POLICY: Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products

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

APPROVAL DATE: 09/18/2019

OVERVIEW
Lupron Depot-Ped and Triptodur are gonadotropin-releasing hormone (GnRH) agonists indicated for the treatment of children with central precocious puberty. Both Lupron Depot-Ped and Triptodur are administered by intramuscular (IM) injection. Lupron Depot-Ped is administered once a month or every 3 months and Triptodur is administered once every 24 weeks.

Guidelines
The standard of care for central precocious puberty is GnRH agonists. 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. In addition, the various GnRH agonists are well-tolerated in children and adolescents.

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. 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. 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. In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.

POLICY STATEMENT
Prior authorization is recommended for medical benefit coverage of GnRH agonists, Lupron Depot-Ped and Triptodur. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). 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 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 is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Central Precocious Puberty.** Approve the requested GnRH agonist (Lupron Depot-Ped or Triptodur) for 1 year.

   **Dosing.** Approve the following doses (A or B):
   A) Lupron Depot-Ped: Approve the following doses (i, ii, iii, or iv)
      i. 1-month depot, ≤ 25 kg: approve 7.5 mg; OR
      ii. 1-month depot, > 25 to 37.5 kg: approve up to 11.25 mg; OR
      iii. 1-month depot, > 37.5 kg: approve up to 15 mg; OR
      iv. 3-month depot: approve up to 30 mg.
   B) Triptodur: Approve up to one injection (22.5 mg) 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 (Lupron Depot-Ped or Triptodur) 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 or B):
   A) Lupron Depot-Ped: Approve the following doses (i or ii)
      i. 1-month depot: Approve up to 15 mg; OR
      ii. 3-month depot: Approve up to 30 mg.
   B) Triptodur: Approve up to one injection (22.5 mg) every 24 weeks.

   There are no specific dosing recommendations for 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
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).**
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Utility Review Policy

Children with peripheral precocious puberty do not respond to GnRH agonist therapy.\(^3\) 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

2. Triptodur\(^™\) [prescribing information]. Atlanta, GA: Arbor Pharmaceuticals, LLC; October 2018.

HISTORY

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<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>Approval Date</th>
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<tr>
<td>NEW Policy</td>
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| 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) .  
• 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) to Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products (Lupron Depot-Ped and Triptodur)  
• 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). | 09/18/2019 |
- 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).