VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

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

- Lupron Depot® (leuprolide acetate suspension for intramuscular [IM] injection – Abbott Laboratories)
- Lupaneta Pack® (leuprolide acetate for depot suspension; norethindrone acetate tablets co-packaged for intramuscular [IM] use and oral use, respectively – AbbVie Inc.)

TAC APPROVAL DATE: 1/30/2019; selected revision 4/10/2019

OVERVIEW

This policy includes only the long-acting leuprolide acetate suspension products: Lupron Depot and Lupaneta Pack. Lupaneta Pack contains a combination pack of leuprolide acetate depot suspension administered IM and norethindrone 5 mg tablets.[1,2] This policy does not cover the short-acting leuprolide products or other long-acting leuprolide products. The indication(s) and dosing for selected medications are in Table 1.

Table 1. Indications, Dosage and Administration for Lupron-Depot, Lupaneta.[1-5]

Products	Dosing and Administration	Indication(s)
Lupron Depot® (leuprolide acetate IM for depot suspension)	7.5 mg IM every 1 month 22.5 mg IM every 3 months 30 mg IM every 4 months 45 mg IM 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)	3.75 mg IM every 1 month with norethindrone acetate 5 mg tablets 11.25 mg IM for 3 months with 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.

IM – Intramuscular; SC – Subcutaneous.

Guidelines

Endometrosis

According to the American College of Obstetricians and Gynecologists (ACOG) practice bulletin on the management of the endometriosis (2010, reaffirmed 2018), after an appropriate pretreatment evaluation (to exclude other causes of chronic pelvic pain) and failure of initial treatment with oral contraceptives and NSAIDs, empiric therapy with a 3-month course of a GnRH agonist is appropriate.[6]

Abnormal Uterine Bleeding

The ACOG practice bulletin regarding the diagnosis of abnormal uterine bleeding in reproductive-aged women discusses the nomenclature of abnormal uterine bleeding (AUB). It can be classified by the acronym PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) and can be further classified by etiology.[7] The term AUB can also be paired with descriptive terms that describe the associated bleeding pattern such as heavy menstrual bleeding (AUB/HMB) or intermenstrual bleeding (AUB/IMB). GnRH analogues are used as short-term preoperative therapy to reduce uterine and leiomyoma volume; long-term therapy should be limited to patients who have contraindications to other medical or surgical treatments.[8] They can also be used for acute AUB with an aromatase inhibitor or antagonist to prevent initial estrogen flare and for the treatment of HMB caused by leiomyoma-associated hormonal imbalance.[9]

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.[10] The American College of Obstetricians and Gynecologists (ACOG) committee opinion on prevention and management of heavy menstrual bleeding in adolescent patients undergoing cancer treatment lists leuprolide as an option for patients.[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 7) document also recommends the use of GnRH analogs in both male and female adolescents as a fully reversible intervention for pubertal suppression.[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 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. The NCCN guidelines for ovarian cancer (version 2.2018) recommend leuprolide as a hormonal therapy option in various settings (e.g., adjuvant therapy, recurrence).[16] The NCCN guidelines for breast cancer (version 3.2018) note that LHRH agonist, such as leuprolide, can be used for ovarian suppression.[17] It is recommended to given leuprolide as monthly injections as the 3-month depots do not reliably suppress estrogen levels in all patients. The NCCN breast cancer guidelines (version 3.2018) also state that randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. The NCCN guidelines for breast cancer (version 3.2018)[17] and adolescent and young adult oncology (version 1.2019)[18] mentions GnRH agonists as a fertility preservation option by suppressing menstrual cycles and/or protecting ovaries, but some results are conflicting. The NCCN guidelines for Head and Neck Cancer (version 2.2018)

recommends the use of androgen receptor therapy (i.e., leuprolide, bicalutamide) for androgen receptor (AR)-positive, recurrent salivary gland tumors with distant metastases.[19]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Lupron-Depot and Lupaneta Pack. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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

2. **Endometriosis.** Approve Lupron Depot or Lupaneta Pack for 1 year if the patient has tried one of the following**:** a contraceptive (e.g., combination oral contraceptives, levonorgestrel-relasing intrauterine systems [e.g., Mirena®, Liletta®]), an oral progesterone (e.g., norethindrone tablets), or 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).** Approve Lupron Depot for 6 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]).** 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.

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

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

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

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

9. **Abnormal Uterine Bleeding.** Approve for 6 months of therapy of Lupron Depot.

10. **Head and Neck Cancer – Salivary Gland Tumors.** Approve for 1 year of therapy of Lupron Depot if the patient meets the following criteria (A,B, and C):

    A) The patient has recurrent disease with distant metastases; AND
    B) The patient has androgen receptor (AR)-positive disease; AND
    C) The medication is prescribed by or in consultation with an oncologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Lupron Depot and Lupaneta Pack 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. **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.[20-22] 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.[20,21] 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.[23]

2. **Menstrual Migraine.** Therapies such as NSAIDs, triptans, and propranolol have been used for the treatment or prophylaxis of menstrual migraines.[24,25] A nonrandomized, 10-month prospective trial[26] 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.[27]

3. **Polycystic Ovarian Syndrome (PCOS).** Leuprolide long-acting has been used in women with PCOS.[28] 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)[29] and review articles[30,31] 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.[32] 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.

REFERENCES

1. Lupaneta Pack® 11.25 mg [prescribing information). North Chicago, IL: AbbVie Inc.; October 2013.
2. Lupaneta Pack® 3.75 mg [prescribing information]. North Chicago, IL: AbbVie Inc.; June 2015.
3. 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.; December 2018.
4. Lupron Depot® – 3 Month 11.25 mg [prescribing information]. North Chicago, IL: AbbVie Inc.; April 2018.
5. Lupron Depot® – 3.75 mg [prescribing information]. North Chicago, IL: AbbVie Inc.; October 2013.
6. Management of Endometriosis. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 114. 2010 (reaffirmed 2018). *Obstetrics & Gynecology*. 2010;116(1):223-236.
7. ACOG practice bulletin No. 128: Diagnosis of abnormal uterine bleeding in reproductive-aged women. *Obstet Gynecol*. 2012 (reaffirmed 2016);120(1):197-206.
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. 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 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 17, 2019.
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. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. Ovarian Cancer including fallopian tube cancer and primary peritoneal cancer (Version 2.2018). Available at http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf. Accessed January 17, 2019.
17. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. Breast cancer (Version 3.2018). Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed January 17, 2019.
18. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. Adolescent and young adult oncology (version 1.2019) Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#supportive. Accessed on January 21, 2019.
19. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (Version 2.2018 – June 20, 2018) © 2018 National Comprehensive Cancer Network, Inc. Available at http://www.nccn.org. Accessed on January 21, 2019
20. Azziz R, Ochoa TM, Bradley EL, et al. Leuprolide and estrogen versus oral contraceptive pills for the treatment of hirsutism: a prospective randomized study. *J Clin Endocrinol Metab*. 1995;80:3406-3411.
21. Bayhan G, Bahceci M, Demirkol T, et al. A comparative study of a gonadotropin-releasing hormone agonist and finasteride on idiopathic hirsutism. *Clin Exp Obstet Gynecol*. 2000;27(3-4):203-206.
22. Rosenfield RL. Hirsutism. *N Engl J Med*. 2005;353:2578-2588.
23. 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.
24. Ashkenazi A, Silberstein S. Menstrual migraine: a review of hormonal causes, prophylaxis and treatment. *Expert Opin Pharmacother*. 2007;8(11):1605-1613.
25. Silberstein SD, Hutchinson SL. Diagnosis and treatment of the menstrual migraine patient. *Headache*. 2008;48 Suppl 3:S115-S123.
26. Murray SC, Muse KN. Effective treatment of severe menstrual migraine headaches with gonadotropin-releasing hormone agonist and "add-back" therapy. *Fertil Steril*. 1997;67(2):390-393.
27. Calhoun AH. Menstrual migraine: update on pathophysiology and approach to therapy and management. *Curr Treat Options Neurol*. 2012;14:1-14.

28. Genazzani AD, Petraglia F, Battaglia C, et al. A long-term treatment with gonadotropin-releasing hormone agonist plus a low-dose oral contraceptive improves the recovery of the ovulatory function in patients with polycystic ovary syndrome. *Fertil Steril*. 1997;67(3):463-468.
29. Diagnosis and treatment of polycystic ovarian syndrome: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98:4565-4592.
30. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. *Int J Womens Health*. 2011;3:25-35.
31. Benjamins LJ, Barratt MS. Evaluation and management of polycystic ovary syndrome. *J Pediatr Health Care.* 2009;23(5):337-343.
32. 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 21, 2019.

OTHER REFERENCES UTILIZED

- University of California, San Francisco. Center of excellence for transgender health. Available at: http://transhealth.ucsf.edu/trans?page=lib-00-02. Accessed on March 29, 2017.
- Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. *Lancet Diabetes Endocrinol.* 2016;4:265-274.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Early annual revision	Added approval condition for gender reassignment use. Also added note to central precocious puberty indication to highlight central vs. peripheral precocious puberty.	03/16/2016
Selected revision	Under Other uses with Supportive Evidence, for "Preserve ovarian function/fertility in women undergoing chemotherapy" and "Prophylaxis or treatment of uterine bleeding in women with hematologic malignancy or prior to bone marrow/stem cell transplantation", changed "women" to "patients". Only wording change; no change in clinical intent.	8/11/2016
Annual revision	No criteria changes	04/05/2017
Selected revision	Added Triptodur to drug targets and for approval in central precocious puberty. Deleted approval of Lupron-Depot Ped for off-label uses.	10/4/2017
Annual revision	No criteria changes	04/25/2018
Selected revision	Updated Lupron Depot and Lupaneta Pack endometriosis criterion: removed initial and recurrent management of symptoms. Added a requirement for a trial of a contraceptive or progesterone product, continuing pain after treatment with these agents, and prescribing by an obstetrician-gynecologist or a health care practitioner who specializes in the treatment of women's health. Also removed Eligard from the approval condition for gender reassignment use.	10/03/2018
Selected revision	Removed Eligard. Eligard is addressed in a newly created policy with Trelstar and Firmagon. Criteria were added for Lupron Depot for the diagnosis of Head and Neck Cancer – Salivary Gland Tumors. See policy for details.	11/28/2018
Early annual revision	• Removal of Lupron-Depot Ped and Triptodur and the indication of central precocious puberty. These medications are addressed in the policy: Gonadotropin-Releasing Hormone Agonists for Central Precocious Puberty PA Policy with Preferred Step Therapy. • Updated the following indication, Prophylaxis or Treatment of Uterine Bleeding in Patients with Hematologic Malignancy or Prior to Bone Marrow/Stem Cell Transplantation to include patients undergoing cancer treatment. • Added "if prescribed by or in consultation with an oncologist" to the following diagnoses: Prostate Cancer, Ovarian Cancer, Breast Cancer,	1/30/2019

	Preserve Ovarian Function/Fertility in Patients undergoing Chemotherapy, and 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) to align with the Lupron Depot MBM policy.	
Selected revision	• Updated endometriosis criterion: removal of continued pain criteria and removal of prescriber's specialty or consultation specialty. • Added the wording Gender Dysphoric/Gender Incongruent Persons to the diagnosis for Gender Reassignment.	4/10/2019

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; BPH – Benign prostatic hyperplasia; IBS – Irritable bowel syndrome.