UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Central Precocious Puberty Utilization Management Medical Policy

- Fensolvi® (leuprolide acetate subcutaneous injection, extended-release – Tolmar)
- Lupron Depot-Ped® (leuprolide acetate depot intramuscular injection – AbbVie)
- Triptodur™ (triptorelin intramuscular injection, extended-release – Azurity)

REVIEW DATE : 10/23/2024

OVERVIEW

Fensolvi, Lupron Depot-Ped, and Triptodur are gonadotropin-releasing hormone (GnRH) agonists indicated for the treatment of **central precocious puberty** in pediatric patients.[1-3]

GnRH agonists can also be used off-label for the treatment of **gender-dysphoric/gender-incongruent persons** to suppress physical changes of puberty and gonadal function.[7,8] Pubertal hormonal suppression should typically be initiated after the adolescent first exhibits physical changes of puberty (Tanner stages G2/B2). 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. 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]

Dosing Information

Fensolvi is administered by a subcutaneous injection and both Lupron Depot-Ped and Triptodur are administered by intramuscular injection.[1-3] Fensolvi is administered once every 6 months, Lupron Depot-Ped is administered once a month, once every 3 months (12 weeks), or once every 6 months (24 weeks), and Triptodur is administered once every 24 weeks. There are no specific dosing recommendations for off-label use of Fensolvi, Lupron Depot-Ped, or Triptodur. Therefore, the FDA-approved dosing in the product labeling for approved uses has been cited for off-label uses. Treatment decisions, including duration of therapy, are individualized with careful consideration of the risks and benefit of the selected regimen.

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 convened a consensus conference to review the use of GnRH agonists in pediatric patients with central precocious puberty (2009).[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.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of the gonadotropin-releasing hormone agonists (Fensolvi, Lupron Depot-Ped, and Triptodur). Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. 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 this condition.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indication

---

1. **Central Precocious Puberty.** Approve the requested gonadotropin-releasing hormone agonist for 1 year.

   Dosing. Approve ONE of the following dosing regimens (A, B, or C):
   - **A)** Fensolvi: Approve up to one injection (45 mg) given subcutaneously once every 6 months; OR
   - **B)** Lupron Depot-Ped: Approve ONE of the following doses (i, ii, iii, iv, or v); OR
     - **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 30 mg) given IM once every 3 months (12 weeks); OR
     - **v.** 6-month depot: Approve up to one 6-month depot (45 mg) given IM once every 6 months (24 weeks); OR
   - **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 gonadotropin-releasing hormone 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 ONE of the following dosing regimen (A, B, or C):
   - **A)** Fensolvi: Approve up to one injection (45 mg) given subcutaneously once every 6 months; OR

B) Lupron Depot-Ped: Approve ONE of the following doses (i, ii, or iii); OR
- **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 (12 weeks); OR
- **iii.** 6-month depot: Approve up to one 6-month depot (45 mg) given IM once every 6 months (24 weeks); OR

C) Triptodur: Approve up to one injection (22.5 mg) given IM once every 24 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of a gonadotropin-releasing hormone agonist (Fensolvi, Lupron Depot-Ped, and Triptodur) is not recommended in the following situations:

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; April 2023.
2. Triptodur™ [prescribing information]. Woburn, MA: Azurity; November 2023.
3. Fensolvi® [prescribing information]. Fort Collins, CO: Tolmar; April 2023.
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 transgender and gender diverse people (version 8). Available at: Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (tandfonline.com). Accessed on October 14, 2024.
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	Review Date
Annual Revision	Lupron Depot-Ped dosage (for each indication): Updated frequency to also include 12 weeks on the 3-month depot. Added the following dosage regimen: 6-month depot: Approve up to one 6-month depot (45 mg) given IM once every 6 months (24 weeks).	11/08/2023
Annual Revision	No criteria changes.	10/23/2024