MEDICAL MUTUAL®

Drug Policy

Policy: **Impacted Drugs:**	**Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products** **Lupron Depot (leuprolide acetate IM for depot suspension)**	**Annual Review Date:** **01/16/2025** **Last Revised Date:** **01/16/2025**

OVERVIEW

Lupron Depot (3.75 mg intramuscular (IM) injection every month, 11.25 mg IM injection every 3 months) is indicated for the following conditions:[3,4]

- Preoperative hematologic improvement of women with **anemia caused by uterine leiomyomata** (fibroids) for whom 3 months of hormonal suppression is deemed necessary. (Lupron Depot in combination with iron therapy).
- **Endometriosis**, including pain relief and reduction of endometriotic lesions (Lupron Depot monotherapy).
- **Endometriosis**, initial management of the painful symptoms of endometriosis and management of recurrence of symptoms (Lupron Depot in combination with norethindrone acetate 5 mg daily).

Lupron Depot (7.5 mg IM injection every month, 22.5 mg IM injection every 3 months, 30 mg IM injection every 4 months, and 45 mg IM injection every 6 months) is indicated for the **palliative treatment of advanced prostate cancer**.[5]

Duration of Treatment:

- Lupron Depot 3.75 mg and 11.25 mg:[3,4]
  - Endometriosis: For the first 6 months of treatment, Lupron Depot may be used as monotherapy or in combination with norethindrone acetate. If retreatment is needed, Lupron Depot must be used in combination with norethindrone acetate (for 6 months). Total duration of treatment is limited to 12 months.
  - Uterine leiomyomata (fibroids): Recommended duration of treatment is up to 3 months.
- Lupron Depot 7.5 mg, 22.5 mg, 30 mg, and 45 mg: Labeling does not specify a treatment duration.

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 Lupron-Depot. Prior authorization is recommended for pharmacy benefit coverage of Lupron-Depot. 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 Lupron-Depot as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Lupron-Depot be prescribed by or

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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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Lupron-Depot is recommended in those who meet the following criteria:

1. **Prostate Cancer**
   Criteria. *Approve Lupron Depot 7.5 mg, 22.5 mg, 30 mg, or 45 mg for 1 year if prescribed by or in consultation with an oncologist. AND the patient has tried Eligard.*

2. **Endometriosis**
   Criteria. *Approve Lupron Depot (3.75 mg or 11.25 mg) for 1 year if the patient has tried one of the following, unless contraindicated (A, B, or C):*

   A) A contraceptive (e.g., combination oral contraceptives, levonorgestrel-releasing intrauterine systems [e.g., Mirena®, Liletta®]), OR
   B) An oral progesterone (e.g., norethindrone tablets), OR
   C) A depo-medroxyprogesterone injection, unless contraindicated.
   NOTE: An exception to the requirement for a trial of the above therapies can be made if the patient has previously used a gonadotropin-releasing hormone [GnRH] agonist (e.g., Lupron-Depot) or antagonist (e.g., Orilissa).

3. **Uterine Leiomyomata (fibroids)**
   Criteria. *Approve Lupron Depot 3.75 mg or 11.25 mg for 3 months.*

   NOTE: Response to therapy is required for continuation of therapy.

Initial Approval/ Extended Approval.
See specific approval duration listed under each approved use.

OTHER USES WITH SUPPORTIVE EVIDENCE

4. **Gender Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male [FTM] or Male-To-Female [MTF])**
   Criteria. *Approve Lupron Depot for 1 year if prescribed by or in consultation with an endocrinologist or a physician who specializes in the treatment of transgender patients.*

   NOTE: Response to therapy is required for continuation of therapy.

5. **Ovarian Cancer, including Fallopian Tube Cancer and Primary Peritoneal Cancer (Lupron Depot)**
   Criteria. *Approve Lupron Depot 3.75 mg, 7.5 mg, 11.25 mg, or 22.5 mg for 1 year if prescribed by or in consultation with an oncologist.*

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6. **Breast Cancer**
Criteria. *Approve Lupron Depot 3.75 mg, 7.5 mg, 11.25 mg, or 22.5 mg for 1 year if prescribed by or in consultation with a hematologist or oncologist.*

7. **Preservation of Ovarian Function/Fertility in Patients undergoing Chemotherapy**
Criteria. *Approve Lupron Depot 3.75 mg or 11.25 mg for 1 year if prescribed by or in consultation with an oncologist.*

8. **Prophylaxis or Treatment of Uterine Bleeding or Menstrual Suppression in Patients with Hematologic Malignancy, or, Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT)**
Criteria. *Approve Lupron Depot 3.75 mg or 11.25 mg for 1 year if prescribed by or in consultation with a hematologist or oncologist.*

9. **Abnormal Uterine Bleeding**
Criteria. *Approve Lupron Depot 3.75 mg or 11.25 mg for up to 3 months of therapy.*

10. **Premenstrual Disorders, including Premenstrual Syndrome and Premenstrual Dysphoric Disorder.**
Criteria. *Approve the 3.75 mg or 11.25 mg for 1 year if the patients meets ALL of the following criteria (A, B, and C):*

A) Patient is ≥ 18 years of age; AND
B) According to the prescriber, the patient has severe, refractory premenstrual symptoms; AND
C) Patient has tried one of the following therapies (i or ii):
  i. A selective serotonin reuptake inhibitor (SSRI); OR
  Note: Examples of SSRI include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.
  ii. A combined oral contraceptive.

11. **Uterine Cancer**
Criteria. *Approve Lupron Depot 7.5 mg, 22.5 mg, 30 mg, or 45 mg for 1 year if prescribed by or in consultation with an oncologist.*

12. **Head and Neck Cancer – Salivary Gland Tumors**
Criteria. *Approve Lupron Depot 3.75 mg, 7.5 mg, 11.25mg, or 22.5 mg for 1 year if the patient meets the following criteria (A, B, and C):*

A) Patient has recurrent, unresectable, or metastatic disease; AND
B) Patient has androgen receptor (AR)-positive disease; AND

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C) The medication is prescribed by or in consultation with an oncologist.

13. **Patients with another indication that is not listed but is cited in the National Comprehensive Cancer Network (NCCN) guidelines as a category 1, 2A, or 2B recommendation**
Criteria. *Prescriber will provide specific diagnosis for documentation. Approve.*

Initial Approval/ Extended Approval.
See specific approval duration listed under each approved use.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lupron-Depot 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. **Menstrual Migraine.** A review article notes that GnRH analogs 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.[22,23]

2. **Polycystic Ovarian Syndrome (PCOS).** Review articles do not recommend GnRH agonists as a treatment modality for this diagnosis.[24,25] Additionally, the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome (2018) only mentions GnRH products as they relate to infertility and assisted reproductive technology procedures.[26]

3. 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.

REFERENCES

1. Lupaneta Pack® 3.75 mg [prescribing information]. North Chicago, IL: AbbVie Inc.; June 2015.
2. Lupaneta Pack® 11.25 mg [prescribing information). North Chicago, IL: AbbVie Inc.; June 2015.
3. Lupron Depot® – 3.75 mg [prescribing information]. North Chicago, IL: AbbVie Inc.; February 2021.

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4. Lupron Depot® –11.25 mg [prescribing information]. North Chicago, IL: AbbVie Inc.; March 2020.
5. Lupron Depot® – 1 Month 7.5 mg, 3 Month 22.5 mg, 4 Month 30 mg, 6 Month 45 mg [prescribing information]. North Chicago, IL: AbbVie Inc.; March 2019.
6. ACOG practice bulletin No. 128: Diagnosis of abnormal uterine bleeding in reproductive-aged women. *Obstet Gynecol*. 2012 (reaffirmed 2016);120(1):197-206.
7. The American College of Obstetricians and Gynecologists (ACOG) Frequently Asked Questions (FAQ) – Gynecologic Problems, #074, December 2018. Available at: https://www.acog.org/Patients/FAQs/Uterine-Fibroids?IsMobileSet=false. Accessed on January 15, 2021.
8. Journal of Obstetrics and Gynecology Canada. Abnormal uterine bleeding in pre-menopausal women. *J Obstet Gynaecol Can*. 2018;40(5):e391-e415.
9. Bradley LD, Gueye NA. The medical management of abnormal uterine bleeding in reproductive-aged women. Gynecology Expert Reviews. *Am J Obstet Gynecol*. 2016;214:31-44.
10. Menstrual suppression in special circumstances. Society of Obstetricians and Gynaecologists of Canada (SOGC) clinical practice guideline. *J Obstet Gynaecol Can*. 2019;41(2):e7-e17.
11. The American College of Obstetricians and Gynecologists. Options for prevention and management of heavy menstrual bleeding in adolescent patients undergoing cancer treatment. Committee Opinion. Number 606. August 2014 (reaffirmed 2018).
12. Management of Endometriosis. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 114. 2010 (reaffirmed 2018). *Obstet & Gynecol*. 2010;116(1):223-236.
13. 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.
14. 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 January 15, 2021.
15. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrine Metab*. 2014;99:4379-4389.
16. Spack NP. Management of transgenderism. *JAMA*. 2013;309:478-484.
17. The NCCN Adolescent and Young Adult Oncology Clinical Practice Guidelines in Oncology (Version 1.2021 – September 10, 2020). ©2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 15, 2021.
18. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 6.2020 – September 8, 2020). ©2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 15, 2021.
19. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (Version 1.2021 – November 9, 2020) © 2020 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed on January 15, 2021.
20. The NCCN Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – January 12,2021). ©2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed January 15, 2021.
21. The Endocrine Society's clinical guidelines. Evaluation and treatment of hirsutism in premenopausal women: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2018;103(4):1233-1257.
22. Calhoun AH. Menstrual migraine: update on pathophysiology and approach to therapy and management. *Curr Treat Options Neurol.* 2012;14:1-14.
23. Del C. Nierenburg H, Ailani J, Malloy M, et al. Systematic Review of Preventive and Acute Treatment of Menstrual Migraine. *Headache*. 2015;55:1052-1071.
24. Management of premenstrual syndrome. Royal College of Obstetricians and Gynaecologists. Green-top Guideline No 48. November 2016. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/gt48managementpremensturalsyndrome.pdf. Accessed on January 15, 2021.
25. Diagnosis and treatment of polycystic ovarian syndrome: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2013;98:4565-4592.
26. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. *Int J Womens Health*. 2011;3:25-35.
27. Benjamins LJ, Barratt MS. Evaluation and management of polycystic ovary syndrome. *J Pediatr Health Care.* 2009;23(5):337-343.

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