Medicare Advantage Medical Utilization Review 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 [IM] use and oral use, respectively – AbbVie [discontinued])
Date:	03/8/2023
Applicable Lines of Business:	Medicare Advantage - Medical
Applicable States:	NGS, J6: Wisconsin, Minnesota, Illinois NGS, JK: New York, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont

*Note: Immediate-release leuprolide acetate 1 mg is a **usually** self-administered form of leuprolide acetate and is not covered under Medicare Part A/B.*[27]

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 indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. All approvals are provided for the durations noted below.

This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage.

Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Lupron Depot is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Prostate Cancer.

Criteria. Approve for 1 year.

Dosing. Approve the following dosing regimens:

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.

2. Endometriosis.

Criteria. Approve 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 the following dosing regimens:
A. 3.75 mg IM once every month; OR
B. 11.25 mg IM once every 3 months.

3. Uterine Leiomyomata (fibroids).

Criteria. Approve for 3 months.

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

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 for 1 year.

Dosing. Approve the following dosage regimens:
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.

5. Ovarian Cancer.

Criteria. Approve for 1 year.

Dosing. Approve the following dosage regimens:
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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6. Breast Cancer.

Criteria. Approve for 1 year.

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

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7. Preservation of Ovarian Function/Fertility in Patients undergoing Chemotherapy.

Criteria. Approve for 1 year.

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

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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 for 1 year.

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

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9. Abnormal Uterine Bleeding.

Criteria. Approve for 6 months.

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

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10. Head and Neck Cancer – Salivary Gland Tumors.

Criteria. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient has recurrent, unresectable, or metastatic disease; AND
B) The patient has androgen receptor positive disease.

Dosing. Approve the following dosage regimens:
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.

11. Chronic Pelvic Pain Caused by Suspected Endometriosis.[28]

Criteria.[28] Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following conditions (i, ii, and iii):
- **i.** The patient is experiencing chronic pelvic pain, defined as 6 months or more; AND
- **ii.** The patient has had an appropriate pretreatment evaluation to exclude other causes; AND
- **iii.** The patient has failed initial treatment with at least one oral contraceptive and at least one non-steroidal anti-inflammatory drugs (NSAID); OR

B) Continuation of Therapy. Approve for 9 months if the patient has experienced significant symptomatic improvement.

Dosing. Approve the following dosage regimens:
A. 3.75 IM every month; OR
B. 11.25 IM every 3 months.

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

II. Coverage of Lupaneta Pack is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Endometriosis.

Criteria. Approve 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 dosage regimens (i or ii):
A) 3.75 mg IM once every month with norethindrone 5 mg orally once daily; OR
B) 11.25 mg IM once every 3 months with norethindrone 5 mg orally once daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lupron Depot and Lupaneta Pack is not recommended in the following situations:

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

REFERENCES

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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.
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HISTORY

Type of Revision	Summary of Changes	Date
Policy created	New policy created containing all LHRH products, see archived policy	7/11/18
Policy revision	Reviewed and revised original policy created 07/11/2018 in accordance with Local Coverage Article A52453 and Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products Utilization Review Policy	08/28/2019
Policy revision	Completion of 2019 monthly monitoring process in accordance with Local Coverage Determination L33394, Local Coverage Article A52453, and Gonadotropin-Releasing Hormone Agonists – Injectable Long-Acting Products (Lupron Depot and Lupaneta Pack) Utilization Review Policy.	11/25/2019
Policy revision	Non-clinical update to policy to add the statement "This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage."	1/30/2020
Policy revision	*Added the following to the Policy Statement "Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles." *Updated references *Updated dosing on all indications *Added the following criteria for Head and Neck Cancer "The patient has recurrent disease with distant metastases; AND The patient has androgen receptor (AR)-positive disease." *Removed requirement that patient be peri- or post-menopausal from breast cancer indication.	08/07/2020
Policy revision	Head and Neck Cancer – Salivary Gland Tumors: revised "Patient has recurrent disease with distant metastases" to "Patient has advanced salivary gland tumors with distant metastases".	01/28/2021

Policy revision	Lupron Depot 3.75 mg and 11.25 mg – Uterine leiomyomata (fibroids): Approval duration is changed from 6 months to 3 months due to revised labeling.	03/08/2021
Policy 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.	03/02/2022
Policy 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. **Endometriosis**: Added "unless contraindicated" exception to trial requirement for this indication	03/08/2023