VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Utilization Management Medical Policy
- Lupron Depot® (leuprolide acetate suspension for intramuscular injection – AbbVie)
- Lupaneta Pack® (leuprolide acetate for depo suspension; norethindrone acetate tablets co-packaged for intramuscular use and oral use, respectively – AbbVie) [discontinued]

REVIEW DATE: 02/22/2023

OVERVIEW

Lupaneta Pack is indicated for the initial management of the painful symptoms of **endometriosis** and for management of recurrence of symptoms.[1,2] Lupaneta Pack was discontinued in 2021.

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 and 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:
- Lupaneta Pack: Initial treatment course is limited to 6 months; a single retreatment course of up to 6 months is allowed. Total duration of treatment is limited to 12 months.[1,2]
- 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.

Guidelines

Abnormal Uterine Bleeding/Uterine Leiomyomata (Fibroids)

The American College of Obstetricians and Gynecologists (ACOG) [2021] practice bulletin regarding the management of symptomatic uterine leiomyomas discuss that gonadotropin-releasing hormone (GnRH) agonists (either with or without add-back hormonal therapy) are recommended for bleeding associated with fibroids, uterine enlargement associated with fibroids, and as a bridge to other treatment strategies (such as surgical management, menopause, or other medical therapies).[6] Add-back hormonal therapy (such as low-dose estrogen or progestin, or both) may help mitigate the hypoestrogenic effects of GnRH agonists, such

as decreased bone mineral density. The guidelines state that the type, dose, and route of delivery of add-back therapy depend on patient preference and the severity of symptoms.

GnRH agonists can also be used for acute abnormal uterine bleeding with an aromatase inhibitor or antagonist to prevent initial estrogen flare and for the treatment of heavy menstrual bleeding caused by leiomyoma-associated hormonal imbalance.[7] A clinical practice guideline from the Society of Obstetricians and Gynaecologists of Canada notes that leuprolide acetate or combined hormonal contraception should be considered highly effective in preventing abnormal uterine bleeding when initiated prior to cancer treatment in premenopausal women at risk of thrombocytopenia.[8] The ACOG committee opinion on options for prevention and management of menstrual bleeding in adolescent patients undergoing cancer treatment states that GnRH agonists are an option for menstrual suppression.[9]

Endometriosis

According to the ACOG practice bulletin on the management of endometriosis (2010, reaffirmed 2018), empiric therapy with a 3-month course of a GnRH agonist is appropriate after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and nonsteroidal anti-inflammatory drugs (NSAIDs).[10] The ACOG committee opinion on dysmenorrhea and endometriosis in the adolescent (2018) notes that patients with endometriosis who have pain after conservative surgical therapy and suppressive hormonal therapy may benefit from at least 6 months of GnRH agonist therapy with add-back medicine.[11]

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.[12] 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 8) document also recommends the use of GnRH analogs to suppress endogenous sex hormones in transgender and gender diverse people for whom pubery blocking is indicated.[13] GnRH 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.[14] In addition to use in adolescents, GnRH analog therapy is also used in adults, particularly male-to-female patients.[15]

In addition to the approved indications, GnRH agonists such as long-acting leuprolide, have been used for other conditions. The National Comprehensive Cancer Network (NCCN) guidelines for Adolescent and Young Adult Oncology (version 3.2023 – January 9, 2023) note GnRH agonists may be used in (oncology) protocols that are predicted to cause prolonged thrombocytopenia and present a risk for menorrhagia.[16] There are some limited data on GnRH agonists to preserve ovarian function during chemotherapy and some have shown that GnRH agonists may be beneficial for fertility preservation, although the guidelines note further investigation is needed. The NCCN guidelines for Breast Cancer (version 2.2023 – February 7, 2023) note that luteinizing hormone-releasing hormone agonists, such as leuprolide, can be used for ovarian suppression.[17] The guidelines further note that randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with breast tumors (regardless of hormone receptor status) may preserve ovarian function and diminish the likelihood

of chemotherapy-induced amenorrhea. The NCCN guidelines for Head and Neck Cancer (version 1.2023 – December 20, 2022) note that a significant number of advanced salivary gland tumors with distant metastases are androgen receptor-positive (AR+), and therefor, the panel recommends patients with tumors that are AR+ receive androgen receptor therapy (i.e., leuprolide, bicalutamide).[18] The NCCN guidelines for Ovarian Cancer, including Fallopian Tube Cancer and Primary Peritoneal Cancer (version 1.2023 – December 22, 2022) recommend leuprolide as a hormonal therapy option in various settings (e.g., primary therapy, adjuvant therapy, recurrence).[19]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Lupron Depot and Lupaneta Pack. 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). **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. All approvals are provided for the durations 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 patients treated with Lupaneta Pack and Lupron-Depot as well as the monitoring required for adverse events and long-term efficacy, approval for some of the conditions requires Lupaneta Pack or Lupron-Depot to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lupron Depot or Lupaneta Pack are recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Endometriosis.** Approve Lupron Depot or Lupaneta Pack 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.

   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).

   Dosing. Approve one of the following dosing regimens (A or B):
   - **A)** For Lupaneta Pack: Approve one of the following dosage regimens (i or ii):
     - **i.** 3.75 mg IM once every month with norethindrone 5 mg orally once daily; OR
     - **ii.** 11.25 mg IM once every 3 months with norethindrone 5 mg orally once daily; OR
   - **B)** For Lupron Depot: Approve one of the following dosage regimens (i or ii):
     - **i.** 3.75 mg IM once every month; OR
     - **ii.** 11.25 mg IM once every 3 months.

2. **Prostate Cancer.** Approve Lupron Depot for 1 year if prescribed by or in consultation with, an oncologist.

   Dosing. Approve one of the following dosing regimens (A, B, C, or D):
   A) 45 mg IM once every 6 months; OR
   B) 30 mg IM once every 4 months; OR
   C) 22.5 mg IM once every 3 months; OR
   D) 7.5 mg IM once every month.

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3. **Uterine Leiomyomata (fibroids).** Approve Lupron Depot for 3 months.

   Dosing. Approve one of the following dosing regimens (A or B):
   A) 3.75 mg IM once every month; OR
   B) 11.25 mg IM once every 3 months.

Other Uses with Supportive Evidence

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4. **Abnormal Uterine Bleeding.** Approve Lupron Depot for 6 months.

   Dosing. Approve one of the following dosage regimens (A or B):
   A) 3.75 IM once every month; OR
   B) 11.25 IM once every 3 months.

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5. **Breast Cancer.** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

   Dosing. Approve one of the following dosage regimens (A or B):
   A) 3.75 mg IM once every month; OR
   B) 11.25 mg IM once every 3 months.

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6. **Gender Dysphoric/Gender-Incongruent Persons; Persons Undergoing Gender Reassignment (Female-To-Male [FTM] or Male-to-Female [MTF]).** 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.

   Dosing. Approve one of the following dosage regimens (A, B, C, or D):
   A) 3.75 or 7.5 mg IM once every month; OR
   B) 11.25 or 22.5 mg IM once every 3 months; OR
   C) 30 mg IM once every 4 months; OR
   D) 45 mg IM once every 6 months.

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7. **Head and Neck Cancer – Salivary Gland Tumors.** Approve Lupron Depot 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-positive disease; AND

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

Dosing. Approve one of the following dosage regimens (A or B):
A) 3.75 mg or 7.5 mg IM every month; OR
B) 11.25 mg or 22.5 mg IM once every 3 months.

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8. **Ovarian Cancer.** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

   Dosing. Approve one of the following dosage regimens (A or B):
   A) 3.75 mg or 7.5 mg IM once every month; OR
   B) 11.25 mg or 22.5 mg IM once every 3 months

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

   Dosing. Approve one of the following dosage regimens (A or B):
   A) 3.75 mg IM once every month; OR
   B) 11.25 mg IM once every 3 months.

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10. **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).** Approve Lupron Depot for 1 year if prescribed by or in consultation with an oncologist.

    Dosing. Approve one of the following dosage regimens (A or B):
    A) 3.75 mg IM once every month; OR
    B) 11.25 mg IM once every 3 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of Lupron Depot and Lupaneta Pack is not recommended in the following situations:

1. **Hirsutism**. The Endocrine Society guidelines on the treatment of hirsutism in premenopausal women (2008) suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia, such as ovarian hyperthecosis, who have had a suboptimal response to oral contraceptives and antiandrogens.[20]

2. **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.[21,22]

3. **Premenstrual Syndrome (PMS)**. On occasion, GnRH analogs are recommended as an aid in the diagnosis of PMS.[23] Use of GnRH analogs results in profound cycle suppression and elimination of PMS symptoms, but these agents should not be used routinely. GnRH analogs are recommended only as a third-line treatment or for the most refractory patients.

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

5. 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. Lupaneta Pack® 3.75 mg [prescribing information]. North Chicago, IL: AbbVie; December 2022.
2. Lupaneta Pack® 11.25 mg [prescribing information]. North Chicago, IL: AbbVie; December 2022.
3. Lupron Depot – 3.75 mg [prescribing information]. North Chicago, IL: AbbVie; January 2023.
4. Lupron Depot –11.25 mg [prescribing information]. North Chicago, IL: AbbVie; 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; April 2022.
6. The American College of Obstetricians and Gynecologists (ACOG) practice bulletin No. 228: Management of Symptomatic Uterine Leiomyomas. June 2021. Available at: https://www.acog.org/. Accessed on February 9, 2023.
7. 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.
8. 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.
9. Options for prevention and management of menstrual bleeding in adolescent patients undergoing cancer treatment. ACOG Committee Opinion. No. 817. January 2021. Available at: https://www.acog.org/. Accessed on February 9, 2023.
10. Management of Endometriosis. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 114. 2010 (reaffirmed 2018). *Obstet & Gynecol*. 2010;116(1):223-236.
11. Dysmenorrhea and endometriosis in the adolescent. ACOG Committee Opinion. No. 760. December 2018. Available at: https://www.acog.org/. Accessed on February 9, 2023.
12. 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.
13. World Professional Association for Transgender Health (WPATH). Standards of care for the health of transgender and gender diverse people (version 8). Available at: https://www.wpath.org/publications/soc. Accessed on February 10, 2023.
14. Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrine Metab*. 2014;99:4379-4389.
15. Spack NP. Management of transgenderism. *JAMA*. 2013;309:478-484.
16. The NCCN Adolescent and Young Adult Oncology Clinical Practice Guidelines in Oncology (version 3.2023 – January 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 13, 2023.
17. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 13, 2023.
18. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 20 2022). © 2023 National Comprehensive Cancer Network. Available at http://www.nccn.org. Accessed on February 13, 2023.
19. The NCCN Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 13, 2023.
20. 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.
21. Calhoun AH. Menstrual migraine: update on pathophysiology and approach to therapy and management. *Curr Treat Options Neurol*. 2012;14:1-14.
22. 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.
23. 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 February 13, 2023.
24. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. *Int J Womens Health*. 2011;3:25-35.
25. Benjamins LJ, Barratt MS. Evaluation and management of polycystic ovary syndrome. *J Pediatr Health Care*. 2009;23(5):337-343.
26. International evidence-based guideline for the assessment and management of polycystic ovary syndrome. Monash University. Mebourne Australia 2018. Available at:

https://www.monash.edu/__data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf. Accessed on February 13, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected revision	**Uterine leiomyomata (fibroids)**: Lupron Depot 3.75 mg and 11.25 mg – Approval duration is changed from 6 months to 3 months due to revised labeling.	3/03/2021
Annual revision	**Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy, or Undergoing Cancer Treatment, or Prior to Bone Marrow/Stem Cell Transplantation (BMT/SCT):** added or Menstrual Suppression. Removed the wording "up to" in all dosage criteria. **Ovarian Cancer:** added 7.5 mg once monthly and 22.5 mg every 3 months in dosage criteria.	2/16/2022
Annual revision	**Head and Neck Cancer – Salivary Gland Tumors**: "Patient has advanced salivary gland tumors with distant metastases" was reworded to "Patient has recurrent, unresectable, or metastatic disease." Also, coverage of strengths 3.75 mg and 11.25 mg were added for this diagnosis.	2/22/2023