POLICY: Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty

- Fensolvi® (leuprolide acetate for injectable suspension – Tolmar)
- Lupron Depot-Ped® (leuprolide acetate for depot suspension – AbbVie)
- Triptodur™ (triptorelin extended-release injectable suspension – Arbor Pharmaceuticals, LLC)

DATE REVIEWED: 09/18/2019; Selected revision, 05/13/2020

OVERVIEW

Fensolvi, Lupron Depot-Ped, and Triptodur are gonadotropin-releasing hormone (GnRH) agonists indicated for the treatment of children with central precocious puberty.[1-3] Fensolvi is administered by a subcutaneous (SC) injection and both Lupron Depot-Ped and Triptodur are administered by intramuscular (IM) injection. Fensolvi is administered once every 6 months, Lupron Depot-Ped is administered once a month or once every 3 months and Triptodur is administered once every 24 weeks.

Guidelines

The standard of care for central precocious puberty is GnRH agonists.[4-6] The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society (2009) note that the available GnRH agonists (including leuprolide and triptorelin) are effective, despite different routes of administration, dosing, and duration of action.[4] The panel noted that the available GnRH agonists (including leuprolide and triptorelin) are effective despite different routes of administration, dosing, and duration of action. In addition, the various GnRH agonists are well-tolerated in children and adolescents. An update by an International Consortium (2019) notes the lack of prospective comparative studies to establish differences in efficacy (if any) among the various GnRH agonists.[5] The Consortium does not prefer one GnRH agonist over another. Discontinuation of GnRH agonist therapy should be individualized, based on the patient's readiness for resumption of puberty, recent growth rates and shifts in height prediction.

Other Uses With Supportive Evidence

The Endocrine Society Guideline (2017) for the Treatment of Gender-Dysphoric/Gender-Incongruent Persons note that persons who fulfill criteria for treatment and who request treatment should initially undergo treatment to suppress physical changes of puberty.[7] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). However, there may be compelling reasons to initiate hormone treatment before the age of 16 years in some adolescents. The guidelines note suppression of pubertal development and gonadal function can be effectively achieved via gonadotropin suppression using GnRH analogs. Long-acting GnRH analogs are the currently preferred treatment option. An advantage to using a GnRH analog is that the effects can be reversed; pubertal suppression can be discontinued if the individual no longer wishes to transition. Upon discontinuation of therapy, spontaneous pubertal development has been shown to resume. The World Professional Association for Transgender Health (WPATH) Standards of Care (version 7) document also recommends the use of GnRH analogs in both male and female adolescents as a fully reversible intervention for pubertal suppression.[8] GnRH analogs can also be used in patients during late puberty to suppress the hypothalamic-pituitary-gonadal axis to allow for lower doses of cross-sex hormones.[9] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[10]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of GnRH agonists (Fensolvi, Lupron Depot-Ped, and Triptodur). Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of gender-dysphoric/gender-incongruent patients treated with Fensolvi, Lupron Depot-Ped, or Triptodur, as well as the monitoring requested for adverse events and long-term efficacy, approval requires that the product be prescribed by, or in consultation with, a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of a GnRH agonist (Fensolvi, Lupron Depot-Ped, and Triptodur) is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Central Precocious Puberty. Approve the requested GnRH agonist for 1 year.

Dosing. Approve the following doses (A, B or C):

A) Fensolvi: Approve up to one injection (45 mg) given subcutaneously once every 6 months.
B) Lupron Depot-Ped: Approve the following doses (i, ii, iii, or iv)
   i. 1-month depot, ≤ 25 kg: approve up to one 1-month depot (7.5 mg) given intramuscularly (IM) once every month; OR
   ii. 1-month depot, > 25 to 37.5 kg: approve up to one 1-month depot (11.25 mg) given IM once every month; OR
   iii. 1-month depot, > 37.5 kg: approve up to one 1-month depot (15 mg) given IM once every month; OR
   iv. 3-month depot: Approve up to one 3-month depot (11.25 mg or 30mg) given IM once every 3 months.
C) Triptodur: Approve up to one injection (22.5 mg) given IM once every 24 weeks.

Other Uses with Supportive Evidence

2. Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-to-Male or Male-to-Female). Approve the requested GnRH agonist for 1 year if prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the treatment of transgender patients.

Dosing. Approve the following doses (A, B or C):

A) Fensolvi: Approve up to one injection (45 mg) given subcutaneously once every 6 months.
B) Lupron Depot-Ped: Approve the following doses (i or ii)
   i. 1-month depot: Approve up to one 1-month depot (7.5 mg, 11.25 mg, or 15 mg) given intramuscularly (IM) once every month; OR
   ii. 3-month depot: Approve up to one 3-month depot (11.25 mg or 30 mg) given IM once every 3 months.
C) Triptodur: Approve up to one injection (22.5 mg) given IM once every 24 weeks.

There are no specific dosing recommendations for Fensolvi, Lupron Depot-Ped, or Triptodur for the management of patients with these conditions. The recommended dosages in the product labeling for central precocious puberty are listed above. Treatment decisions, including duration of therapy, are individualized with careful consideration of the risks and benefit of the selected regimen.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

GnRH agonists (Fensolvi, Lupron Depot-Ped, and Triptodur) have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Peripheral Precocious Puberty (also known as GnRH-independent precocious puberty)**.
   Children with peripheral precocious puberty do not respond to GnRH agonist therapy.[4] Treatment is directed at removing or blocking the production and/or response to the excess sex steroids, depending on the cause (e.g., surgically removing human chorionic gonadotropin-secreting tumors or using glucocorticoids to treat defects in adrenal steroidogenesis [such as classic congenital adrenal hyperplasia]).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Lupron Depot-Ped® [prescribing information]. North Chicago, IL; AbbVie, Inc.; May 2017.
2. Triptodur™ [prescribing information]. Atlanta, GA: Arbor Pharmaceuticals, LLC; October 2018.
3. Fensolvi® [prescribing information]. Fort Collins, CO: Tolmar Pharmaceuticals, Inc; May 2020
4. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009;123(4):e752-62.
5. Krishna KB, Fuqua JS, Rogol AD, et al. Use of gonadotropin-releasing hormone analogs in children: update by an international consortium. *Horm Res Paediatr*. 2019;91:357-372.
6. Eugster EA. Treatment of central precocious puberty. *J Endo Soc*. 2019;3:965-972.
7. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guidelines. *J Clin Endocrinol Metab*. 2017;102:3869-3903.
8. World Professional Association for Transgender Health (WPATH). Standards of Care for the health of transsexual, transgender, and gender non-conforming people (version 7). Available at: https://s3.amazonaws.com/amo_hub_content/Association140/files/Standards%20of%20Care%20V7%20-%202011%20WPATH%20%282%29%281%29.pdf. Accessed on September 13, 2019.
9. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrine Metab*. 2014;99:4379-4389.
10. Spack NP. Management of transgenderism. *JAMA*. 2013;309:478-484.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
NEW Policy	--	10/17/2018
Selected revision	• Changed the policy name from Gonadotropin-Releasing Hormone (GnRH) Agonists for Central Precocious Puberty to Gonadotropin-Releasing Hormone Agonists – Injectable Products (Lupron Depot-Ped and Triptodur) CC. • Addition of approval for gender-dysphoric/gender-incongruent persons; persons undergoing gender reassignment.	03/20/2019
Annual revision	• Changed the policy name from Gonadotropin-Releasing Hormone Agonists – Injectable Products (Lupron Depot-Ped and Triptodur) CC to Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products (Lupron Depot-Ped and Triptodur) CC • Central Precocious Puberty: o Lupron Depot-Ped: ▪ 1-month depot, >25 to 37.5 kg: Adjust approval to allow authorization of up to 11.25 mg (previously, dose was 11.25 mg); ▪ 1-month depot, > 37.5 kg: Adjust approval to allow authorization of up to 15 mg (previously, dose was 15 mg); ▪ 3-month depot: Adjust approval to allow for authorization of up to 30 mg (previously, dose was 11.25 or 30 mg). o Triptodur: Adjust approval to allow authorization of up one injection (22.5 mg) every 24 weeks (previously, dose was one injection every 24 weeks). • Gender-Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-to-Male or Male-to-Female): o Lupron Depot-Ped: ▪ 1-month depot: Adjust approval to allow authorization of up to 15 mg (previously, dose was 7.5 mg, 11.25 mg, or 15 mg); ▪ 3-month depot: Adjust approval to allow for authorization of up to 30 mg (previously, dose was 11.25 or 30 mg). o Triptodur: Adjust approval to allow authorization of up one injection (22.5 mg) every 24 weeks (previously, dose was 22.5 mg every 24 weeks). • Revised Precocious Precocity (also known as GnRH-independent precocious puberty or peripheral precocious puberty) to Peripheral Precocious Puberty (also known as GnRH-independent precocious puberty).	09/18/2019
Update	• Change policy name from "Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products (Lupron Depot-Ped and Triptodur) " to "Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty (Lupron Depot-Ped and Triptodur) "	11/21/2019
Selected revision	• Added Fensolvi (leuprolide acetate for injectable suspension) to the policy. • Clarified the dosing for Lupron Depot-Ped and Triptodur by adding the route of administration. • Changed policy name from Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty (Lupron Depot-Ped and Triptodur) Policy to Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty (Fensolvi, Lupron Depot-Ped and Triptodur) Policy.	05/13/2020