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PUBERTY SUPPRESSION THERAPY
GENERALLY ACCEPTED PROFESSIONAL MEDICAL STANDARDS (GAPMS)
DETERMINATION REPORT WITH RECOMMENDATION

Date: September 14, 2016

To: Justin Senior, Deputy Secretary for Medicaid

From: Bureau of Medicaid Policy

Subject: **Puberty Suppression Therapy**

PURPOSE

In order for the use of puberty suppression therapy to be covered under the Florida Medicaid program, it must meet medical necessity criteria as defined in Rule 59G-1.010, Florida Administrative Code (F.A.C.), and be funded through the General Appropriations Act of Chapter 216, Florida Statutes (F.S.).

Pursuant to the criteria set forth in Rule 59G-1.010, F.A.C., the use of puberty suppression therapy must be consistent with generally accepted professional medical standards (GAPMS) as determined by the Medicaid program, and not experimental or investigational.

In accordance with the determination process established in Rule 59G-1.035, F.A.C., the Deputy Secretary for Medicaid will make the final determination as to whether the use of puberty suppression therapy is consistent with generally accepted professional medical standards and not experimental or investigational.

If it is determined that puberty suppression therapy is consistent with generally accepted professional medical standards, this report will be supplemented with an addendum which analyzes additional factors to determine whether this health service should be covered under the Florida Medicaid program.

REPORT WITH RECOMMENDATION

This report with recommendation is presented as the summary assessment considering the factors identified in Rule 59G-1.035, F.A.C., based on the collection of information from credible sources of reliable evidence-based information. The intent is to provide a brief analysis with justification in support of the final recommendation.

The analysis described in this report includes:

- A high level review of relevant disease processes.
- An overview of the health service information.
- Clearance from the government regulatory body (e.g., Food and Drug Administration).

- Evidence based clinical practice guidelines.
- A review of the literature considered by the relevant medical community or practitioner specialty associations from credible scientific evidence-based literature published in peer reviewed journals and consensus of coverage policy from commercial and other state Medicaid insurers.

HEALTH SERVICE SUMMARY

Hormones

Hormones are important chemical messengers in the body that effectively transfer signals and instructions from one set of cells to another. Hormones are secreted into the bloodstream by a collection of glands inside the body referred to as the endocrine system. A gland is a group of cells that produces and secretes chemicals into the body. The major glands that make up the endocrine system include the hypothalamus, pituitary gland, thyroid and parathyroid, adrenals, pineal body, and the ovaries and testes.

In a laboratory setting, hormones are produced synthetically and are prescribed by physicians to treat disease or hormone deficiencies. An instance where synthetic hormones may be needed is when an individual has their thyroid gland surgically removed; a practitioner may prescribe synthetic thyroid hormones to replace those that their body can no longer produce.

Over 50 different hormones have been identified in the human body, and more are still being discovered. Hormones influence and regulate practically every cell, tissue, organ, and function of the body, including growth, development, metabolism, homeostasis, and sexual and reproductive function.[20]

Reproductive Hormones

The hormones commonly considered as reproductive hormones in the body are testosterone, estrogen, and progesterone. Testosterone is often referred to as a male hormone, and estrogen and progesterone are often referred to as female hormones. However, there are no exclusively male or female hormones that have been identified. The physical manifestations of gender result from differences in the amounts of individual hormones in the body and differences in their patterns of secretion, first in utero and then again during puberty. In other words, testosterone, estrogen, and progesterone are produced by men and women, but in differing amounts and in different patterns.[20]

Reproductive Hormone Suppression Therapy

There are many disease processes in which increased levels of reproductive hormones are released. They include, but are not limited to, prostate cancer, breast cancer, severe endometriosis, and central precocious puberty. To address the over-secretion of reproductive hormones, several drugs have been developed to aid in reducing hormone levels, including those hormones released during puberty.

For the purposes of this report, an analysis is being performed on the use of hormone treatment to suppress puberty. Currently, there are a number of drugs used to suppress puberty, which all use gonadotropin-releasing hormone (GnRH) agonists. Agonists function to stop receptors from connecting with the appropriate transmitter. For a hormone to perform its primary function in the

brain and body it must find the correct receptor to transmit its response; the GnRH agonists prevent this natural cycle.[20]

Government Regulatory Body Approval

The Food and Drug Administration (FDA) has approved three drugs for the use in children for the purpose of puberty suppression therapy, as follows:

- Lupron[44]
  - Indications for use: Palliative treatment of advanced prostatic cancer and central precocious puberty in children of both sexes.
- Synarel[47]
  - Indications for use: Central precocious puberty (gonadotropin-dependent precocious puberty) in children of both sexes and endometriosis.
- Supprelin[46]
  - Indications for use: Central precocious puberty in both sexes.

Each of these drugs has specific indications for use and dosing information. Additionally, these medications have approved off-label uses. This permits usage in other than the approved FDA indications. These approved off-label uses are compiled in three compendia: American Hospital Formulary Service Drug Information (AHFS), United States Pharmacopeia-Drug Information (or its successor publications), and DRUGDEX Information System.[7] The drugs specified above are authorized in the respective compendia to treat the following conditions:

- Lupron:
  - Breast cancer
  - In vitro fertilization
  - Ovarian cancer
  - Premenstrual syndrome
  - Prostate cancer
  - Prostate cancer, Neoadjuvant treatment
  - Uterine leiomyoma
- Synarel:
  - Benign prostatic hyperplasia
  - Contraception, Female; prophylaxis
  - Contraception, Male; prophylaxis
  - Crohn's disease
  - Hirsutism
  - In vitro fertilization
  - Uterine leiomyoma
- Supprelin:
  - Acute intermittent porphyria
  - Endometriosis
  - Female infertility; Adjunct
  - Polycystic ovary syndrome
  - Uterine leiomyoma

While all of these drugs may be utilized to treat other conditions, as indicated above and specified in the compendia, none of them are authorized or specified in the compendia for use in treating individuals diagnosed with gender dysphoria.[7]

LITERATURE REVIEW

This analysis summarizes information obtained from scientific literature published in credible peer-reviewed journals related to the use of puberty suppression therapy. This section also briefly cites the positions from the relevant medical societies, and summarizes the key articles referenced in support of their positions.

Central Precocious Puberty

Central precocious puberty (CPP) develops due to premature pubertal changes and rapid bone development. CPP is associated with lower adult height and increased risk for development of psychological problems.

Reproductive hormone suppression therapy (also referred to as puberty suppression therapy in this document) has been the standard of care for CPP for the last 15-20 years. The standard treatment for CPP is GnRH analogs. Although there are many different analogs with different routes of administration, the primary agent in the United States for many years was depot intramuscular injections administered every four weeks, but in the last ten years, a subdermal or under the skin implant has been developed, which has been shown to be effective for up to two years.[17, 39, 41]

In a recent study, researchers explored the difference in cognitive function, behavior, emotional reactivity, and psychosocial problems between young females treated with GnRH and age-matched controls. They concluded that young females treated with GnRH do not differ in their cognitive functioning, behavioral, and social problems from their same age peers. However, they did find a significant difference in heart rate that increased with treatment duration and suggested a follow-up study with an emphasis on cardiac health.[55]

Gender Dysphoria

Gender dysphoria is an individual's affective or cognitive discontent with their assigned gender (gender at birth).[14] Gender dysphoria refers to the distress that may accompany the incongruence between the individual's experienced or expressed gender and their assigned gender. Evidence of this distress is the hallmark of the disorder. The diagnostic criteria are divided into a category for children and a category for adolescents and adults. The disorder is manifested differently as an individual ages or enters different developmental stages. Both categories require marked incongruence between the individual's experienced or expressed gender and their assigned gender of at least a six months' duration and clinically significant distress or impairment in social, school (occupation for adults), or other important areas of functioning.[14]

Diagnostic criteria in children include: a strong desire to be the other gender or an insistence that they are the other gender; a preference for wearing clothing associated with the other gender; preference for cross gender roles in simulated play; preference for toys games, or activities usually associated with the other gender; preference for playmates of the other gender; and the dislike of their sexual anatomy. The prevalence of this diagnosis among the general population ranges from 0.005% to 0.014% in males and 0.002% to 0.003% in females.[14]

Studies have shown that the majority of children (80%) diagnosed with gender dysphoria will not continue to be gender dysphoric after puberty.[31]

In adolescents and adults, diagnostic criteria include: a strong desire to be and to be treated as the other gender and a strong desire to have the sex characteristics of the other gender (or in the case of adolescents, the wish to prevent the development of their assigned gender's characteristics).[14]

Gender dysphoria is associated with high levels of stigmatization, discrimination, and victimization, leading to negative self-concept, increased rates of mental disorder comorbidity, school dropout, and economic marginalization.[14] Adolescents that do not receive treatment during this already vulnerable period of development might engage in risky or self-harming behaviors , such as self-harm, self-mutilation, suicidal ideation, or suicide.[22]

For the 20% of children who persist in their feelings of gender dysphoria, clinicians may begin to explore alternative treatment approaches beyond psychotherapy after the onset of puberty, including medical interventions such as the use of GnRH analogs to suppress puberty.[38] The use of puberty suppression therapy is used as a diagnostic aid in adolescents contending with gender dysphoria.[6, 10, 11, 24, 31, 50] The use of GnRH analogs is generally prescribed in adolescents ages 12-16. In addition to puberty suppression therapy, a physician may also begin to prescribe cross-sex hormones, though the latter does not generally begin until the ages of 16-18.[10, 11]

The use of GnRH analogs will delay reproductive development in this population. However, there remains a great deal of concern and lack of consensus in the medical community of the potential risks, including: misdiagnosis, sterilization, adverse medical effect on the metabolic and endocrine system, impaired bone mass and brain development, etc.[51, 6] To date, there have been no randomized controlled clinical trials on the use of GnRH analogs in the treatment of gender dysphoria (on large cohorts) that have been shown to be efficacious with tolerable side effects. This is in large part due to the small number of patients diagnosed with gender dysphoria, which makes any statement on the general efficacy of a treatment approach challenging.[31] However, there have been case-studies (qualitative) that have been conducted that review the outcomes on small cohorts. These studies have concluded that there are limited negative side effects from the use of puberty suppression drugs in adolescents contending with gender dysphoria.[54, 55]

Clinicians who support the use of puberty suppression therapy in the treatment of gender dysphoria argue that the risks of misdiagnosis are significantly reduced if the treatment is delayed until the initiation of puberty. They also contend that this treatment may relieve emotional distress in the individual (including reducing suicidal ideation in severe cases) and may "buy time" for the child to explore their feelings of gender dysphoria without contending with physical changes that cannot be undone (e.g., breast development).[22] Most treatment protocols recommend extensive psychological evaluations/assessments and psychotherapy by mental health professionals prior to the initiation of medical interventions. This is especially important given the changing thoughts and feelings of prepubescent children versus adolescents with persistent gender dysphoria and in adolescents presenting with co-morbid conditions.

It is important to note that most of the literature reviewed in development of this analysis concluded that more systematic research is required to determine the long-term efficacy of medical treatment for adolescents with gender dysphoria.[21, 24, 25, 28, 50, 51]

Evidence-Based Clinical Practice Guidelines

The American Academy of Pediatrics published a consensus statement on the use of GnRH analogs in children in March 2009. They concluded that GnRH use was undisputed in the treatment of CPP early-onset (less than six years old). However, the use of GnRH for conditions other than CPP requires additional investigation and cannot be suggested routinely.[3] The consensus statement does not specifically address the use of GnRH in the treatment of gender dysphoria.

The Endocrine Society published guidelines for the endocrine treatment of transsexual persons. The Society concluded that transsexual persons seeking to develop the physical characteristics of the desired gender require safe, effective hormone regimen that will 1) suppress endogenous hormone secretion determined by the person's genetic/biological sex and 2) maintain sex hormone levels within the normal range for the person's desired gender. They recommend that a mental health professional make the referral and participate in ongoing care and an endocrinologist must confirm the diagnostic criteria. They do not recommend endocrine treatment of prepubertal children. The recommendations are as follows:

- Treatment of transsexual adolescents (Tanner stage two, generally achieved around the age of 12 years) by suppressing puberty with GnRH analogues until the age of 16 years.
- Initiation of cross-sex hormones at the age of 16 years with continued suppression of biological sex hormones.
- Maintaining physiologic levels of gender-appropriate sex hormones and monitoring for known risks throughout adulthood.[19, 18, 32]

In making these recommendations, however, the Endocrine Society identified the strength of the evidence used to support its conclusions. For all of the recommendations listed above, the Society acknowledged the strength of the evidence as low or very low.

COVERAGE POLICY

Federal Regulations

Federal regulations for Medicaid specify that a state may limit coverage of a drug with respect to the treatment of a specific disease or condition for an identified population (if any) based on the drug's labeling, if it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome of such treatment for such population over other drugs included in the formulary. In addition, states may exclude a drug when the prescribed use of the drug is not for a medically accepted indication, either approved by the FDA or supported by information from the appropriate compendia. These guidelines apply to a state's administration of its Medicaid prescribed drug benefit in both managed care and non-managed care delivery systems.

States are also required to implement a drug use review program for covered outpatient drugs in order to assure that prescriptions are appropriate, medically necessary, and are not likely to result in adverse medical results. The program is required to assess data on drug use against predetermined standards, consistent with the following:

1. Compendia, consisting of the following:
   a. American Hospital Formulary Service Drug Information;
   b. United States Pharmacopeia-Drug Information (or its successor publications); and
   c. the DRUGDEX Information System; and
2. The peer-reviewed medical literature.

Federal law requires states to provide services to eligible recipients under the age of 21 years, if such services are medically necessary to correct or ameliorate a defect, a condition, or a physical or mental illness. This is known as the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) benefit. Included are diagnostic services, treatment, equipment, supplies, and other measures described in section 1905(a) of the Social Security Act, codified in Title 42 of the United States Code 1396d (a). As such, services for recipients under the age of 21 years exceeding any coverage limitations specified within a state's policies maybe approved, if medically necessary.

Florida Medicaid

In order to be reimbursed by Florida Medicaid, a drug must be medically necessary and either (a) prescribed for medically accepted indications and dosages found in the drug labeling or drug compendia in accordance with section 1927(k) (6) of the Social Security Act, or (b) prior authorized by a qualified clinical specialist approved by the Agency for Health Care Administration (Agency).[1]

The criteria that are utilized under the Florida Medicaid program in the authorization of drugs for off-label purposes are as follows:

1. Documentation submitted with trial and failure or intolerance to all FDA- approved medications for the indication **AND**
2. Phase III clinical studies published in peer review journals to support the non-FDA approved use **AND**
3. Usage supported by publications in peer reviewed medical literature **and** one or more citations in at least one of the following compendia:
   a. American Hospital Formulary Service Drug Information (AHFS)
   b. United States Pharmacopeia-Drug Information (or its successor publications)
   c. DRUGDEX Information System[1]

Florida Medicaid covers reproductive hormone suppression therapy (including puberty suppression therapy) for all FDA approved indications/uses or when the information in the appropriate compendium supports the use of the drug in the treatment of the specific disease state or condition. Since the use of GnRH agonists are not FDA approved or listed in the appropriate compendia for the treatment of gender dysphoria, Florida Medicaid does not authorize these drugs for such uses. However, children/adolescents diagnosed with gender dysphoria are eligible to receive an array of other medical and behavioral health interventions (e.g., individual and family therapy, psychological evaluations/assessments, other medical evaluation and management services) necessary to address their presenting signs and symptoms.

Health plans contracted to provide services under the Florida Medicaid Statewide Medicaid Managed Care program are required to cover all prescription drugs listed in the Agency's Medicaid Preferred Drug List (PDL). In addition, the health plan's prior authorization criteria and protocols may not be more restrictive than those used by the Agency as indicated in the Florida Statutes, the Florida Administrative Code, the Medicaid State Plan and those posted on the Agency website.

Florida Medicaid provides services to eligible recipients under the age of 21 years, if such services are medically necessary to correct or ameliorate a defect, a condition, or a physical or mental illness. Medical necessity in the State of Florida must meet the following conditions:

1. Be necessary to protect life, to prevent significant illness or significant disability, or to alleviate severe pain;
2. Be individualized, specific, and consistent with symptoms or confirmed diagnosis of the illness or injury under treatment, and not in excess of the patient's needs;
3. Be consistent with generally accepted professional medical standards as determined by the Medicaid program, and not experimental or investigational;
4. Be reflective of the level of service that can be safely furnished, and for which no equally effective and more conservative or less costly treatment is available statewide; and
5. Be furnished in a manner not primarily intended for the convenience of the recipient, the recipient's caretaker, or the provider.

If a service exceeds the coverage described within a Florida Medicaid policy or the associated fee schedule, a request (along with all supporting documentation) may be submitted to the Agency or its designee for review.

Medicare

Medicare covers reproductive hormone suppression for all FDA approved use. The *Medicare Benefit Policy Manual*, Chapter 15, page 15, subsection 50.4.2, discusses the unlabeled use of a drug. The policy states that "FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if the carrier determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice."[5] However, because Medicare covers primarily elderly adults and disabled adults, its coverage policies have little or no application in this analysis.

State Medicaid Programs

All state Medicaid programs cover reproductive hormone suppression therapy for the approved FDA indications and when the criteria for off-label use are met. Some state Medicaid programs are also adopting coverage policies that allow for reimbursements of puberty suppression therapy in adolescents diagnosed with gender dysphoria. It appears at this time as though most states do not cover this service although that may change over time. This report highlights the coverage policies for four Medicaid programs that do cover the service, as follows:

1. Colorado Medicaid covers behavioral health services, GnRH analogs/agonists, cross-sex hormone therapy, gender confirmation surgery, and pre and post-operative care.
2. Maryland Medicaid covers GnRH treatment if the recipient has a diagnosis of gender dysphoria.
3. Rhode Island Medicaid covers behavioral health services, pharmacological and hormonal therapy to delay physical changes of puberty, and pharmacological and hormonal therapy that is non-reversible and produces masculinization or feminization. Some services require prior authorization.
4. Washington State Medicaid covers behavioral health services, puberty suppression therapy, hormonal therapy, and gender reassignment surgery.

GENERALLY ACCEPTED PROFESSIONAL MEDICAL STANDARDS RECOMMENDATION

Puberty suppression therapy is considered a health service that is consistent with generally accepted professional medical standards for the approved FDA indications (i.e., central precocious puberty) and for off-label use when supported by citations in at least one of the compendia. Since Florida Medicaid already provides coverage of puberty suppression therapy in the treatment of central precious puberty and for use in treating the conditions cited in the compendia, no further policy coverage analyses are needed to supplement this report on this point.

Based upon the available published literature, it is inconclusive whether puberty suppression therapy is considered a health service that is consistent with generally accepted professional medical standards in the treatment of gender dysphoria. Most of the studies published thus far on the use of puberty suppression in gender dysphoric children/adolescents have concluded that further systematic research is required to determine the long-term safety and efficacy of this approach and there remains a lack of consensus within the medical community on its appropriateness (both from an ethical and safety perspective). As the research on this topic continues to evolve, more conclusive evidence may emerge that supports the long-term efficacy and effectiveness of this treatment approach. At any time, a follow-up analysis can be performed that could change this recommendation.

EPSDT Considerations:

While the Agency cannot make a blanket determination on puberty suppression therapy for gender dysphoria, we also cannot categorically exclude this treatment for children. Clinical guidelines from the Endocrine Society do recommend this therapy for certain adolescents, albeit based upon a combination of weak and very weak evidence. In certain circumstances, the risks of not treating an adolescent may be worse than the potential long-term consequences of treatment. Moreover, it is noted extensively in the literature that adolescents contending with gender dysphoria often experience a myriad of emotional, physical, and societal challenges. Unresolved, the distress can manifest into a host of behavioral health problems including depression, anxiety, and suicidal ideation and self-mutilation. Florida pays for services for children when they protect life and /or prevent significant disability or harm, in accordance with the state's medical necessity definition.

Given these concerns, while it is not recommended that any further analyses be conducted to expand Florida Medicaid's coverage of puberty suppression therapy beyond those indications/uses approved by the FDA or authorized in the appropriate compendium, it is recommended that any individualized request for such therapy be reviewed as a part of the Agency's special services process. Consistent with EPSDT requirements, the request can be evaluated on an individualized basis to determine if the service is medically necessary (e.g. it is administered to protect life and/or prevent significant disability, such as to prevent suicide or self-mutilation) to ensure that all less invasive interventions have been exhausted, and to ensure that this treatment approach presents as the best alternative given the adolescent's psychological state and presenting signs and symptoms.

✓ **Concur** ____ **Do not Concur**

Comments:

Brad Thomas for Justin Senior

Deputy Secretary for Medicaid (or designee)

9/15/16

Date