MEDICAL MUTUAL®

Drug Policy

Policy: **Impacted Drugs:**	**Leuprolide Long-acting** **Eligard (leuprolide acetate suspension for SC injection)** **Lupaneta Pack (leuprolide acetate for IM depot suspension; norethindrone acetate oral tablets co-packaged)** **Lupron Depot (leuprolide acetate IM for depot suspension)** **Lupron Depot-Ped (leuprolide acetate for depot suspension)** **Triptodur (triptorelin extended-release injectable suspension)** **Fensolvi (leuprolide acetate injectable suspension for SC use)**	**Annual Review Date:** **05/21/2020** **Last Revised Date:** **05/21/2020**

OVERVIEW

Leuprolide is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone or leutinizing hormone-releasing hormone (GnRH or LHRH), which possesses greater potency compared with the natural hormone (generally considered a GnRH agonist). It acts as a potent inhibitor of gonadotropin secretion when administered continuously in therapeutic doses. Following initial stimulation of gonadotropins, chronic administration of leuprolide leads to suppression of ovarian and testicular steroidogenesis. These effects are reversible after drug discontinuation.

This policy includes only the long-acting leuprolide acetate suspension products that are administered intramuscularly (IM) [Lupron Depot, Lupaneta Pack, and Lupron Depot-Ped], subcutaneously (SC) [Eligard] and the triptorelin extextended-release IM injectable [Triptodur]. Lupaneta Pack contains a combination pack of leuprolide acetate depot suspension administered IM and norethindrone 5 mg tablets. This policy does not cover the short-acting leuprolide products (Lupron® and Lupron® for pediatric use). The indication(s) and dosing for the long-acting leuprolide and triptorelin products are in Table 1.

Table 1. Indications, Dosage and Administration for Lupron-Depot, Lupaneta Pack, Eligard, Lupron Depot-Ped and Triptodur.

Products	Dosing and Administration	Indication(s)
Lupron Depot® (leuprolide acetate IM for depot suspension)	7.5 mg IM every 1 month	Prostate cancer: palliative treatment of advanced prostate cancer
	22.5 mg IM every 3 months	
	30 mg IM every 4 months	
	45 mg IM every 6 months	

Eligard® (leuprolide acetate suspension for SC injection)	7.5 mg SC every 1 month 22.5 mg SC every 3 months 30 mg SC every 4 months 45 mg SC every 6 months	Prostate cancer: palliative treatment of advanced prostate cancer
Lupron Depot® (leuprolide acetate IM for depot suspension)	3.75 mg IM every 1 month 11.25 mg IM every 3 months	Endometriosis: initial management and for recurrence of symptoms (including pain relief and reduction of endometriotic lesions). Limitation of Use: Duration of initial treatment or re-treatment should be limited to 6 months. Uterine leiomyomata (Fibroids): preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata; taken with iron therapy. Recommended duration of therapy is up to 3 months.
Lupaneta Pack® (leuprolide acetate for IM depot suspension; norethindrone acetate oral tablets co-packaged)	11.25 mg IM for 3 months Norethindrone acetate 5 mg tablets	Endometriosis: initial management and for recurrence of painful symptoms of endometriosis. Limitation of Use: Duration of use is limited due to adverse impact on bone mineral density. The initial treatment course is limited to 6 months. A single retreatment course of not more than 6 months may be administered if symptoms recur. Use of Lupaneta Pack for longer than total of 12 months is not recommended.
Lupron Depot-Ped® (leuprolide acetate for depot suspension)	Starting dose of 7.5 mg, 11.25 mg, or 15 mg IM for 1 month administration; starting dose based on child's weight 11.25 mg IM for 3 months 30 mg IM for 3 months	Central precocious puberty (CPP)
Triptodur™ (triptorelin extended-release injectable suspension)	22.5 mg IM for 24 weeks (6 months)	Central precocious puberty
Fensolvi (leuprolide acetate injectable suspension)	45 mg SC every 6 months	Central precocious puberty

IM – Intramuscular; SC – Subcutaneous.

In addition to the approved indications, GnRH agonists such as leuprolide long-acting, have been used for other conditions and various guidelines (e.g., guidelines from the National Comprehensive Cancer Center [NCCN]) discuss its use.

POLICY STATEMENT

This policy involves the use of leuprolide long-acting products (e.g., Lupron-Depot, Eligard, Lupron Depot-Ped, and Lupaneta Pack) and Triptodur and Fensolvi. Prior authorization is recommended for pharmacy benefit coverage of leuprolide long-acting products (e.g., Lupron-Depot, Eligard, Lupron Depot-Ped, and Lupaneta Pack) and Triptodur and Fensolvi. Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval** for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with leuprolide long-acting products (e.g., Lupron-Depot, Eligard, Lupron Depot-Ped, and Lupaneta Pack) and Triptodur and Fensolvi as well as the monitoring required for adverse events and long-term efficacy, initial approval requires leuprolide long-acting products

(e.g., Lupron-Depot, Eligard, Lupron Depot-Ped, and Lupaneta Pack) and Triptodur and Fensolvi be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of leuprolide long-acting products (e.g., Lupron-Depot, Eligard, Lupron Depot-Ped, and Lupaneta Pack) and Triptodur and Fensolvi is recommended in those who meet the following criteria:

1. **Prostate Cancer (Lupron Depot, Eligard)**
   Criteria. *Approve if prescribed by or in consultation with a hematologist or oncologist.*

2. **Endometriosis (Lupron Depot, Lupaneta Pack)**
   Criteria. *Approve if patient meets the following criteria (A or B):*

   A. Initial management of symptoms; OR
   B. Management of recurrence of symptoms after initial therapy.

   Note: The recommended duration of continuous therapy (initial and recurrence) is limited to a total of 12 months.

3. **Uterine Leiomyomata (fibroids) [Lupron Depot]**
   Criteria. *Approve.*

4. **Central Precocious Puberty (CPP) [Lupron Depot-Ped, Triptodur, Fensolvi]**
   Criteria. *Approve.*

Initial Approval/ Extended Approval.

A) *Initial Approval:*	180 days for endometriosis, uterine leiomyomata, and abnormal uterine bleeding 365 days for all other indications listed as an approval in this document
B) *Extended Approval:*	180 days for endometriosis (maximum therapy of 12 months) and uterine leiomyomata 365 days for all other indications listed as an approval in this document Abnormal uterine bleeding not recommended for extended approval

OTHER USES WITH SUPPORTIVE EVIDENCE

5. **Gender Reassignment (Female-To-Male [FTM] or Male-To-Female [MTF]) [Lupron Depot, Eligard]**
   Criteria. *Approve if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.*

6. **Ovarian Cancer (Lupron Depot)**
   Criteria. *Approve if prescribed by or in consultation with a hematologist or oncologist.*

7. **Breast Cancer (Lupron Depot)**
   Criteria. *Approve if prescribed by or in consultation with a hematologist or oncologist.*

8. **Preserve Ovarian Function/Fertility in Patients undergoing Chemotherapy (Lupron Depot)**
   Criteria. *Approve if prescribed by or in consultation with a hematologist or oncologist.*

9. **Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT) [Lupron Depot]**
   Criteria. *Approve if prescribed by or in consultation with a hematologist or oncologist.*

10. **Abnormal Uterine Bleeding (Lupron Depot)**
    Criteria. *Approve for up to 6 months of therapy.*

Initial Approval/ Extended Approval.

A) *Initial Approval:* 180 days for endometriosis, uterine leiomyomata, and abnormal uterine bleeding
365 days for all other indications listed as an approval in this document

B) *Extended Approval:* 180 days for endometriosis (maximum therapy of 12 months) and uterine leiomyomata
365 days for all other indications listed as an approval in this document
Abnormal uterine bleeding not recommended for extended approval

CONDITIONS NOT RECOMMENDED FOR APPROVAL

leuprolide long-acting products (e.g., Lupron-Depot, Eligard, Lupron Depot-Ped, and Lupaneta Pack) and Triptodur and Fensolvi 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. **Hirsutism.** Patients with hirsutism, either idiopathic or due to polycystic ovarian syndrome (PCOS), have received leuprolide long-acting, usually 3.75 mg or 7.5 mg IM monthly. Sometimes conjunctive therapy with estrogen replacement or OCs was used. Patients receiving leuprolide long-acting for up to 6 months experienced positive benefits such as decreases in the Ferriman-Gallwey scores, in hair growth rate and/or in the percentage hair growth rate. The Endocrine Society guidelines (2008) on the treatment of hirsutism in premenopausal women suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia, such as ovarian hyperthecosis, who have had a suboptimal response to OCs and antiandrogens.

2. **Menstrual Migraine.** Therapies such as NSAIDs, triptans, and propranolol have been used for the treatment or prophylaxis of menstrual migraines. A nonrandomized, 10-month prospective trial assessed the effects of leuprolide long-acting 3.75 mg IM monthly in five women with severe menstrual migraines who were not responsive to

previous treatment. Treatment led to a reduction in mean cumulative monthly headache score. Also, patient global assessment of therapy was positive and a decrease in the use of analgesic medication for headache was noted. A review article notes that GnRH analogues are effective in eliminating menstrual migraines, but their use is limited due to the significant adverse effects of estrogen deficiency, including severe vasomotor symptoms, sleep disruption, and a marked reduction in bone density.

3. **Polycystic Ovarian Syndrome (PCOS).** Leuprolide long-acting has been used in women with PCOS. Patients with PCOS receiving leuprolide long acting 3.75 mg IM every 4 weeks plus an OC for six months experienced a restoration of normal ovulatory cycles and a greater reduction in ovarian volume compared with women just receiving an OC. PCOS guidelines from the Endocrine Society (2013) and review articles do not recommend this as a treatment modality.

4. **Premenstrual Syndrome (PMS).** For PMS, low-dose selective serotonin reuptake inhibitors (SSRIs) [e.g., fluoxetine, sertraline] are recommended as first-line agents for severe PMS. Other first-line options for PMS include exercise, vitamin B6, combined contraceptive pills, and cognitive behavioral therapy. Use of GnRH analogues results in profound cycle suppression and elimination of PMS symptoms, but these agents should not be used routinely. It is recommended sometimes to aid in the diagnosis of PMS. Otherwise it is recommended only as a third-line treatment or for the most refractory patients.

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

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

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