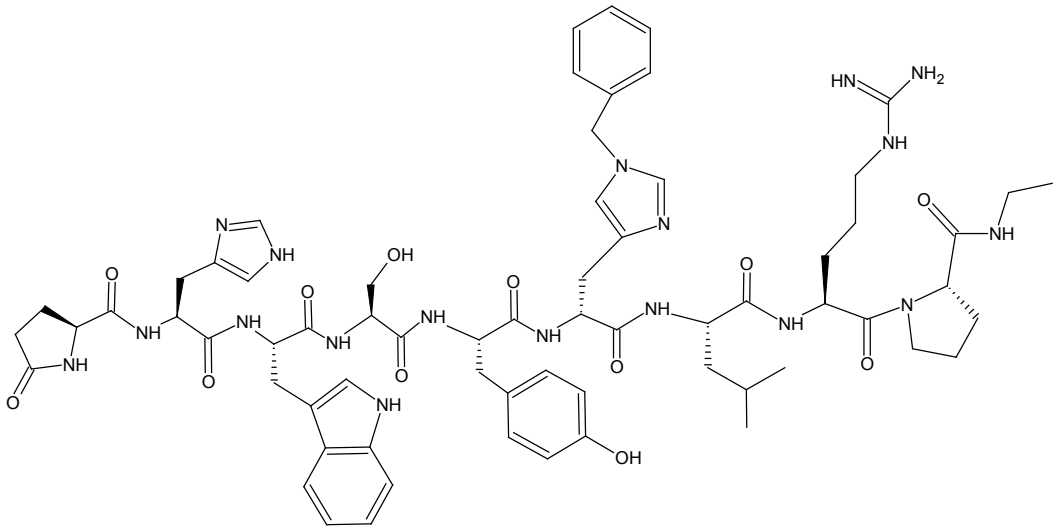
Figure 1. SUPPRELIN LA Implant Diagram (not to scale)



The chemical name of histrelin acetate is: L-Pyroglutamyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-N-benzyl-D-histidyl-L-leucyl-L-arginyl-L-proline N-ethylamide, acetate salt.

The molecular formula for histrelin acetate is $C_{66}H_{86}N_{18}O_{12}$ x 2 CH_3COOH and its molecular weight is 1443.70 (or 1323.52 as free base). Histrelin is also chemically described as 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Nt-benzyl-D-histidyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide diacetate. The chemical structure of the free base (histrelin) is represented below in Figure 2.

Figure 2. Structure of Histrelin



The drug core also contains the inactive ingredient stearic acid NF. The hydrogel polymer reservoir is a hydrophilic cartridge composed of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, Perkadox-16, and Triton X-100. Each implant is packaged hydrated in a glass vial containing 2 mL of sterile 1.8% sodium chloride solution, so that it is primed for immediate release of the drug upon insertion.

A single use, sterile, Insertion Tool is provided along with the implant that can be used for the placement of the SUPPRELIN LA implant into the subcutaneous tissue of the inner aspect of the upper arm. The Insertion Tool is enclosed in a sterile bag and is provided separately from the implant in the Implantation Kit [*see Recommended Procedure for Implant Insertion and Removal (2.2)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SUPPRELIN LA is a GnRH agonist and an inhibitor of gonadotropin secretion when given continuously. It delivers approximately 65 mcg histrelin acetate per day. Both animal and human studies indicate that following an initial stimulatory phase, chronic, subcutaneous administration of histrelin acetate desensitizes responsiveness of the pituitary gonadotropin which, in turn causes a reduction in ovarian and testicular steroidogenesis.

In humans, administration of histrelin acetate results in an initial increase in circulating levels of LH and FSH, leading to a transient increase in concentration of gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females).

However, continuous administration of histrelin acetate causes a reversible down-regulation of the GnRH receptors in the pituitary gland and desensitization of the pituitary gonadotropes. These inhibitory effects result in decreased levels of LH and FSH.

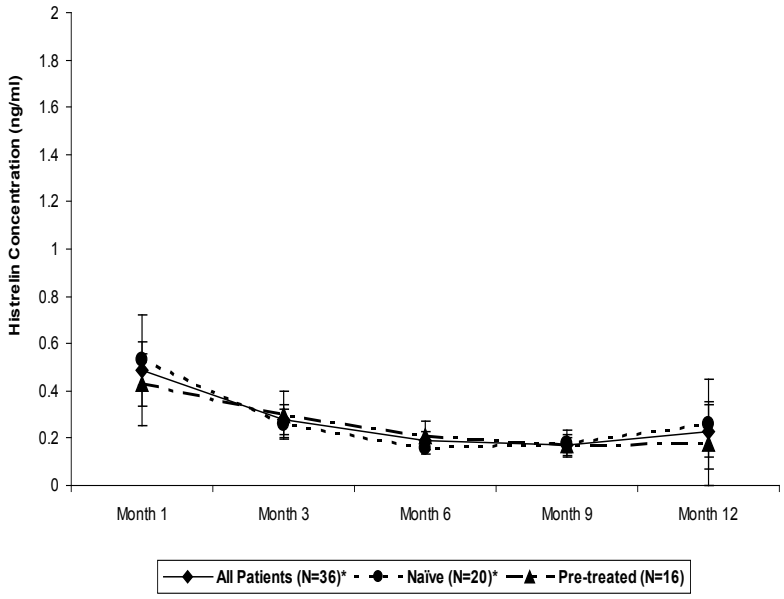
12.2 Pharmacodynamics

Long-term treatment with histrelin acetate suppresses the LH response to GnRH causing LH levels to decrease to prepubertal levels within 1 month of treatment. As a result, serum concentrations of sex steroids (estrogen or testosterone) also decrease. Consequently, secondary sexual development ceases to progress in most patients. Additionally, linear growth velocity is slowed which improves the chance of attaining predicted adult height.

12.3 Pharmacokinetics

Pharmacokinetics of histrelin after implantation of SUPPRELIN LA was evaluated in a total of 47 children with CPP (11 subjects in Study 1 and 36 subjects in Study 2). Patients were examined at 4 weeks after implant insertion and a few times throughout the treatment period. Median serum histrelin concentrations remained above the limit of quantification for the treatment period. Histrelin acetate levels were sustained throughout the study period for most subjects (Figure 3). The median of maximum serum histrelin concentrations over the study period was 0.43 ng/mL, which is expected to maintain gonadotropins at prepubertal levels. There was no apparent pharmacokinetic difference between naïve subjects to a LHRH agonist treatment and subjects who had previous treatment with a LHRH agonist (Figure 3).

Figure 3. Mean and Standard Deviation of Serum Histrelin Concentrations (ng/mL) Results at Each Visit



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in rats for 2 years at doses of 5, 25 or 150 mcg/kg/day (up to 11 times human exposures using body surface area comparisons, based on a 65 mcg/day dose in humans) and in mice for 18 months at doses of 20, 200, or 2000 mcg/kg/day (at less than therapeutic exposure to 70 times human exposure using body surface area comparisons, based on a 65 mcg/day dose in humans). As seen with other GnRH agonists, histrelin injection

administration was associated with an increase in tumors of hormonally responsive tissues. There was a significant increase in pituitary adenomas in rats at mid and high doses (2-11 times human exposure based on body surface area comparisons with a 65 mcg/day human dose). There was an increase in pancreatic islet-cell adenomas in treated female rats and a non-dose-related increase in testicular Leydig-cell tumors (highest incidence in the low-dose group). In mice, there was significant increase in mammary-gland adenocarcinomas in all treated females. In addition, there were increases in stomach papillomas in male rats given high doses, and an increase in histiocytic sarcomas in female mice at the highest dose.

Mutagenicity studies have not been performed with histrelin acetate. Saline extracts of implants with and without histrelin acetate were negative in a battery of genotoxicity studies. Fertility studies have been conducted in rats and monkeys given subcutaneous daily doses of histrelin acetate up to 180 mcg/kg/day (up to 13 and 30 times human exposure, respectively using body surface area comparisons, based on a 65 mcg/day human dose) for 6 months and full reversibility of fertility suppression was demonstrated. The development and reproductive performance of offspring from parents treated with histrelin acetate has not been investigated.

14 CLINICAL STUDIES

The efficacy of SUPPRELIN LA in children with CPP has been evaluated in two single-arm, open label studies. Study 1 was conducted in 11 pretreated female patients, 3.7 to 11.0 years of age. Study 2 was conducted in 36 patients (33 females and 3 males), 4.5 to 11.6 years of age. Sixteen pretreated and 20 treatment-naïve patients were enrolled in Study 2. Baseline patient characteristics were typical of patients with CPP. Efficacy assessments were similar in both studies and included endpoints that measured the suppression of gonadotropins (luteinizing hormone and follicle stimulating hormone) and gonadal sex steroids (estrogen in girls and testosterone in boys, respectively) on treatment. Other assessments were clinical (evidence of stabilization or regression of signs of puberty) or gonadal steroid-dependent (bone age, linear growth). In Study 2, the primary measure of efficacy was LH suppression.

In Study 2, suppression of LH was induced in all treatment naïve subjects and maintained in all pretreated subjects at Month 1 after implantation and continued through Month 12 (suppression was defined as a peak LH < 4 mIU/mL following stimulation with the GnRH analog leuprolide acetate).

Secondary efficacy hormone assessments (FSH, estradiol and testosterone) and additional efficacy assessments (bone age advancement, linear growth, clinical progression of puberty) indicated stabilization of disease. Estradiol suppression was present in all 33 girls (100%) through Month 9 and 97% at Month 12. Testosterone suppression was maintained in the three pre-treated males participating in Study 2. The SUPPRELIN LA effect on efficacy endpoints in the Study 1 was consistent with that observed in Study 2.

16 HOW SUPPLIED/STORAGE AND HANDLING

SUPPRELIN LA (NDC 67979-002-01) is supplied in a corrugated shipping carton that contains 2 inner cartons: a small one for the vial containing the SUPPRELIN LA implant, which is shipped with a cold pack inside a polystyrene cooler that must be refrigerated upon arrival, and a larger one comprising the Implantation Kit, which must *not* be refrigerated, for use during insertion or removal of SUPPRELIN LA.

The SUPPRELIN LA implant contains 50 mg of histrelin acetate. The SUPPRELIN LA implant carton contains a cold pack for refrigerated shipment and a small carton containing an amber plastic pouch. Inside the pouch is a glass vial with a Teflon-coated stopper and an aluminum seal, containing the implant in 2 mL of sterile 1.8% sodium chloride solution. (**Note**: The 3.5 mL vial is not completely filled with saline).

Upon receipt, refrigerate the small carton containing the amber plastic pouch and glass vial (with the implant inside) until the day of insertion. The implant vial should not be opened until just before the time of insertion.

SUPPRELIN LA is stable when stored refrigerated, in its sealed vial, pouch, and carton, at 2-8ºC (36-46ºF) until the expiration date provided. Excursion permitted to 25°C (77°F) for 7 days. Do not freeze. Protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved patient labeling (Medication Guide).

Initial Agonistic Action

Patients should be advised that a transient worsening of symptoms of puberty or onset of new symptoms may occur initially. However, within 4 weeks of histrelin therapy, complete suppression of gonadal steroids occurs and manifestations of puberty decrease *[see Warnings and Precautions (5.1)]*.

Post-insertion Care

Patients should be instructed to refrain from getting the inserted arm wet for 24 hours and from strenuous exertion of the inserted arm for 7 days after implant insertion to allow the incision to fully close. The adhesive elastic bandage can be removed at that time. The patient should not remove the surgical strips; rather, the strips should be allowed to fall off on their own after several days.

Psychiatric Adverse Events

Inform caregivers that symptoms of emotional lability, such as crying, irritability, impatience, anger, and aggression, have been observed in patients receiving GnRH agonists, including SUPPRELIN LA . Alert caregivers to the possibility of development or worsening of psychiatric symptoms, including depression, during treatment with SUPPRELIN LA *[see Warnings and Precautions (5.3), Adverse Reactions (6.3)]*.

Convulsions
Inform caregivers that reports of convulsions have been observed in patients receiving GnRH agonists, including SUPPRELIN LA. Patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions may be at risk *[see Warnings and Precautions (5.4)]*.

Common Adverse Reactions
Patients should be advised to report to their physician any severe pain, redness, or swelling in and around the implant site. Infrequently, SUPPRELIN LA may be expelled from the body through the original incision site, rarely without the patient noticing. The patient should be instructed to monitor the incision site until it is healed. The patient should also return for routine checks of their condition and to ensure that SUPPRELIN LA is present and functioning in his/her body *[see Warnings and Precautions (5.2, 5.4)]*.

For more information, call 1-800-462-3636 or visit www.supprelinla.com.

Distributed by:
Endo Pharmaceuticals Inc.
Malvern, PA 19355 USA

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Revised: 11/2019

Medication Guide
SUPPRELIN® LA [Suh-Preh-Lin El-Ay]
(histrelin acetate) subcutaneous implant

What is the most important information I should know about SUPPRELIN LA?

- In the first week of treatment, SUPPRELIN LA can cause an increase in some hormones. During this time you may notice more signs of puberty in your child, including light vaginal bleeding and breast enlargement in girls. Within 4 weeks of treatment, you should see signs in your child that puberty is stopping.
- Some people who had SUPPRELIN LA placed in their arm have had the implant come through the skin (extrusion). **Call your child's doctor right away if the SUPPRELIN LA implant comes through the skin.**
- Some people taking GnRH agonists like SUPPRELIN LA have had new or worsening mental (psychiatric) problems. Mental (psychiatric) problems may include emotional symptoms such as:
  - crying
  - irritability
  - restlessness (impatience)
  - anger
  - acting aggressive

Call your child's doctor right away if your child has any new or worsening mental symptoms or problems while taking SUPPRELIN LA.

- Some people taking GnRH agonists like SUPPRELIN LA have had seizures. The risk of seizures may be higher in people who:
  - have a history of seizures
  - have a history of epilepsy
  - have a history of brain or brain vessel (cerebrovascular) problems or tumors
  - are taking a medicine that has been connected to seizures such as bupropion or selective serotonin reuptake inhibitors (SSRIs)

Seizures have also happened in people who have not had any of these problems.

Call your child's doctor right away if your child has a seizure while taking SUPPRELIN LA.

What is SUPPRELIN LA?

- SUPPRELIN LA is an implanted gonadotropin releasing hormone (GnRH) medicine used for the treatment of children with central precocious puberty (CPP).
- It is not known if SUPPRELIN LA is safe and effective in children under 2 years of age.

SUPPRELIN LA should not be taken if your child is:

- allergic to gonadotropin releasing hormone (GnRH), GnRH agonist medicines, or any ingredients in the SUPPRELIN LA implant. See the end of this Medication Guide for a complete list of ingredients in SUPPRELIN LA.
- pregnant or becomes pregnant. SUPPRELIN LA can cause birth defects or loss of the baby. If your child becomes pregnant call your doctor.

Before your child receives SUPPRELIN LA, tell the doctor about all of your child's medical conditions, including if they:

- have a history of mental (psychiatric) problems.
- have a history of seizures.
- have a history of epilepsy.
- have a history of brain or brain vessel (cerebrovascular) problems or tumors.
- are taking a medicine that has been connected to seizures such as bupropion or selective serotonin reuptake inhibitors (SSRIs).

Tell your doctor about all the medicines your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will your child receive SUPPRELIN LA?

- Your child's doctor should do tests to make sure your child has CPP before treating with SUPPRELIN LA.
- SUPPRELIN LA lasts for 12 months. One implant will give the medicine for 12 months. After 12 months, the SUPPRELIN LA implant must be removed. The doctor may place a new SUPPRELIN LA implant at this time to continue treatment.
- SUPPRELIN LA is placed under the skin of the inside of the upper arm. The doctor will numb the arm of your child, make a small cut, and then place the SUPPRELIN LA implant under the skin. The cut may be closed with stitches or surgical strips and covered with a pressure bandage.
- Your child should keep the arm clean and dry and should not swim or bathe for 24 hours after receiving the SUPPRELIN LA implant. The bandage can be removed after 24 hours. **Do not** remove any surgical strips. Surgical strips will fall off on their own in a few days.

- Your child should avoid heavy play or exercise that uses the arm where the implant was placed for 7 days. After the cut has healed, your child can go back to his or her normal activities. The doctor will give you complete instructions.
- Keep all scheduled visits to the doctor. The doctor will do regular exams and blood tests to check for signs of puberty.
- Sometimes the doctor will have to do special tests, such as an ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI) if the SUPPRELIN LA implant is hard to find under your child's skin.

What are the possible side effects of SUPPRELIN LA?
SUPPRELIN LA may cause serious side effects. See **"What is the most important information I should know about SUPPRELIN LA?"**

The most common side effect of SUPPRELIN LA includes skin reactions at the place where the implant is inserted. These reactions may include pain, redness, bruising, soreness, and swelling in and around the implant site. Call your child's doctor if your child has bleeding, redness, or severe pain where the implant was inserted.

These are not all the possible side effects of SUPPRELIN LA. **Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

What are the ingredients in SUPPRELIN LA?
Active ingredient: histrelin acetate

Inactive ingredients: stearic acid NF, hydrogel polymer reservoir composed of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, Perkadox-16, and Triton X-100

Distributed by: Endo Pharmaceuticals Inc., Malvern, PA 19355, **www.endo.com or call 1-800-462-3636.**

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Rev: 10/2019

Exhibit

M

ALDACTONE- spironolactone tablet, film coated
Pfizer Laboratories Div Pfizer Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ALDACTONE safely and effectively. See full prescribing information for ALDACTONE.

ALDACTONE® (spironolactone) tablets for oral use
Initial U.S. Approval: 1960

INDICATIONS AND USAGE

ALDACTONE is an aldosterone antagonist indicated for:

- The treatment of NYHA Class III–IV heart failure and reduced ejection fraction to increase survival, manage edema, and to reduce the need for hospitalization for heart failure (1.1)
- Use as an add-on therapy for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions (1.2)
- The management of edema in adult patients who are cirrhotic when edema is not responsive to fluid and sodium restrictions and in the setting of nephrotic syndrome when treatment of the underlying disease, restriction of fluid and sodium intake, and the use of other diuretics produce an inadequate response (1.3).
- Treatment of primary hyperaldosternism for: (1.4)
  - Short-term preoperative treatment
  - Long-term maintenance for patients with discrete aldosterone-producing adrenal adenomas who are not candidates for surgery and patients with bilateral micro or macronodular adrenal hyperplasia

DOSAGE AND ADMINISTRATION

- Heart Failure: Initiate treatment at 25 mg once daily (2.2).
- Hypertension: Initiate treatment at 25 to 100 mg daily in either single or divided doses (2.3).
- Edema: Initiate therapy in a hospital setting and titrate slowly. The recommended initial daily dose is 100 mg in single or divided doses (2.4).
- Primary hyperaldosteronism: Initiate treatment at 100 to 400 mg in preparation for surgery. In patients unsuitable for surgery use the lowest effective dosage determined for the individual patient (2.5).

DOSAGE FORMS AND STRENGTHS

Tablets: 25 mg, 50 mg, and 100 mg (3)

CONTRAINDICATIONS

ALDACTONE is contraindicated in patients with (4):

- Hyperkalemia
- Addison's disease
- Concomitant use of eplerenone

WARNINGS AND PRECAUTIONS

- Hyperkalemia: Monitor serum potassium within one week of initiation and regularly thereafter (5.1).
- Hypotension and Worsening Renal Function: Monitor volume status and renal function periodically (5.2).
- Electrolyte and Metabolic Abnormalities: Monitor serum electrolytes, uric acid and blood glucose periodically (5.3).
- Gynecomastia: ALDACTONE can cause gynecomastia (5.4).

ADVERSE REACTIONS

The most common adverse reaction with ALDACTONE treatment is gynecomastia (5.4, 6).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Agents increasing serum potassium: Concomitant administration can lead to hyperkalemia (5.1, 7.1).
- Lithium: Increased risk of lithium toxicity (7.2).
- NSAIDs: May reduce the diuretic, natriuretic and antihypertensive effect of ALDACTONE (7.3).

- Digoxin: ALDACTONE can interfere with radioimmunologic assays of digoxin exposure (7.4).
- Cholestyramine: Hyperkalemic metabolic acidosis has been reported with concomitant use (7.5).
- Acetylsalicylic Acid (ASA): ASA may reduce the efficacy of ALDACTONE (7.6).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, ALDACTONE may affect sex differentiation of the male during embryogenesis (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Heart Failure

ALDACTONE is indicated for treatment of NYHA Class III–IV heart failure and reduced ejection fraction to increase survival, manage edema, and reduce the need for hospitalization for heart failure.

ALDACTONE is usually administered in conjunction with other heart failure therapies.

1.2 Hypertension

ALDACTONE is indicated as add-on therapy for the treatment of hypertension, to lower blood pressure in patients who are not adequately controlled on other agents. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the

absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

1.3 Edema Associated with Hepatic Cirrhosis or Nephrotic Syndrome

ALDACTONE is indicated for the management of edema in the following settings:

- Cirrhosis of the liver when edema is not responsive to fluid and sodium restriction.
- Nephrotic syndrome when treatment of the underlying disease, restriction of fluid and sodium intake, and the use of other diuretics produce an inadequate response.

Because it increases serum potassium, ALDACTONE may be useful for treating edema when administration of other diuretics has caused hypokalemia.

1.4 Primary Hyperaldosteronism

ALDACTONE is indicated in the following settings:

- Short-term preoperative treatment of patients with primary hyperaldosteronism.
- Long-term maintenance therapy for patients with discrete aldosterone-producing adrenal adenomas who are not candidates for surgery.
- Long-term maintenance therapy for patients with bilateral micro or macronodular adrenal hyperplasia (idiopathic hyperaldosteronism).

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

ALDACTONE can be taken with or without food, but should be taken consistently with respect to food *[see Clinical Pharmacology (12.3)]*.

2.2 Treatment of Heart Failure

In patients with serum potassium ≤5.0 mEq/L and eGFR >50 mL/min/1.73 m^2, initiate treatment at 25 mg once daily. Patients who tolerate 25 mg once daily may have their dosage increased to 50 mg once daily as clinically indicated. Patients who develop hyperkalemia on 25 mg once daily may have their dosage reduced to 25 mg every other day *[see Warnings and Precautions (5.1)]*. In patients with an eGFR between 30 and 50 mL/min/1.73 m^2, consider initiating therapy at 25 mg every other day because of the risk of hyperkalemia *[see Use in Specific Populations (8.6)].*

2.3 Treatment of Essential Hypertension

The recommended initial daily dose is 25 to 100 mg of ALDACTONE administered in

either single or divided doses is recommended. Dosage can be titrated at two-week intervals. Doses greater than 100 mg/day generally do not provide additional reductions in blood pressure.

2.4 Treatment of Edema

In patients with cirrhosis, initiate therapy in a hospital setting and titrate slowly *[see Use in Specific Populations (8.7)]*. The recommended initial daily dosage is 100 mg of ALDACTONE administered in either single or divided doses, but may range from 25 to 200 mg daily. When given as the sole agent for diuresis, administer for at least five days before increasing dose to obtain desired effect.

2.5 Treatment of Primary Hyperaldosteronism

Administer ALDACTONE in doses of 100 to 400 mg daily in preparation for surgery. For patients who are considered unsuitable for surgery, ALDACTONE can be used as long-term maintenance therapy at the lowest effective dosage determined for the individual patient.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 25 mg round, light yellow, film-coated, with SEARLE and 1001 debossed on one side and ALDACTONE and 25 on the other side.

Tablets: 50 mg oval, light orange, scored, film-coated, with SEARLE and 1041 debossed on the scored side and ALDACTONE and 50 on the other side.

Tablets: 100 mg round, peach-colored, scored, film-coated, with SEARLE and 1031 debossed on the scored side and ALDACTONE and 100 on the other side.

4 CONTRAINDICATIONS

ALDACTONE is contraindicated in the patients with:

- Hyperkalemia
- Addison's disease
- Concomitant use of eplerenone

5 WARNINGS AND PRECAUTIONS

5.1 Hyperkalemia

ALDACTONE can cause hyperkalemia. This risk is increased by impaired renal function or concomitant potassium supplementation, potassium-containing salt substitutes or drugs that increase potassium, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers *[see Drug Interactions (7.1)]*.

Monitor serum potassium within 1 week of initiation or titration of ALDACTONE and regularly thereafter. More frequent monitoring may be needed when ALDACTONE is given with other drugs that cause hyperkalemia or in patients with impaired renal function.

If hyperkalemia occurs, decrease the dose or discontinue ALDACTONE and treat hyperkalemia.

5.2 Hypotension and Worsening Renal Function

Excessive diuresis may cause symptomatic dehydration, hypotension and worsening renal function, particularly in salt-depleted patients or those taking angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. Worsening of renal function can also occur with concomitant use of nephrotoxic drugs (e.g., aminoglycosides, cisplatin, and NSAIDs). Monitor volume status and renal function periodically.

5.3 Electrolyte and Metabolic Abnormalities

In addition to causing hyperkalemia, ALDACTONE can cause hyponatremia, hypomagnesemia, hypocalcemia, hypochloremic alkalosis, and hyperglycemia. Asymptomatic hyperuricemia can occur and rarely gout is precipitated. Monitor serum electrolytes, uric acid and blood glucose periodically.

5.4 Gynecomastia

ALDACTONE can cause gynecomastia. In RALES, patients with heart failure treated with a mean dose of 26 mg of spironolactone once daily, about 9% of the male subjects developed gynecomastia. The risk of gynecomastia increases in a dose-dependent manner with an onset that varies widely from 1–2 months to over a year. Gynecomastia is usually reversible.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hyperkalemia *[see Warnings and Precautions (5.1)]*
- Hypotension and Worsening Renal Function *[see Warnings and Precautions (5.2)]*
- Electrolyte and Metabolic Abnormalities *[see Warnings and Precautions (5.3)]*
- Gynecomastia *[see Warnings and Precautions (5.4]*
- Impaired neurological function/ coma in patients with hepatic impairment, cirrhosis and ascites *[see Use in Specific Populations (8.7)]*

The following adverse reactions associated with the use of spironolactone were identified in clinical trials or postmarketing reports. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency, reliably, or to establish a causal relationship to drug exposure.

Digestive: Gastric bleeding, ulceration, gastritis, diarrhea and cramping, nausea, vomiting.

Reproductive: Decreased libido, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, breast and nipple pain.

Hematologic: Leukopenia (including agranulocytosis), thrombocytopenia.

Hypersensitivity: Fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis.

Metabolism: Hyperkalemia, electrolyte disturbances *[see Warnings and Precautions (5.1, 5.3)]*, hyponatremia, hypovolemia.

Musculoskeletal: Leg cramps.

Nervous system/psychiatric: Lethargy, mental confusion, ataxia, dizziness, headache, drowsiness.

Liver/biliary: A very few cases of mixed cholestatic/hepatocellular toxicity, with one reported fatality, have been reported with spironolactone administration.

Renal: Renal dysfunction (including renal failure).

Skin: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), alopecia, pruritis.

7 DRUG INTERACTIONS

7.1 Drugs and Supplements Increasing Serum Potassium

Concomitant administration of ALDACTONE with potassium supplementation or drugs that can increase potassium may lead to severe hyperkalemia. In general, discontinue potassium supplementation in heart failure patients who start ALDACTONE *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*. Check serum potassium levels when ACE inhibitor or ARB therapy is altered in patients receiving ALDACTONE.

Examples of drugs that can increase potassium include:

- ACE inhibitors
- angiotensin receptor blockers
- non-steroidal anti-inflammatory drugs (NSAIDs)
- heparin and low molecular weight heparin
- trimethoprim

7.2 Lithium

Like other diuretics, ALDACTONE reduces the renal clearance of lithium, thus increasing the risk of lithium toxicity. Monitor lithium levels periodically when ALDACTONE is coadministered *[see Clinical Pharmacology (12.3)]*.

7.3 Nonsteroidal anti-inflammatory drugs (NSAIDs)

In some patients, the administration of an NSAID can reduce the diuretic, natriuretic, and antihypertensive effect of diuretics. Therefore, when ALDACTONE and NSAIDs are used concomitantly, monitor closely to determine if the desired effect of the diuretic is obtained *[see Clinical Pharmacology (12.3)]*.

7.4 Digoxin

Spironolactone and its metabolites interfere with radioimmunoassays for digoxin and increase the apparent exposure to digoxin. It is unknown to what extent, if any, spironolactone may increase actual digoxin exposure. In patients taking concomitant digoxin, use an assay that does not interact with spironolactone.

7.5 Cholestyramine

Hyperkalemic metabolic acidosis has been reported in patients given ALDACTONE concurrently with cholestyramine.

7.6 Acetylsalicylic Acid

Acetylsalicylic acid may reduce the efficacy of spironolactone. Therefore, when ALDACTONE and acetylsalicylic acid are used concomitantly, ALDACTONE may need to be titrated to higher maintenance dose and the patient should be observed closely to determine if the desired effect is obtained *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on mechanism of action and findings in animal studies, spironolactone may affect sex differentiation of the male during embryogenesis *(see Data)*. Rat embryofetal studies report feminization of male fetuses and endocrine dysfunction in females exposed to spironolactone in utero. Limited available data from published case reports and case series did not demonstrate an association of major malformations or other adverse pregnancy outcomes with spironolactone. There are risks to the mother and fetus associated with heart failure, cirrhosis and poorly controlled hypertension during pregnancy *(see Clinical Considerations)*. Because of the potential risk to the male fetus due to anti-androgenic properties of spironolactone and animal data, avoid spironolactone in pregnant women or advise a pregnant woman of the potential risk to a male fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnant women with congestive heart failure are at increased risk for preterm birth. Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. Clinical classification of heart disease may worsen with pregnancy and lead to maternal death. Closely monitor pregnant patients for destabilization of their heart failure.

Pregnant women with symptomatic cirrhosis generally have poor outcomes including hepatic failure, variceal hemorrhage, preterm delivery, fetal growth restriction and maternal death. Outcomes are worse with coexisting esophageal varices. Pregnant women with cirrhosis of the liver should be carefully monitored and managed accordingly.

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean

section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death.

Data

Animal Data

Teratology studies with ALDACTONE have been carried out in mice and rabbits at doses of up to 20 mg/kg/day. On a body surface area basis, this dose in the mouse is substantially below the maximum recommended human dose and, in the rabbit, approximates the maximum recommended human dose. No teratogenic or other embryotoxic effects were observed in mice, but the 20 mg/kg dose caused an increased rate of resorption and a lower number of live fetuses in rabbits. Because of its antiandrogenic activity and the requirement of testosterone for male morphogenesis, ALDACTONE may have the potential for adversely affecting sex differentiation of the male during embryogenesis. When administered to rats at 200 mg/kg/day between gestation days 13 and 21 (late embryogenesis and fetal development), feminization of male fetuses was observed. Offspring exposed during late pregnancy to 50 and 100 mg/kg/day doses of ALDACTONE exhibited changes in the reproductive tract including dose-dependent decreases in weights of the ventral prostate and seminal vesicle in males, ovaries and uteri that were enlarged in females, and other indications of endocrine dysfunction, that persisted into adulthood. ALDACTONE has known endocrine effects in animals including progestational and antiandrogenic effects.

8.2 Lactation

Risk Summary

Spironolactone is not present in breastmilk; however, limited data from a lactating woman at 17 days postpartum reports the presence of the active metabolite, canrenone, in human breast milk in low amounts that are expected to be clinically inconsequential. In this case, there were no adverse effects reported for the breastfed infant after short term exposure to spironolactone; however, long term effects on a breastfed infant are unknown. There are no data on spironolactone effects on milk production. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for spironolactone and any potential adverse effects on the breastfed child from spironolactone or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

ALDACTONE is substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, monitor renal function.

8.6 Use in Renal Impairment

ALDACTONE is substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Patients with renal impairment are at increased risk of hyperkalemia. Monitor potassium closely.

8.7 Use in Hepatic Impairment

ALDACTONE can cause sudden alterations of fluid and electrolyte balance which may precipitate impaired neurological function, worsening hepatic encephalopathy and coma in patients with hepatic disease with cirrhosis and ascites. In these patients, initiate ALDACTONE in the hospital *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

Clearance of spironolactone and its metabolites is reduced in patients with cirrhosis. In patients with cirrhosis, start with lowest initial dose and titrate slowly *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

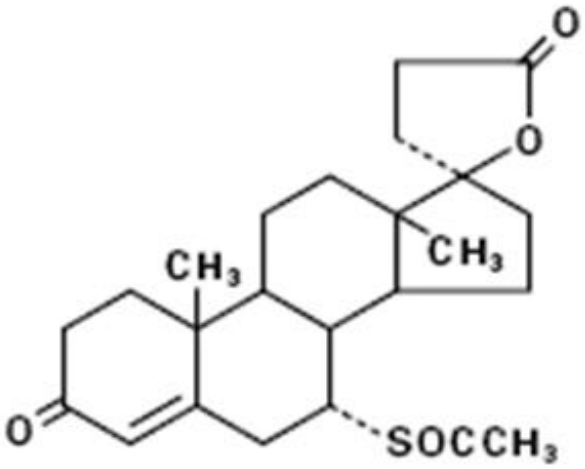
The oral LD_{50} of ALDACTONE is greater than 1000 mg/kg in mice, rats, and rabbits.

Acute overdosage of ALDACTONE may be manifested by drowsiness, mental confusion, maculopapular or erythematous rash, nausea, vomiting, dizziness, or diarrhea. Rarely, instances of hyponatremia, hyperkalemia, or hepatic coma may occur in patients with severe liver disease, but these are unlikely due to acute overdosage. Hyperkalemia may occur, especially in patients with impaired renal function.

Treatment: Induce vomiting or evacuate the stomach by lavage. There is no specific antidote. Treatment is supportive to maintain hydration, electrolyte balance, and vital functions. Patients who have renal impairment may develop hyperkalemia. In such cases, discontinue ALDACTONE.

11 DESCRIPTION

ALDACTONE oral tablets contain 25 mg, 50 mg, or 100 mg of the aldosterone antagonist spironolactone, 17-hydroxy-7α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid γ-lactone acetate, which has the following structural formula:



Spironolactone is practically insoluble in water, soluble in alcohol, and freely soluble in benzene and in chloroform.

Inactive ingredients include calcium sulfate, corn starch, flavor, hypromellose, iron oxide, magnesium stearate, polyethylene glycol, povidone, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Spironolactone and its active metabolites are specific pharmacologic antagonists of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. Spironolactone causes increased amounts of sodium and water to be excreted, while potassium is retained. Spironolactone acts both as a diuretic and as an antihypertensive drug by this mechanism. It may be given alone or with other diuretic agents that act more proximally in the renal tubule.

12.2 Pharmacodynamics

Aldosterone antagonist activity: Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism. Edematous states in which secondary aldosteronism is usually involved include congestive heart failure, hepatic cirrhosis, and nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone provides effective therapy for the edema and ascites in those conditions. Spironolactone counteracts secondary aldosteronism induced by the volume depletion and associated sodium loss caused by active diuretic therapy.

12.3 Pharmacokinetics

Absorption

The mean time to reach peak plasma concentration of spironolactone and the active metabolite, canrenone, in healthy volunteers is 2.6 and 4.3 hours, respectively.

Effect of food: Food increased the bioavailability of spironolactone (as measured by AUC) by approximately 95.4%. Patients should establish a routine pattern for taking ALDACTONE with regard to meals *[see Dosage and Administration (2.1)]*.

Distribution

Spironolactone and its metabolites are more than 90% bound to plasma proteins.

Elimination

The mean half-life of spironolactone is 1.4 hour.The mean half-life values of its metabolites including canrenone, 7-α-(thiomethyl) spirolactone (TMS), and 6-β-hydroxy-7-α-(thiomethyl) spirolactone (HTMS) are 16.5, 13.8, and 15 hours, respectively.

Metabolism: Spironolactone is rapidly and extensively metabolized. Metabolites can be divided into two main categories: those in which sulfur of the parent molecule is removed (e.g., canrenone) and those in which the sulfur is retained (e.g., TMS and HTMS). In humans, the potencies of TMS and 7-α-thiospirolactone in reversing the effects of the synthetic mineralocorticoid, fludrocortisone, on urinary electrolyte composition were approximately a third relative to spironolactone. However, since the serum concentrations of these steroids were not determined, their incomplete absorption and/or first-pass metabolism could not be ruled out as a reason for their

reduced in vivo activities.

Excretion: The metabolites are excreted primarily in the urine and secondarily in bile.

Specific Populations

The impact of age, sex, race/ethnicity, and renal impairment on the pharmacokinetics of spironolactone have not been specifically studied.

Patients with Hepatic Impairment: The terminal half-life of spironolactone has been reported to be increased in patients with cirrhotic ascites *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies:

Drugs and Supplements Increasing Serum Potassium: Concomitant administration of ALDACTONE with potassium supplementation, salt substitutes containing potassium, a diet rich in potassium, or drugs that can increase potassium, including ACE inhibitors, angiotensin II antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), heparin and low molecular weight heparin, may lead to severe hyperkalemia *[see Warnings and Precautions (5.1)and Drug Interactions (7.1)]*.

Lithium: ALDACTONE reduces the renal clearance of lithium, inducing a high risk of lithium toxicity *[see Drug Interactions (7.2)]*.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In some patients, the administration of an NSAID can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing, and thiazide diuretics *[see Drug Interactions (7.3)]*.

Acetylsalicylic acid: A single dose of 600 mg of acetylsalicylic acid inhibited the natriuretic effect of spironolactone, which was hypothesized be due to inhibition of tubular secretion of canrenone, causing decreased effectiveness of spironolactone *[see Drug Interactions (7.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Orally administered ALDACTONE has been shown to be a tumorigen in dietary administration studies performed in rats, with its proliferative effects manifested on endocrine organs and the liver. In an 18-month study using doses of about 50, 150, and 500 mg/kg/day, there were statistically significant increases in benign adenomas of the thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules). In a 24-month study in which the same strain of rat was administered doses of about 10, 30, and 100 mg ALDACTONE/kg/day, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial stromal polyps in females. No increased tumors were seen at doses of 100 mg/kg/day. This dose represents about 5× the human recommended daily dose of 200 mg/day, when based on body surface area.

Mutagenesis

Neither ALDACTONE nor potassium canrenoate produced mutagenic effects in tests using bacteria or yeast. In the absence of metabolic activation, neither ALDACTONE nor potassium canrenoate has been shown to be mutagenic in mammalian tests *in vitro.* In the presence of metabolic activation, ALDACTONE has been reported to be negative in some mammalian mutagenicity tests *in vitro* and inconclusive (but slightly positive) for mutagenicity in other mammalian tests *in vitro.* In the presence of metabolic activation, potassium canrenoate has been reported to test positive for mutagenicity in some mammalian tests *in vitro,* inconclusive in others, and negative in still others.

Impairment of Fertility

In a three-litter reproduction study in which female rats received dietary doses of 15 and 50 mg ALDACTONE/kg/day, there were no effects on mating and fertility, but there was a small increase in incidence of stillborn pups at 50 mg/kg/day. When injected into female rats (100 mg/kg/day for 7 days, i.p.), ALDACTONE was found to increase the length of the estrous cycle by prolonging diestrus during treatment and inducing constant diestrus during a two-week post-treatment observation period. These effects were associated with retarded ovarian follicle development and a reduction in circulating estrogen levels, which would be expected to impair mating, fertility, and fecundity. ALDACTONE (100 mg/kg/day), administered i.p. to female mice during a two-week cohabitation period with untreated males, decreased the number of mated mice that conceived (effect shown to be caused by an inhibition of ovulation) and decreased the number of implanted embryos in those that became pregnant (effect shown to be caused by an inhibition of implantation), and at 200 mg/kg, also increased the latency period to mating.

14 CLINICAL STUDIES

14.1 Heart Failure

The Randomized Aldactone Evaluation Study (RALES) was a placebo controlled, double-blind study of the effect of spironolactone on mortality in patients with highly symptomatic heart failure and reduced ejection fraction. To be eligible to participate patients had to have an ejection fraction of ≤ 35%, NYHA class III–IV symptoms, and a history of NYHA class IV symptoms within the last 6 months before enrollment. Patients with a baseline serum creatinine of >2.5 mg/dL or a recent increase of 25% or with a baseline serum potassium of >5.0 mEq/L were excluded.

Follow-up visits and laboratory measurements (including serum potassium and creatinine) were performed every four weeks for the first 12 weeks, then every 3 months for the first year, and then every 6 months thereafter.

The initial dose of spironolactone was 25 mg once daily. Patients who were intolerant of the initial dosage regimen had their dose decreased to one 25 mg tablet every other day at one to four weeks. Patients who were tolerant of one tablet daily at 8 weeks may have had their dose increased to 50 mg daily at the discretion of the investigator. The mean daily dose at study end for patients randomized to spironolactone was 26 mg.

1663 patients were randomized 1:1 to spironolactone or placebo. 87% of patients were white, 7% black, 2% Asian. 73% were male and median age was 67. The median ejection

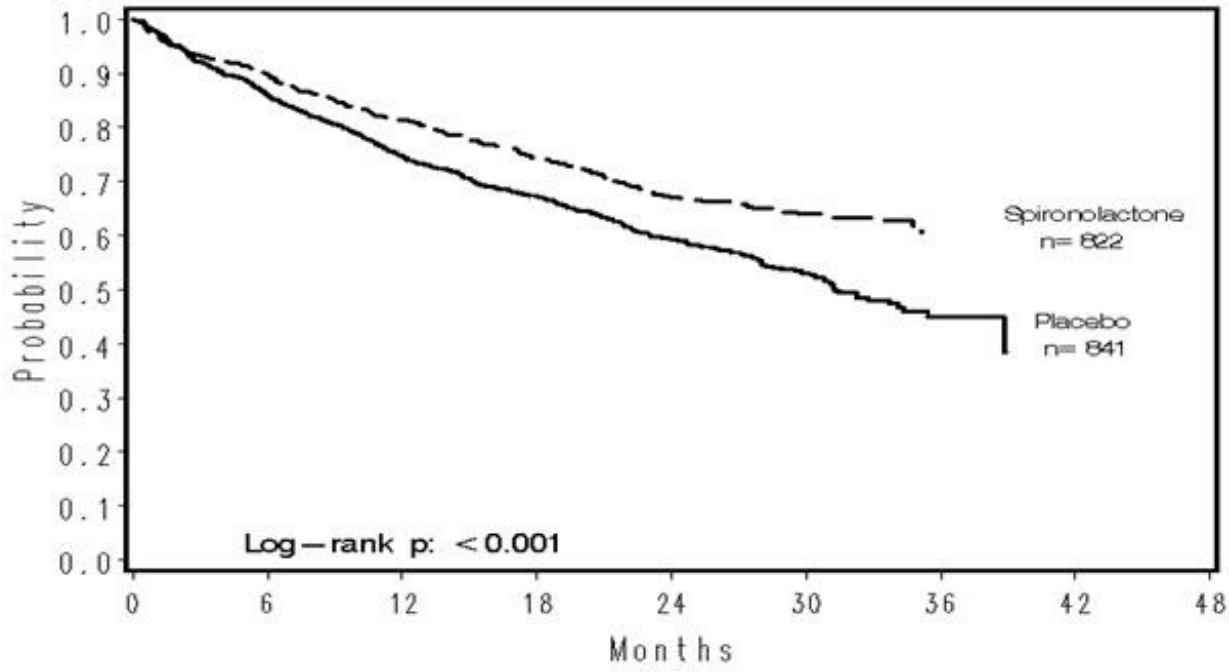
fraction was 26%. 70% were NYHA class III and 29% class IV. The etiology of heart failure was ischemic in 55%, and non-ischemic in 45%. There was a history of myocardial infarction in 28%, of hypertension in 24%, and of diabetes in 22%. The median baseline serum creatinine was 1.2 mg/dL and the median baseline creatinine clearance was 57 mL/min.

At baseline 100% of patients were taking loop diuretic and 95% were taking an ACE inhibitor. Other medications used at any time during the study included digoxin (78%), anticoagulants (58%), aspirin (43%), and beta-blockers (15%).

The primary endpoint for RALES was time to all-cause mortality. RALES was terminated early because of significant mortality benefit demonstrated during a planned interim analysis. Compared to placebo, spironolactone reduced the risk of death by 30% ($p<0.001$; 95% confidence interval 18% to 40%). Spironolactone also reduced the risk of hospitalization for cardiac causes (defined as worsening heart failure, angina, ventricular arrhythmias, or myocardial infarction) by 30% ($p <0.001$; 95% confidence interval 18% to 41%).

The survival curves by treatment group are shown in Figure 1.

Figure 1. Survival by Treatment Group in RALES



Mortality hazard ratios for some subgroups are shown in Figure 2. The favorable effect of spironolactone on mortality appeared similar for both genders and all age groups except patients younger than 55. There were too few non-whites in RALES to evaluate if the effects differ by race. Spironolactone's benefit appeared greater in patients with low baseline serum potassium levels and less in patients with ejection fractions <0.2. These subgroup analyses must be interpreted cautiously.

Figure 2. Hazard Ratios of All-Cause Mortality by Subgroup in RALES

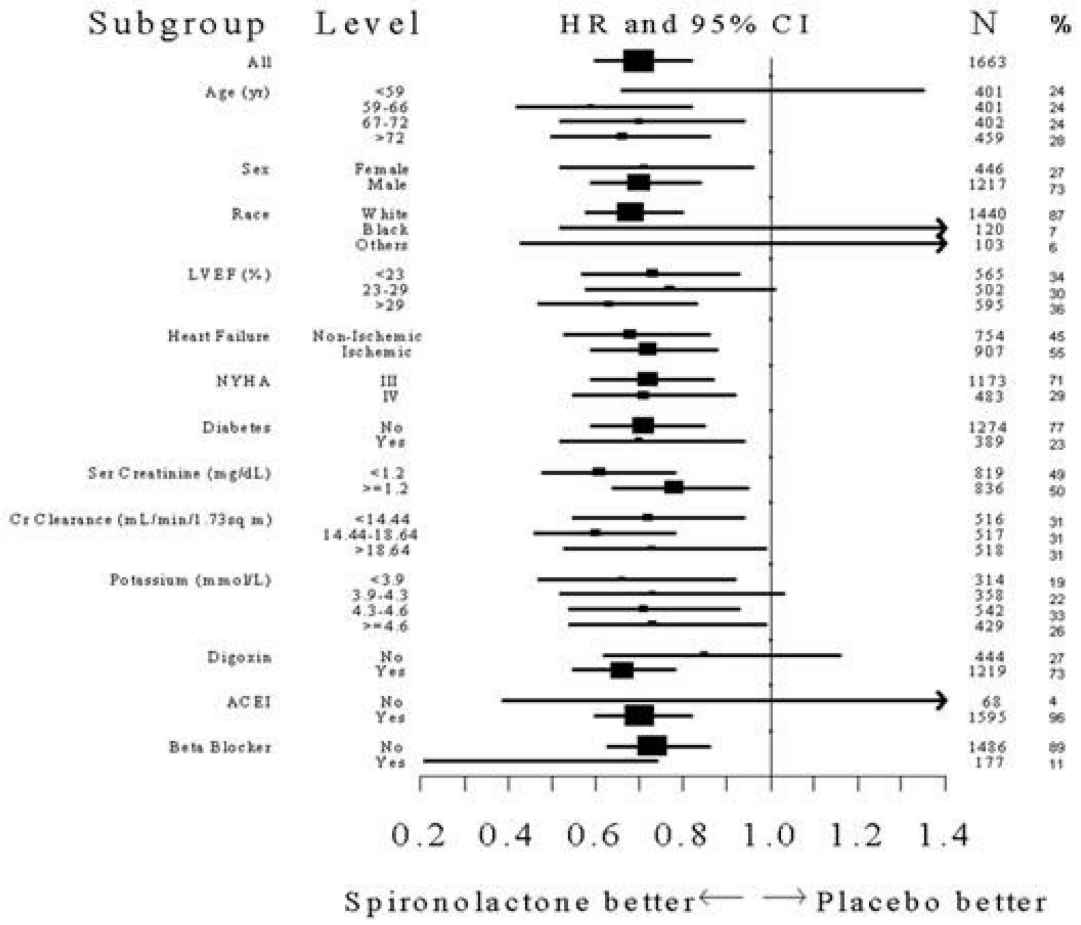


Figure 2: The size of each box is proportional to the sample size as well as the event rate. LVEF denotes left ventricular ejection fraction, Ser Creatinine denotes serum creatinine, Cr Clearance denotes creatinine clearance, and ACEI denotes angiotensin-converting enzyme inhibitor.

14.2 Hypertension

The dose response of spironolactone for hypertension has not been well characterized. In patients with hypertension, decreases in systolic blood pressure have been observed at doses ranging from 25 to 100 mg/day. Doses greater than 100 mg/day generally do not provide additional reductions in blood pressure *[see Dosage and Administration (2.3)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

ALDACTONE 25 mg tablets are round, light yellow, film-coated, with SEARLE and 1001 debossed on one side and ALDACTONE and 25 on the other side, supplied as:

NDC Number	Size
0025-1001-31	bottle of 100

ALDACTONE 50 mg tablets are oval, light orange, scored, film-coated, with SEARLE and 1041 debossed on the scored side and ALDACTONE and 50 on the other side, supplied as:

NDC Number	Size
0025-1041-31	bottle of 100

ALDACTONE 100 mg tablets are round, peach-colored, scored, film-coated, with SEARLE and 1031 debossed on the scored side and ALDACTONE and 100 on the other side, supplied as:

NDC Number	Size
0025-1031-31	bottle of 100

Store below 77°F (25°C).

17 PATIENT COUNSELING INFORMATION

Patients who receive ALDACTONE should be advised to avoid potassium supplements and foods containing high levels of potassium, including salt substitutes.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

LAB-0231-15.0

PRINCIPAL DISPLAY PANEL - 25 mg Tablet Bottle Label

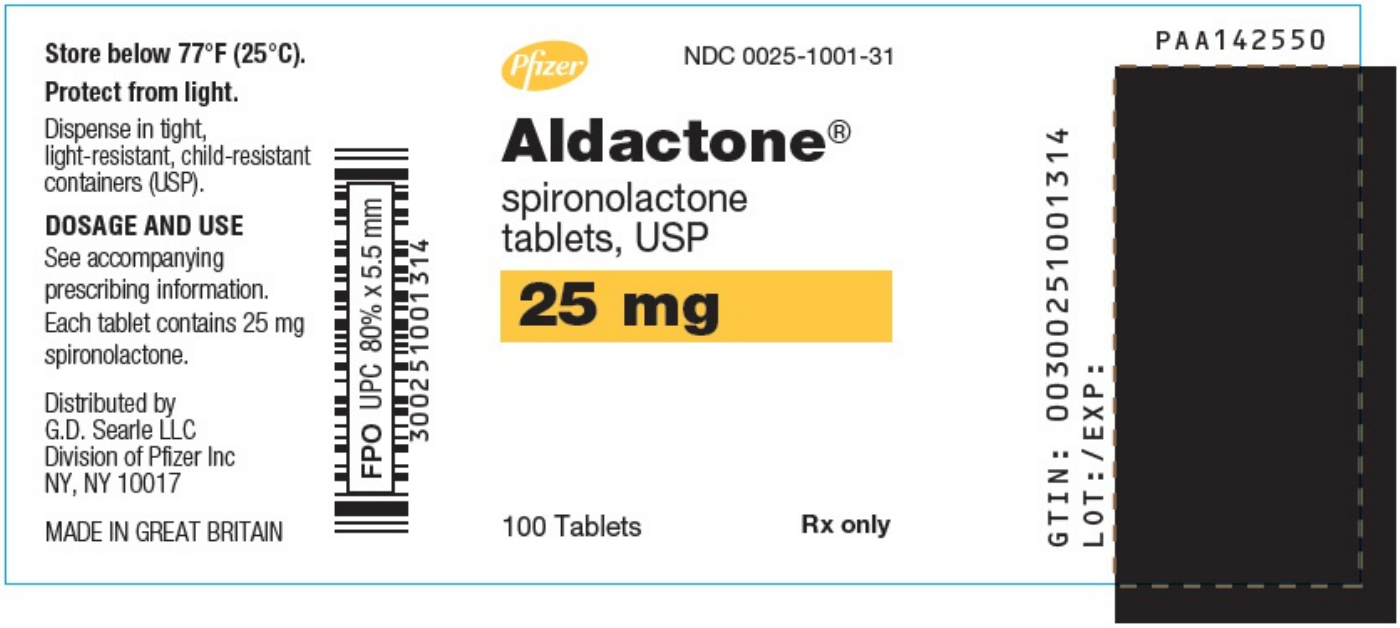
Pfizer

NDC 0025-1001-31

Aldactone®
spironolactone
tablets, USP

25 mg

100 Tablets
Rx only



PRINCIPAL DISPLAY PANEL - 50 mg Tablet Bottle Label

Pfizer

NDC 0025-1041-31

Aldactone®
spironolactone
tablets, USP

50 mg

100 Tablets
Rx only

PRINCIPAL DISPLAY PANEL - 100 mg Tablet Bottle Label

Pfizer

NDC 0025-1031-31

Aldactone®
spironolactone
tablets, USP

100 mg

100 Tablets
Rx only

ALDACTONE

spironolactone tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0025-1001
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
SPIRONOLACTONE (UNII: 27O7W4T232) (SPIRONOLACTONE - UNII:27O7W4T232)	SPIRONOLACTONE	25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
STARCH, CORN (UNII: O8232NY3SJ)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
HYPROMELLOSE 2910 (15000 MPA.S) (UNII: 288VBX44JC)	
CALCIUM SULFATE DIHYDRATE (UNII: 4846Q921YM)	
PEPPERMINT (UNII: V95R5KMY2B)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	

CARNAUBA WAX (UNII: R12CBM0EIZ)	
STEARIC ACID (UNII: 4ELV7Z65AP)	

Product Characteristics			
Color	YELLOW (light yellow)	**Score**	no score
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	SEARLE;1001;ALDACTONE;25
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0025-1001-31	100 in 1 BOTTLE; Type 0: Not a Combination Product	01/21/1960	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA012151	01/21/1960	

ALDACTONE

spironolactone tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0025-1041
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SPIRONOLACTONE (UNII: 27O7W4T232) (SPIRONOLACTONE - UNII:27O7W4T232)	SPIRONOLACTONE	50 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
HYPROMELLOSE 2910 (15000 MPA.S) (UNII: 288VBX44JC)	
CALCIUM SULFATE DIHYDRATE (UNII: 4846Q921YM)	
PEPPERMINT (UNII: V95R5KMY2B)	

POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
CARNAUBA WAX (UNII: R12CBM0EIZ)	
STEARIC ACID (UNII: 4ELV7Z65AP)	

Product Characteristics

Color	ORANGE (light orange)	**Score**	2 pieces
Shape	OVAL	**Size**	14mm
Flavor		**Imprint Code**	SEARLE;1041;ALDACTONE;50
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0025-1041-31	100 in 1 BOTTLE; Type 0: Not a Combination Product	01/21/1960	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA012151	01/21/1960	

ALDACTONE

spironolactone tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0025-1031
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
SPIRONOLACTONE (UNII: 27O7W4T232) (SPIRONOLACTONE - UNII:27O7W4T232)	SPIRONOLACTONE	100 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
HYPROMELLOSE 2910 (15000 MPA.S) (UNII: 288VBX44JC)	
CALCIUM SULFATE DIHYDRATE (UNII: 4846Q921YM)	

PEPPERMINT (UNII: V95R5KMY2B)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
CARNAUBA WAX (UNII: R12CBM0EIZ)	
STEARIC ACID (UNII: 4ELV7Z65AP)	

Product Characteristics

Color	ORANGE (peach)	**Score**	2 pieces
Shape	ROUND	**Size**	11mm
Flavor		**Imprint Code**	SEARLE;1031;ALDACTONE;100
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0025-1031-31	100 in 1 BOTTLE; Type 0: Not a Combination Product	01/21/1960	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA012151	01/21/1960	

Labeler - Pfizer Laboratories Div Pfizer Inc (134489525)

Registrant - Pfizer Inc (113480771)

Establishment

Name	Address	ID/FEI	Business Operations
Packaging Coordinators, LLC		078525133	PACK(0025-1001, 0025-1031, 0025-1041) , LABEL(0025-1001, 0025-1031, 0025-1041)

Establishment

Name	Address	ID/FEI	Business Operations
Pfizer Inc		943955690	ANALYSIS(0025-1001, 0025-1031, 0025-1041)

Revised: 2/2021 Pfizer Laboratories Div Pfizer Inc

Exhibit

N

FINASTERIDE- finasteride tablet
Cipla USA Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FINASTERIDE tablets, USP safely and effectively. See full prescribing information for FINASTERIDE tablets, USP
FINASTERIDE tablets, USP for oral use
Initial U.S. Approval:1992

INDICATIONS AND USAGE

- Finasteride tablet, USP is a 5α-reductase inhibitor indicated for the treatment of male pattern hair loss (androgenetic alopecia) in**MEN ONLY** (1).
- Finasteride tablet, USP is not indicated for use in women (1, 4, 5.1).

DOSAGE AND ADMINISTRATION

- Finasteride tablets, USP may be administered with or without meals (2).
- One tablet (1 mg) taken once daily (2).
- In general, daily use for three months or more is necessary before benefit is observed (2).

DOSAGE FORMS AND STRENGTHS

1 mg tablets (3).

CONTRAINDICATIONS

- Pregnancy (4, 5.1,8.1, 16).
- Hypersensitivity to any components of this product (4).

WARNINGS AND PRECAUTIONS

- Finasteride tablet is not indicated for use in women or pediatric patients (5.1, 5.4).
- Women should not handle crushed or broken Finasteride tablets when they are pregnant or may potentially be pregnant due to potential risk to a male fetus (5.1, 8.1,16).
- Finasteride tablet causes a decrease in serum PSA levels. Any confirmed increase in PSA while on Finasteride tablets may signal the presence of prostate cancer and should be evaluated, even if those values are still within the normal range for men not taking a 5α-reductase inhibitor (5.2).
- 5 α -reductase inhibitors may increase the risk of high-grade prostate cancer (5.3,6.1).

ADVERSE REACTIONS

The most common adverse reactions, reported in ≥1% of patients treated with Finasteride tablets and greater than in patients treated with placebo are: decreased libido, erectile dysfunction and ejaculation disorder (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Cipla Limited, India at 1- 866 -604 -3268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Finasteride tablet, USP is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in **MEN ONLY**.

Efficacy in bitemporal recession has not been established.

Finasteride tablet, USP is not indicated for use in women.

2 DOSAGE AND ADMINISTRATION

Finasteride tablets, USP may be administered with or without meals.

The recommended dose of Finasteride tablets, USP is one tablet taken once daily.

In general, daily use for three months or more is necessary before benefit is observed. Continued use is recommended to sustain benefit, which should be re-evaluated periodically. Withdrawal of treatment leads to reversal of effect within 12 months.

3 DOSAGE FORMS AND STRENGTHS

Finasteride tablets, USP (1mg) are reddish brown, circular, biconvex, film coated tablets, debossed with 'C' on one side and '112' on other side.

4 CONTRAINDICATIONS

Finasteride tablet is contraindicated in the following:

- Pregnancy. Finasteride use is contraindicated in women when they are or may potentially be pregnant. Because of the ability of Type II 5 α-reductase inhibitors to inhibit the conversion of testosterone to 5α-dihydrotestosterone (DHT), finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the pregnant woman should be apprised of the potential hazard to the male fetus. [*See Warnings and Precautions (5.1), Use in Specific Populations (8.1), How Supplied/Storage and Handling (16) and Patient Counseling Information (17.1).*] In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring.
- Hypersensitivity to any component of this medication.

5 WARNINGS AND PRECAUTIONS

5.1 Exposure of Women — Risk to Male Fetus

Finasteride tablet is not indicated for use in women. Women should not handle crushed or broken Finasteride tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. Finasteride tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. [S*ee Indications and Usage (1), Contraindications (4), Use in Specific Populations (8.1), How Supplied/Storage and Handling (16) and Patient Counseling Information (17.1).*]

5.2 Effects on Prostate Specific Antigen (PSA)

In clinical studies with Finasteride tablet, 1 mg in men 18-41 years of age, the mean value of serum prostate specific antigen (PSA) decreased from 0.7 ng/mL at baseline to 0.5 ng/mL at Month 12. Further, in clinical studies with PROSCAR (finasteride, 5 mg) when used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Other studies with PROSCAR showed it may also cause decreases in serum PSA in the presence of prostate cancer. These findings should be taken into account for proper interpretation of serum PSA when evaluating men treated with finasteride. Any confirmed increase from the lowest PSA value while on Finasteride tablets may signal the presence of prostate cancer and should be evaluated, even if PSA levels are still within the normal range for men not taking a 5α-reductase inhibitor. Non-compliance to therapy with Finasteride tablets may also affect PSA test results.

5.3 Increased Risk of High-Grade Prostate Cancer with 5a-Reductase Inhibitors

Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day (5 times the dose of Finasteride tablet) in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). [*See Adverse Reactions (6.1).*] Similar results were observed in a 4-year placebo-controlled clinical trial with another 5α-reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo). 5α-reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5α-reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

5.4 Pediatric Patients

Finasteride tablet is not indicated for use in pediatric patients [*see Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Studies for Finasteride tablets, 1 mg in the Treatment of Male Pattern Hair Loss

In three controlled clinical trials for Finasteride tablets of 12-month duration, 1.4% of patients taking Finasteride tablets (n=945) were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (1.6% for placebo; n=934).

Clinical adverse experiences that were reported as possibly, probably or definitely drug-related in ≥1% of patients treated with Finasteride tablets or placebo are presented in Table 1.

TABLE 1: Drug-Related Adverse Experiences for Finasteride tablets, 1 mg in Year 1 (%)
MALE PATTERN HAIR LOSS

	Finasteride N=945	Placebo N=934
Decreased Libido	1.8	1.3
Erectile Dysfunction	1.3	0.7
Ejaculation Disorder *(Decreased Volume of Ejaculate)*	1.2 *(0.8)*	0.7 *(0.4)*
Discontinuation due to drug-related sexual adverse experiences	1.2	0.9

Integrated analysis of clinical adverse experiences showed that during treatment with Finasteride tablets, 36 (3.8%) of 945 men had reported one or more of these adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo (p=0.04). Resolution occurred in men who discontinued therapy with Finasteride tablets due to these side effects and in most of those who continued therapy. The incidence of each of the above adverse experiences decreased to ≤0.3% by the fifth year of treatment with Finasteride tablets.

In a study of finasteride 1 mg daily in healthy men, a median decrease in ejaculate volume of 0.3 mL (-11%) compared with 0.2 mL (-8%) for placebo was observed after 48 weeks of treatment. Two other studies showed that finasteride at 5 times the dosage of Finasteride tablets (5 mg daily) produced significant median decreases of approximately 0.5 mL (-25%) compared to placebo in ejaculate volume, but this was reversible after discontinuation of treatment.

In the clinical studies with Finasteride tablets, the incidences for breast tenderness and enlargement, hypersensitivity reactions, and testicular pain in finasteride-treated patients were not different from those in patients treated with placebo.

Controlled Clinical Trials and Long-Term Open Extension Studies for PROSCAR® (finasteride 5 mg) and AVODART (dutasteride) in the Treatment of Benign Prostatic Hyperplasia

In the PROSCAR Long-Term Efficacy and Safety Study (PLESS), a 4-year controlled clinical study, 3040 patients between the ages of 45 and 78 with symptomatic BPH and an enlarged prostate were

evaluated for safety over a period of 4 years (1524 on PROSCAR 5 mg/day and 1516 on placebo). 3.7% (57 patients) treated with PROSCAR 5 mg and 2.1% (32 patients) treated with placebo discontinued therapy as a result of adverse reactions related to sexual function, which are the most frequently reported adverse reactions.

Table 2 presents the only clinical adverse reactions considered possibly, probably or definitely drug related by the investigator, for which the incidence on PROSCAR was ≥1% and greater than placebo over the 4 years of the study. In years 2-4 of the study, there was no significant difference between treatment groups in the incidences of impotence, decreased libido and ejaculation disorder.

TABLE 2: Drug-Related Adverse Experiences for PROSCAR (finasteride 5 mg) BENIGN PROSTATIC HYPERPLASIA

	Year 1 (%)		Years 2, 3 and 4* (%)	
	Finasteride, 5 mg	Placebo	Finasteride, 5 mg	Placebo
Impotence	8.1	3.7	5.1	5.1
Decreased Libido	6.4	3.4	2.6	2.6
Decreased Volume of Ejaculate	3.7	0.8	1.5	0.5
Ejaculation Disorder	0.8	0.1	0.2	0.1
Breast Enlargement	0.5	0.1	1.8	1.1
Breast Tenderness	0.4	0.1	0.7	0.3
Rash	0.5	0.2	0.5	0.1

*Combined Years 2-4
N = 1524 and 1516, finasteride vs placebo, respectively

The adverse experience profiles in the 1-year, placebo-controlled, Phase III BPH studies and the 5-year open extensions with PROSCAR 5 mg and PLESS were similar.

There is no evidence of increased sexual adverse experiences with increased duration of treatment with PROSCAR 5mg. New reports of drug-related sexual adverse experiences decreased with duration of therapy.

During the 4- to 6-year placebo- and comparator-controlled Medical Therapy of Prostatic Symptoms (MTOPS) study that enrolled 3047 men, there were 4 cases of breast cancer in men treated with PROSCAR but no cases in men not treated with PROSCAR. During the 4-year placebo-controlled PLESS study that enrolled 3040 men, there were 2 cases of breast cancer in placebo-treated men, but no cases were reported in men treated with PROSCAR.

During the 7-year placebo-controlled Prostate Cancer Prevention Trial (PCPT) that enrolled 18,882 men, there was 1 case of breast cancer in men treated with PROSCAR, and 1 case of breast cancer in men treated with placebo. The relationship between long-term use of finasteride and male breast neoplasia is currently unknown.

The PCPT trial was a 7-year randomized, double-blind, placebo-controlled trial that enrolled 18,882 healthy men ≥55 years of age with a normal digital rectal examination and a PSA ≤3.0 ng/mL. Men received either PROSCAR (finasteride 5 mg) or placebo daily. Patients were evaluated annually with PSA and digital rectal exams. Biopsies were performed for elevated PSA, an abnormal digital rectal exam, or the end of study. The incidence of Gleason score 8-10 prostate cancer was higher in men treated with finasteride (1.8%) than in those treated with placebo (1.1%). In a 4-year placebo-controlled clinical trial with another 5α-reductase inhibitor [AVODART (dutasteride)], similar results for Gleason score 8-10 prostate cancer were observed (1% dutasteride vs 0.5% placebo). The clinical significance

of these findings with respect to use of Finasteride tablets by men is unknown.

No clinical benefit has been demonstrated in patients with prostate cancer treated with PROSCAR. PROSCAR is not approved to reduce the risk of developing prostate cancer.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Finasteride tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Hypersensitivity Reaction: hypersensitivity reactions such as rash, pruritus, urticaria, and angioedema (including swelling of the lips, tongue, throat, and face);

Reproductive System: sexual dysfunction that continued after discontinuation of treatment, including erectile dysfunction, libido disorders, ejaculation disorders, and orgasm disorders; male infertility and/or poor seminal quality (normalization or improvement of seminal quality has been reported after discontinuation of finasteride); testicular pain. [*See Adverse Reactions (6.1).*]

Neoplasms: male breast cancer;

Breast disorders: breast tenderness and enlargement;

Nervous System/Psychiatric: depression

7 DRUG INTERACTIONS

7.1 Cytochrome P450-Linked Drug Metabolizing Enzyme System

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug-metabolizing enzyme system. Compounds that have been tested in man include antipyrine, digoxin, propranolol, theophylline, and warfarin and no clinically meaningful interactions were found.

7.2 Other Concomitant Therapy

Although specific interaction studies were not performed, finasteride doses of 1 mg or more were concomitantly used in clinical studies with acetaminophen, acetylsalicylic acid, α-blockers, analgesics, angiotensin-converting enzyme (ACE) inhibitors, anticonvulsants, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H_2 antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (also referred to as NSAIDs), and quinolone anti-infectives without evidence of clinically significant adverse interactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [*see Contraindications (4)*].

Finasteride tablet is contraindicated for use in women who are or may become pregnant. Finasteride tablet is a Type II 5α-reductase inhibitor that prevents conversion of testosterone to 5α-dihydrotestosterone (DHT), a hormone necessary for normal development of male genitalia. In animal studies, finasteride caused abnormal development of external genitalia in male fetuses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the male fetus.

Abnormal male genital development is an expected consequence when conversion of testosterone to 5α-dihydrotestosterone (DHT) is inhibited by 5α-reductase inhibitors. These outcomes are similar to those reported in male infants with genetic 5α-reductase deficiency. Women could be exposed to finasteride

through contact with crushed or broken Finasteride tablets or semen from a male partner taking Finasteride tablets. With regard to finasteride exposure through the skin, Finasteride tablets are coated and will prevent skin contact with finasteride during normal handling if the tablets have not been crushed or broken. Women who are pregnant or may become pregnant should not handle crushed or broken Finasteride tablets because of possible exposure of a male fetus. If a pregnant woman comes in contact with crushed or broken Finasteride tablets, the contact area should be washed immediately with soap and water. With regard to potential finasteride exposure through semen, a study has been conducted in men receiving Finasteride tablet, 1 mg/day that measured finasteride concentrations in semen [*see Clinical Pharmacology (12.3)*].

In an embryo-fetal development study, pregnant rats received finasteride during the period of major organogenesis (gestation days 6 to 17). At maternal doses of oral finasteride approximately 1 to 684 times the recommended human dose (RHD) of 1 mg/day (based on AUC at animal doses of 0.1 to 100 mg/kg/day) there was a dose-dependent increase in hypospadias that occurred in 3.6 to 100% of male offspring. Exposure multiples were estimated using data from nonpregnant rats. Days 16 to 17 of gestation is a critical period in male fetal rats for differentiation of the external genitalia. At oral maternal doses approximately 0.2 times the RHD (based on AUC at animal dose of 0.03 mg/kg/day), male offspring had decreased prostatic and seminal vesicular weights, delayed preputial separation and transient nipple development. Decreased anogenital distance occurred in male offspring of pregnant rats that received approximately 0.02 times the RHD (based on AUC at animal dose of 0.003 mg/kg/day). No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities were observed in the offspring of untreated females mated with finasteride-treated male rats that received approximately 488 times the RHD (based on AUC at animal dose of 80 mg/kg/day). Slightly decreased fertility was observed in male offspring after administration of about 20 times the RHD (based on AUC at animal dose of 3 mg/kg/day) to female rats during late gestation and lactation. No effects on fertility were seen in female offspring under these conditions.

No evidence of male external genital malformations or other abnormalities were observed in rabbit fetuses exposed to finasteride during the period of major organogenesis (gestation days 6-18) at maternal doses up to 100 mg/kg/day (finasteride exposure levels were not measured in rabbits). However, this study may not have included the critical period for finasteride effects on development of male external genitalia in the rabbit.

The fetal effects of maternal finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), in a species and development period more predictive of specific effects in humans than the studies in rats and rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (estimated maximal blood concentration of 1.86 ng/mL or about 930 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a dose of finasteride (2 mg/kg/day or approximately 120,000 times the highest estimated blood levels of finasteride from semen of men taking 1 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

8.3 Nursing Mothers

Finasteride tablet is not indicated for use in women.

It is not known whether finasteride is excreted in human milk.

8.4 Pediatric Use

Finasteride tablet is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical efficacy studies with Finasteride tablets did not include subjects aged 65 and over. Based on the pharmacokinetics of finasteride 5 mg, no dosage adjustment is necessary in the elderly for Finasteride tablets [*see Clinical Pharmacology (12.3)*]. However the efficacy of Finasteride tablets in the elderly has not been established.

8.6 Hepatic Impairment

Caution should be exercised in the administration of Finasteride tablets in those patients with liver function abnormalities, as finasteride is metabolized extensively in the liver [*see Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

No dosage adjustment is necessary in patients with renal impairment [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

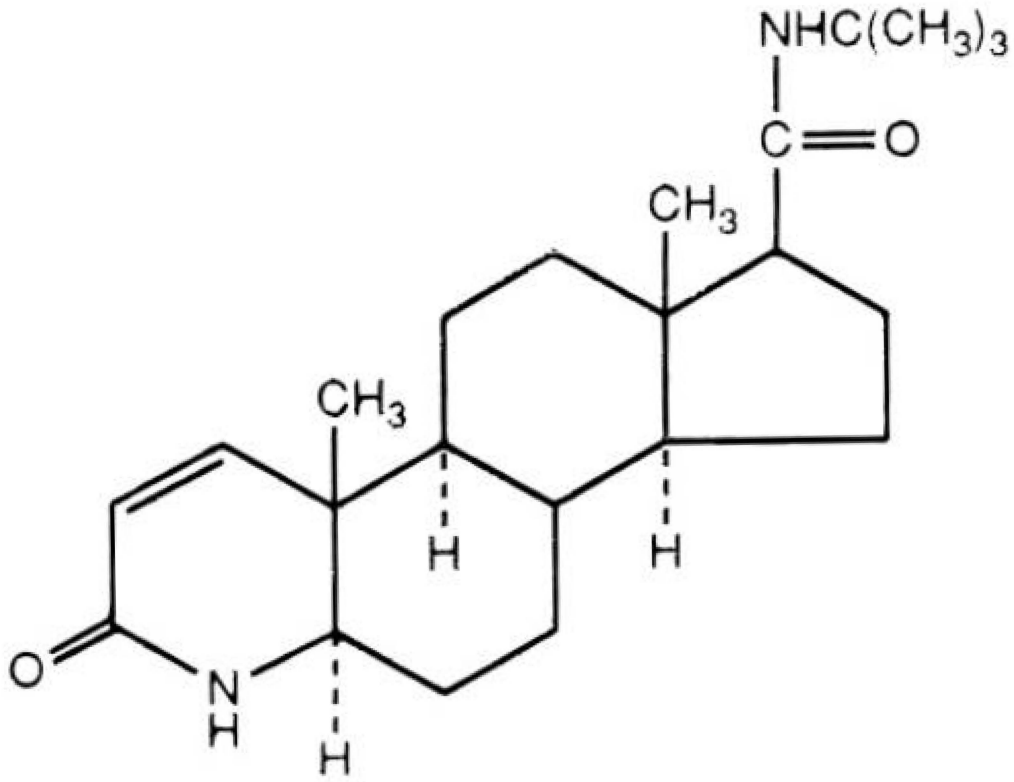
In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months did not result in adverse reactions. Until further experience is obtained, no specific treatment for an overdose with finasteride can be recommended.

Significant lethality was observed in male and female mice at single oral doses of 1500 mg/m^2 (500 mg/kg) and in female and male rats at single oral doses of 2360 mg/m^2 (400 mg/kg) and 5900 mg/m^2 (1000 mg/kg), respectively.

11 DESCRIPTION

Finasteride tablets, USP contain finasteride as the active ingredient. Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT).

The chemical name of finasteride is *N-tert*-Butyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55. Its structural formula is:



Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents but is practically insoluble in water.

Finasteride tablets, USP are film-coated tablets for oral administration. Each tablet contains 1 mg of finasteride and the following inactive ingredients: colloidal silicon dioxide, docusate sodium benzoate, lactose monohydrate, magnesium stearate, sodium starch glycolate, starch (corn), FD&C yellow #6, FD&C blue #2, FD&C red #40, hypromellose, polyethylene glycol and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into DHT. Two distinct isozymes are found in mice, rats, monkeys, and humans: Type I and II. Each of these isozymes is differentially expressed in tissues and developmental stages. In humans, Type I 5α-reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5α-reductase is responsible for approximately one-third of circulating DHT. The Type II 5α-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT.

In humans, the mechanism of action of finasteride is based on its preferential inhibition of the Type II isozyme. Using native tissues (scalp and prostate), *in vitro* binding studies examining the potential of finasteride to inhibit either isozyme revealed a 100-fold selectivity for the human Type II 5α-reductase over Type I isozyme (IC_{50}=500 and 4.2 nM for Type I and II, respectively). For both isozymes, the inhibition by finasteride is accompanied by reduction of the inhibitor to dihydrofinasteride and adduct formation with NADP+. The turnover for the enzyme complex is slow ($t_{1/2}$ approximately 30 days for the Type II enzyme complex and 14 days for the Type I complex). Inhibition of Type II 5α-reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations.

In men with male pattern hair loss (androgenetic alopecia), the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with hairy scalp. Administration of finasteride decreases scalp and serum DHT concentrations in these men. The relative contributions of these reductions to the treatment effect of finasteride have not been defined. By this mechanism, finasteride appears to interrupt a key factor in the development of androgenetic alopecia in those patients genetically predisposed.

12.2 Pharmacodynamics

Finasteride produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with a 1-mg tablet. Mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline, but these remained within the physiologic range.

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH) or prolactin were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone indicating that the hypothalamic-pituitary-testicular axis was not affected. Finasteride had no effect on circulating levels of cortisol, thyroid-stimulating hormone, or thyroxine, nor did it affect the plasma lipid profile (e.g., total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides) or bone mineral density.

12.3 Pharmacokinetics

Absorption

In a study in 15 healthy young male subjects, the mean bioavailability of finasteride 1-mg tablets was 65% (range 26-170%), based on the ratio of area under the curve (AUC) relative to an intravenous (IV) reference dose. At steady state following dosing with 1 mg/day (n=12), maximum finasteride plasma concentration averaged 9.2 ng/mL (range, 4.9-13.7 ng/mL) and was reached 1 to 2 hours postdose; $AUC_{(0\text{-}24\ hr)}$ was 53 ng•hr/mL (range, 20-154 ng•hr/mL). Bioavailability of finasteride was not affected by food.

Distribution

Mean steady-state volume of distribution was 76 liters (range, 44-96 liters; n=15). Approximately 90% of circulating finasteride is bound to plasma proteins. There is a slow accumulation phase for finasteride after multiple dosing.

Finasteride has been found to cross the blood-brain barrier.

Semen levels have been measured in 35 men taking finasteride 1 mg/day for 6 weeks. In 60% (21 of 35) of the samples, finasteride levels were undetectable (<0.2 ng/mL). The mean finasteride level was 0.26 ng/mL and the highest level measured was 1.52 ng/mL. Using the highest semen level measured and assuming 100% absorption from a 5-mL ejaculate per day, human exposure through vaginal absorption would be up to 7.6 ng per day, which is 650-fold less than the dose of finasteride (5 µg) that had no effect on circulating DHT levels in men. [*See Use in Specific Populations (8.1).*]

Metabolism

Finasteride is extensively metabolized in the liver, primarily via the cytochrome P450 3A4 enzyme subfamily. Two metabolites, the t-butyl side chain monohydroxylated and monocarboxylic acid metabolites have been identified that possess no more than 20% of the 5α-reductase inhibitory activity of finasteride.

Excretion

Following intravenous infusion in healthy young subjects (n=15), mean plasma clearance of finasteride was 165 mL/min (range, 70-279 mL/min). Mean terminal half-life in plasma was 4.5 hours (range, 2.3-

was 165 mL/min (range, 70-275 mL/min). Mean terminal half-life in plasma was 4.5 hours (range, 3.5-13.4 hours; n=12). Following an oral dose of ^{14}C-finasteride in man (n=6), a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces.

Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age.

TABLE 3:Mean (SD) Pharmacokinetic Parameters in Healthy Men (ages 18-26)

	Mean (± SD) n=15
Bioavailability	65% (26-170%)*
Clearance (mL/min)	165 (55)
Volume of Distribution (L)	76 (14)

*Range

TABLE 4: Mean (SD) Noncompartmental Pharmacokinetic Parameters After Multiple Doses of 1 mg/day in Healthy Men (ages 19-42)

	Mean (± SD) (n=12)
AUC (ng.hr/mL)	53 (33.8)
Peak Concentration (ng/mL)	9.2 (2.6)
Time to Peak (hours)	1.3 (0.5)
Half-Life (hours)*	4.5 (1.6)

*First-dose values; all other parameters are last-dose values

Renal Impairment

No dosage adjustment is necessary in patients with renal impairment. In patients with chronic renal impairment, with creatinine clearances ranging from 9.0 to 55 mL/min, AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ^{14}C-finasteride were similar to those obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). However, finasteride has been tolerated in men with normal renal function receiving up to 80 mg/day for 12 weeks where exposure of these patients to metabolites would presumably be much greater.

Hepatic Impairment

The effect of hepatic impairment on finasteride pharmacokinetics has not been studied. Caution should be used in the administration of Finasteride tablets in patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 888 and 2192 times those observed in man receiving the recommended human dose of 1 mg/day. All exposure calculations were based on calculated $AUC_{(0-24\ hr)}$ for animals and mean $AUC_{(0-24\ hr)}$ for man (0.05 µg•hr/mL).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenomas was observed at 1824 times the human exposure (250 mg/kg/day). In mice at 184 times the human exposure, estimated (25 mg/kg/day) and in rats at 312 times the human exposure (≥40 mg/kg/day) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2- to 3-fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at 240 and 2800 times (20 mg/kg/day and 45 mg/kg/day, respectively), or in mice treated for 19 months at 18.4 times the human exposure, estimated (2.5 mg/kg/day).

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay, using Chinese hamster ovary cells, there was a slight increase in chromosome aberrations. In an *in vivo* chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (1824 times the human exposure) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 4344 times the human exposure (80 mg/kg/day) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 488 times the human exposure (80 mg/kg/day), there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility, fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats but is not relevant in man.

14 CLINICAL STUDIES

14.1 Studies in Men

The efficacy of Finasteride tablets was demonstrated in men (88% Caucasian) with mild to moderate androgenetic alopecia (male pattern hair loss) between 18 and 41 years of age. In order to prevent seborrheic dermatitis which might confound the assessment of hair growth in these studies, all men, whether treated with finasteride or placebo, were instructed to use a specified, medicated, tar-based shampoo (Neutrogena T/Gel® Shampoo) during the first 2 years of the studies.

There were three double-blind, randomized, placebo-controlled studies of 12-month duration. The two primary endpoints were hair count and patient self-assessment; the two secondary endpoints were investigator assessment and ratings of photographs. In addition, information was collected regarding sexual function (based on a self-administered questionnaire) and non-scalp body hair growth. The three studies were conducted in 1879 men with mild to moderate, but not complete, hair loss. Two of the studies enrolled men with predominantly mild to moderate vertex hair loss (n=1553). The third enrolled men having mild to moderate hair loss in the anterior mid-scalp area with or without vertex balding (n=326).

Studies in Men with Vertex Baldness

Of the men who completed the first 12 months of the two vertex baldness trials, 1215 elected to continue in double-blind, placebo-controlled, 12-month extension studies. There were 547 men receiving Finasteride tablets for both the initial study and first extension periods (up to 2 years of treatment) and 60 men receiving placebo for the same periods. The extension studies were continued for 3 additional years, with 323 men on Finasteride tablets and 23 on placebo entering the fifth year of the study.

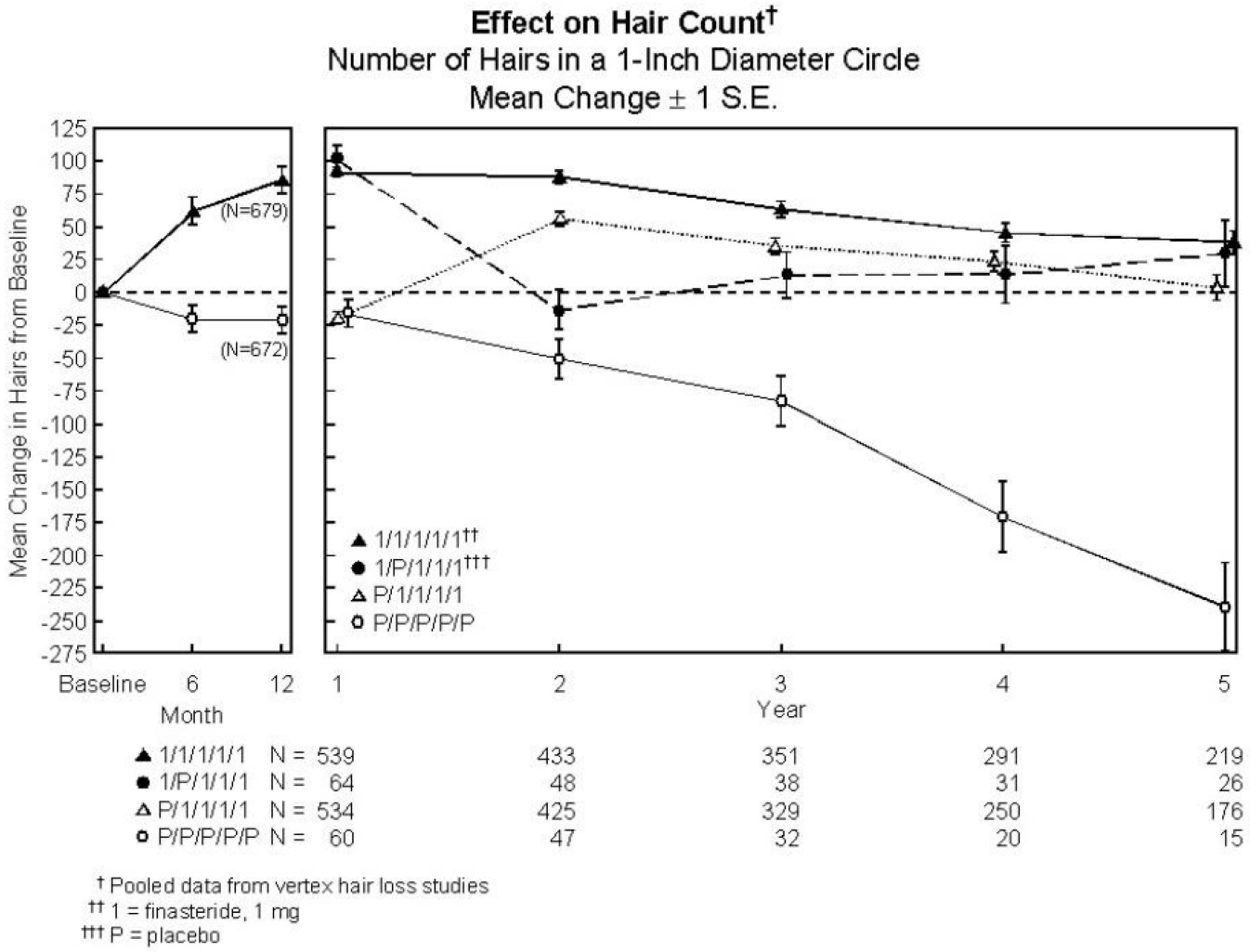
In order to evaluate the effect of discontinuation of therapy, there were 65 men who received Finasteride tablets for the initial 12 months followed by placebo in the first 12-month extension period. Some of these men continued in additional extension studies and were switched back to treatment with Finasteride tablets, with 32 men entering the fifth year of the study. Lastly, there were 543 men who received placebo for the initial 12 months followed by Finasteride tablets in the first 12-month extension period. Some of these men continued in additional extension studies receiving Finasteride tablets, with 290 men entering the fifth year of the study (see Figure 1 below).

Hair counts were assessed by photographic enlargements of a representative area of active hair loss. In these two studies in men with vertex baldness, significant increases in hair count were demonstrated at 6 and 12 months in men treated with Finasteride tablets, while significant hair loss from baseline was demonstrated in those treated with placebo. At 12 months there was a 107-hair difference from placebo ($p<0.001$, Finasteride tablets [n=679] vs placebo [n=672]) within a 1-inch diameter circle (5.1 cm^2). Hair count was maintained in those men taking Finasteride tablets for up to 2 years, resulting in a 138-hair difference between treatment groups ($p<0.001$, Finasteride tablets [n=433] vs placebo [n=47]) within the same area. In men treated with Finasteride tablets, the maximum improvement in hair count compared to baseline was achieved during the first 2 years. Although the initial improvement was followed by a slow decline, hair count was maintained above baseline throughout the 5 years of the studies. Furthermore, because the decline in the placebo group was more rapid, the difference between treatment groups also continued to increase throughout the studies, resulting in a 277-hair difference ($p<0.001$, Finasteride tablets [n=219] vs placebo [n=15]) at 5 years (see Figure 1 below).

Patients who switched from placebo to Finasteride tablets (n=425) had a decrease in hair count at the end of the initial 12 month placebo period, followed by an increase in hair count after 1 year of treatment with Finasteride tablets. This increase in hair count was less (56 hairs above original baseline) than the increase (91 hairs above original baseline) observed after 1 year of treatment in men initially randomized to Finasteride tablets. Although the increase in hair count, relative to when therapy was initiated, was comparable between these two groups, a higher absolute hair count was achieved in patients who were started on treatment with Finasteride tablets in the initial study. This advantage was maintained through the remaining 3 years of the studies. A change of treatment from Finasteride tablets to placebo (n=48) at the end of the initial 12 months resulted in reversal of the increase in hair count 12 months later, at 24 months (see Figure 1 below).

At 12 months, 58% of men in the placebo group had further hair loss (defined as any decrease in hair count from baseline), compared with 14% of men treated with Finasteride tablets. In men treated for up to 2 years, 72% of men in the placebo group demonstrated hair loss, compared with 17% of men treated with Finasteride tablets. At 5 years, 100% of men in the placebo group demonstrated hair loss, compared with 35% of men treated with Finasteride tablets.

Figure 1



Patient self-assessment was obtained at each clinic visit from a self-administered questionnaire, which included questions on their perception of hair growth, hair loss, and appearance. This self-assessment demonstrated an increase in amount of hair, a decrease in hair loss, and improvement in appearance in men treated with Finasteride tablets. Overall improvement compared with placebo was seen as early as 3 months ($p<0.05$), with improvement maintained over 5 years.

Investigator assessment was based on a 7-point scale evaluating increases or decreases in scalp hair at each patient visit. This assessment showed significantly greater increases in hair growth in men treated with Finasteride tablets compared with placebo as early as 3 months ($p<0.001$). At 12 months, the investigators rated 65% of men treated with Finasteride tablets as having increased hair growth compared with 37% in the placebo group. At 2 years, the investigators rated 80% of men treated with Finasteride tablets as having increased hair growth compared with 47% of men treated with placebo. At 5 years, the investigators rated 77% of men treated with Finasteride tablets as having increased hair growth, compared with 15% of men treated with placebo.

An independent panel rated standardized photographs of the head in a blinded fashion based on increases or decreases in scalp hair using the same 7-point scale as the investigator assessment. At 12 months, 48% of men treated with Finasteride tablets had an increase as compared with 7% of men treated with placebo. At 2 years, an increase in hair growth was demonstrated in 66% of men treated with Finasteride tablets, compared with 7% of men treated with placebo. At 5 years, 48% of men treated with Finasteride tablets demonstrated an increase in hair growth, 42% were rated as having no change (no further visible progression of hair loss from baseline) and 10% were rated as having lost hair when compared to baseline. In comparison, 6% of men treated with placebo demonstrated an increase in hair growth, 19% were rated as having no change and 75% were rated as having lost hair when compared to baseline.

A 48-week, placebo-controlled study designed to assess by phototrichogram the effect of Finasteride tablets on total and actively growing (anagen) scalp hairs in vertex baldness enrolled 212 men with androgenetic alopecia. At baseline and 48 weeks, total and anagen hair counts were obtained in a 1-cm^2 target area of the scalp. Men treated with Finasteride tablets showed increases from baseline in total and anagen hair counts of 7 hairs and 18 hairs, respectively, whereas men treated with placebo had decreases of 10 hairs and 9 hairs, respectively. These changes in hair counts resulted in a between-group difference of 17 hairs in total hair count ($p<0.001$) and 27 hairs in anagen hair count ($p<0.001$), and an improvement in the proportion of anagen hairs from 62% at baseline to 68% for men treated with Finasteride tablets.

Other Results in Vertex Baldness Studies

A sexual function questionnaire was self-administered by patients participating in the two vertex baldness trials to detect more subtle changes in sexual function. At Month 12, statistically significant differences in favor of placebo were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems). However, no significant difference was seen in the question on overall satisfaction with sex life.

In one of the two vertex baldness studies, patients were questioned on non-scalp body hair growth. Finasteride tablets did not appear to affect non-scalp body hair.

Study in Men with Hair Loss in the Anterior Mid-Scalp Area

A study of 12-month duration, designed to assess the efficacy of Finasteride tablets in men with hair loss in the anterior mid-scalp area, also demonstrated significant increases in hair count compared with placebo. Increases in hair count were accompanied by improvements in patient self-assessment, investigator assessment, and ratings based on standardized photographs. Hair counts were obtained in the anterior mid-scalp area, and did not include the area of bitemporal recession or the anterior hairline.

Summary of Clinical Studies in Men

Clinical studies were conducted in men aged 18 to 41 with mild to moderate degrees of androgenetic alopecia. All men treated with Finasteride tablets or placebo received a tar-based shampoo (Neutrogena T/Gel® Shampoo) during the first 2 years of the studies. Clinical improvement was seen as early as 3 months in the patients treated with Finasteride tablets and led to a net increase in scalp hair count and hair re-growth. In clinical studies for up to 5 years, treatment with Finasteride tablets slowed the further progression of hair loss observed in the placebo group. In general, the difference between treatment groups continued to increase throughout the 5 years of the studies.

Ethnic Analysis of Clinical Data from Men

In a combined analysis of the two studies on vertex baldness, mean hair count changes from baseline were 91 vs -19 hairs (Finasteride tablets vs placebo) among Caucasians (n=1185), 49 vs -27 hairs among Blacks (n=84), 53 vs -38 hairs among Asians (n=17), 67 vs 5 hairs among Hispanics (n=45) and 67 vs -15 hairs among other ethnic groups (n=20). Patient self-assessment showed improvement across racial groups with Finasteride tablets treatment, except for satisfaction of the frontal hairline and vertex in Black men, who were satisfied overall.

14.2 Study in Women

In a study involving 137 postmenopausal women with androgenetic alopecia who were treated with Finasteride tablets (n=67) or placebo (n=70) for 12 months, effectiveness could not be demonstrated. There was no improvement in hair counts, patient self-assessment, investigator assessment, or ratings of standardized photographs in the women treated with Finasteride tablets when compared with the placebo group [*see Indications and Usage (1)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

Finasteride tablets, USP are reddish brown, circular, biconvex, film-coated tablets, debossed with 'G' on

one side and '112' on other side

Finasteride tablets, USP are available in

bottles of 30 tablets (NDC 69097-112-02)

bottles of 90 tablets (NDC 69097-112-05).

Storage and Handling

Store at 20° to 25° C (68° to 77° F) [See USP Controlled Room Temperature]. Keep container closed and protect from light and moisture.

Women should not handle crushed or broken Finasteride tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. Finasteride tablets1mg are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed [*see Warnings and Precautions (5.1), Use in Specific Populations (8.1) and Patient Counseling Information (17.1)*].

17 PATIENT COUNSELING INFORMATION

"See FDA-approved patient labeling (Patient Information)"

17.1 Exposure of Women — Risk to Male Fetus

Physicians should inform patients that women who are pregnant or may potentially be pregnant should not handle crushed or broken Finasteride tablets because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. Finasteride tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. If a woman who is pregnant or may potentially be pregnant comes in contact with crushed or broken Finasteride tablets, the contact area should be washed immediately with soap and water [s*ee Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1) and How Supplied/Storage and Handling (16)*].

17.2 Increased Risk of High-Grade Prostate Cancer

Patients should be informed that there was an increase in high-grade prostate cancer in men treated with 5α-reductase inhibitors indicated for BPH treatment, compared to those treated with placebo in studies looking at the use of these drugs to prevent prostate cancer [*see Warnings and Precautions (5.3) and Adverse Reactions (6.1)*].

17.3 Additional Instructions

Physicians should instruct their patients to promptly report any changes in their breasts such as lumps, pain or nipple discharge. Breast changes including breast enlargement, tenderness and neoplasm have been reported [*see Adverse Reactions (6.1)*].

Physicians should instruct their patients to read the patient package insert before starting therapy with Finasteride tablets and to read it again each time the prescription is renewed so that they are aware of current information for patients regarding Finasteride tablets.

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Manufactured by:

Cipla, Ltd.,

Verna Goa, INDIA

Manufactured for:

Cipla USA, Inc.

1560 Sawgrass Corporate Parkway, Suite 130, Sunrise, FL 33323

Revised: 05/2017

Patient Information

Finasteride Tablets, USP

Finasteride tablets, USP is for use by **MEN ONLY** and should **NOT** be used by women or children.

Read this Patient Information before you start taking Finasteride tablets, USP and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is Finasteride tablet, USP?

Finasteride tablets, USP is a prescription medicine used for the treatment of male pattern hair loss (androgenetic alopecia).

It is not known if Finasteride tablets, USP works for a receding hairline on either side of and above your forehead (temporal area).

Finasteride tablets, USP is not for use by women and children.

Who should not take Finasteride tablets, USP?

Do not take Finasteride tablets, USP if you:

- are pregnant or may become pregnant. Finasteride tablets, USP may harm your unborn baby.

o Finasteride tablets, USP are coated and will prevent contact with the medicine during handling, as long as the tablets are not broken or crushed. Females who are pregnant or who may become pregnant should not come in contact with broken or crushed Finasteride tablets, USP. If a pregnant woman comes in contact with crushed or broken Finasteride tablets, USP, wash the contact area right away with soap and water. If a woman who is pregnant comes into contact with the active ingredient in Finasteride tablets, USP, a healthcare provider should be consulted.

o If a woman who is pregnant with a male baby swallows or comes in contact with the medicine in Finasteride tablets, USP, the male baby may be born with sex organs that are not normal.

- are allergic to any of the ingredients in Finasteride tablets, USP. See the end of this leaflet for a complete list of ingredients in Finasteride tablets, USP.

What should I tell my healthcare provider before taking Finasteride tablets, USP?

Before taking Finasteride tablets, USP, tell your healthcare provider if you:

- have any other medical conditions, including problems with your prostate or liver

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Finasteride tablets, USP?

- Take Finasteride tablets, USP exactly as your healthcare provider tells you to take it.
- You may take Finasteride tablets, USP with or without food.
- If you forget to take Finasteride tablets, USP do not take an extra tablet. Just take the next tablet as usual.

Finasteride tablets, USP will not work faster or better if you take it more than once a day.

What are the possible side effects of Finasteride tablets, USP?

- **Decrease in your blood Prostate Specific Antigen (PSA) levels.** Finasteride tablets, USP can affect a blood test called PSA (Prostate Specific Antigen) for the screening of prostate cancer. If you have a PSA test done you should tell your healthcare provider that you are taking Finasteride tablets, USP because Finasteride tablets, USP decreases PSA levels. Changes in PSA levels will need to be evaluated by your healthcare provider. Any increase in follow-up PSA levels from their lowest point may signal the presence of prostate cancer and should be evaluated, even if the test results are still within the normal range for men not taking Finasteride tablets, USP. You should also tell your healthcare provider if you have not been taking Finasteride tablets, USP as prescribed because this may affect the PSA test results. For more information, talk to your healthcare provider.
- There may be an increased risk of a more serious form of prostate cancer in men taking finasteride at 5 times the dose of Finasteride tablets, USP.

The most common side effects of Finasteride tablets, USP include:

- decrease in sex drive
- trouble getting or keeping an erection
- a decrease in the amount of semen

The following have been reported in general use with Finasteride tablets, USP:

- breast tenderness and enlargement. Tell your healthcare provider about any changes in your breasts such as lumps, pain or nipple discharge.
- depression;
- decrease in sex drive that continued after stopping the medication;
- allergic reactions including rash, itching, hives and swelling of the lips, tongue, throat, and face;
- problems with ejaculation that continued after stopping medication;
- testicular pain;
- difficulty in achieving an erection that continued after stopping the medication;
- male infertility and/or poor quality of semen.
- in rare cases, male breast cancer.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Finasteride tablets, USP. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Finasteride tablets, USP?

- Store Finasteride tablets, USP at room temperature between 68˚F to 77˚F (20˚C to 25˚C).
- Keep Finasteride tablets, USP in a closed container and keep Finasteride tablets, USP dry (protect from light and moisture).

Keep Finasteride tablets, USP and all medicines out of the reach of children.

General information about the safe and effective use of Finasteride tablets, USP.

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information leaflet. Do not use Finasteride tablets, USP for a condition for which it was not prescribed. Do not give Finasteride tablets, USP to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about Finasteride tablets, USP. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Finasteride tablets, USP that is written for health professionals.

What are the ingredients in Finasteride tablets, USP?

Active ingredient: finasteride.

Inactive ingredients: colloidal silicon dioxide, docusate sodium benzoate, lactose monohydrate, magnesium stearate, sodium starch glycolate, starch (corn), FD&C yellow #6, FD&C blue #2, FD&C red #40, hypromellose, polyethylene glycol and titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Cipla, Ltd.,

Verna Goa, INDIA

Manufactured for: Cipla USA, Inc.

1560 Sawgrass Corporate Parkway, Suite 130, Sunrise, FL 33323

Revised: 05/2017

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

PRINCIPLE DISPLAY PANEL

NDC 69097-**112**-02 Rx ONLY

Finasteride

Tablets, USP

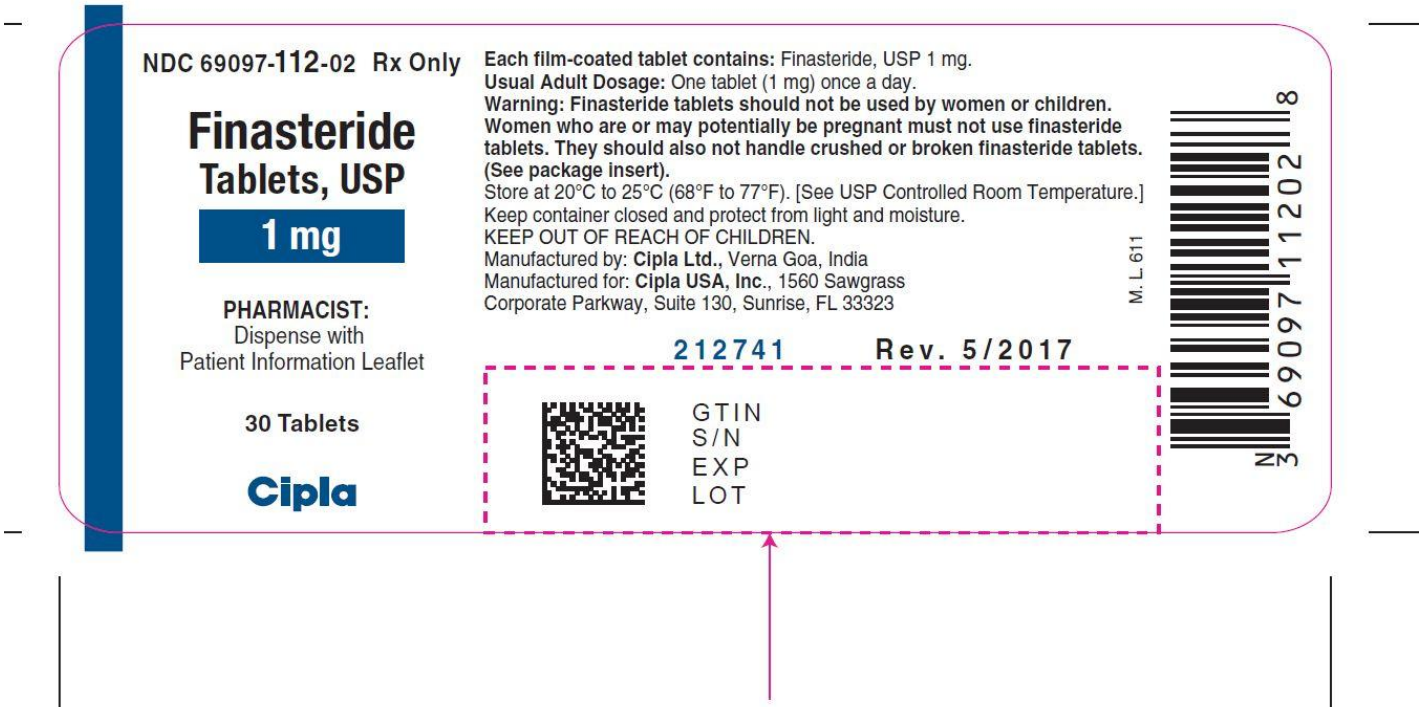
1 mg

PHARMACIST:

Dispense with Patient Information Leaflet

30 Tablets

Cipla



Area for Batch overprinting
(Product GTIN, Serial No., Expiry & Lot will be overprinted during commercial packing)

FINASTERIDE

finasteride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69097-112
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FINASTERIDE (UNII: 57GNO57U7G) (FINASTERIDE - UNII:57GNO57U7G)	FINASTERIDE	1 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
DOCUSATE SODIUM/SODIUM BENZOATE (UNII: 656HXR6YXN)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
STARCH, CORN (UNII: O8232NY3SJ)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

FD&C RED NO. 40 (UNII: WZB9127XOA)	
HYPROMELLOSE 2910 (15 MPA.S) (UNII: 36SFW2JZ0W)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	BROWN (Reddish brown)	**Score**	no score
Shape	ROUND (Circular biconvex)	**Size**	7mm
Flavor		**Imprint Code**	C112
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69097-112-02	30 in 1 BOTTLE; Type 1: Convenience Kit of Co-Package	11/20/2014	
2	NDC:69097-112-05	90 in 1 BOTTLE; Type 1: Convenience Kit of Co-Package	11/20/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077335	11/20/2014	

Labeler - Cipla USA Inc. (078719707)

Revised: 12/2018 Cipla USA Inc.