**Lupron Depot (leuprolide acetate)**
**Lupron Depot-PED (leuprolide acetate)**
**Lupaneta Pack (leuprolide acetate/norethindrone)**
**Leuprolide acetate (generic)**

**Line(s) of Business:**
HMO; PPO; QUEST Integration

**Original Effective Date:**
10/01/2015

**Current Effective Date:**
05/01/2019

**POLICY**

**A. INDICATIONS**

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

**FDA-Approved Indications**

- **Endometriosis**
  - Lupron Depot 3.75 mg, Lupron Depot-3 Month 11.25 mg, and Lupaneta Pack are indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions. Lupron Depot and Lupaneta Pack with norethindrone acetate 5 mg daily are also indicated for initial management of endometriosis and for management of recurrent symptoms. Duration of initial treatment and retreatment should be limited to six months each and use is not recommended longer than a total of 12 months.

- **Uterine Leiomyomata (Fibroids)**
  - When used concomitantly with iron therapy, Lupron Depot 3.75 mg and Lupron Depot-3 Month 11.25 mg are indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. The clinician may wish to consider a one-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. Lupron may be added if the response to iron alone is considered inadequate. Recommended duration of therapy is up to 3 months, either given as Lupron Depot 3.75 mg monthly or as a single injection of Lupron Depot-3 Month 11.25 mg. The Lupron Depot-3 Month 11.25 mg is indicated only for women for whom three months of hormonal suppression is deemed necessary.

- **Central Precocious Puberty (CPP)**
  - Lupron Depot-PED and leuprolide (generic) are indicated in the treatment of children with CPP until appropriate age of onset of puberty.

- **Prostate Cancer**
  - Lupron Depot (7.5 mg, 22.5 mg, 30 mg, 45 mg) and leuprolide (generic) are indicated in the palliative treatment of advanced prostatic cancer.
Compendial Uses
• Ovarian cancer:
  o Serous/endometrioid epithelial carcinoma: as a single agent for pathologic stage IC-IV low-grade disease
  o Ovarian malignant sex-cord stromal tumors (Lupron Depot 3.75 mg, 11.25 mg): for clinical relapse in patients with stage II-IV granulosa cell tumors
  o Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer (Lupron Depot 3.75 mg, 11.25 mg): as a single agent for persistent disease or recurrence
• Breast cancer (Lupron Depot 3.75 mg only):
  o In combination with endocrine therapy in premenopausal women with hormone receptor-positive recurrent or metastatic disease
  o In combination with adjuvant endocrine therapy in premenopausal women
• Prostate cancer (Lupron Depot 7.5 mg, 22.5 mg, 30 mg, 45 mg) and leuprolide (generic):
  o Adjuvant androgen deprivation therapy if positive pelvic lymph nodes are found during pelvic lymph node dissection
  o Clinically localized disease
    ▪ In combination with radiation therapy for patients with intermediate- or high-risk stratification
    ▪ Patients with very high risk stratification
  o Metastatic disease
  o Progressive castration-naïve disease
  o Castration-recurrent disease
• Puberty suppression therapy for gender dysphoria (leuprolide [generic], Lupron Depot, Lupron Depot-PED)

B. REQUIRED DOCUMENTATION
The following information is necessary to initiate the prior authorization review:
• Initial therapy
  o Uterine leiomyoma: documentation of the reason for delay in surgery when a second course of treatment is requested
  o Endometriosis: documentation of the reason for retreatment when a second course of treatment is requested
  o Central precocious puberty:
    ▪ Diagnosis confirmed by a pubertal response to a GnRH agonist test or a third generation basal LH assay
    ▪ Documentation that supports the need to delay puberty for the continuation of treatment

C. EXCLUSIONS
• Pregnancy
• Breastfeeding
• Undiagnosed abnormal vaginal bleeding

D. CRITERIA FOR APPROVAL
1. Uterine fibroids (Lupron Depot 3.75 mg, 11.25 mg)
   Authorization of 3 months (one treatment course) may be granted for adult female members for initial treatment of uterine fibroids when the following criteria are met:
a. The member has a diagnosis of iron deficiency anemia secondary to vaginal bleeding associated with uterine leiomyomas (Hct < 33% and/or Hgb < 11 g/dL)
b. It is essential to increase hemoglobin/hematocrit prior to leiomyoma removal surgery

2. **Endometriosis (Lupron Depot 3.75 mg and 11.25 mg; Lupaneta Pack)**
   Authorization of 6 months (one treatment course) may be granted for adult female members (≥ 18 years of age) for initial treatment of symptomatic endometriosis.

3. **Prostate cancer (Leuprolide [generic]; Lupron Depot [7.5 mg, 22.5 mg, 30 mg, 45 mg])**
   Authorization of 12 months may be granted when either a., b., or c. below are met:
   a. Adjuvant androgen deprivation therapy if positive pelvic lymph nodes are found on pelvic lymph node dissection
   b. Member has a diagnosis of clinically localized prostate cancer and
      i. Leuprolide is NOT being used as neoadjuvant therapy prior to radical prostatectomy
      ii. Leuprolide is being used in combination with radiation therapy for intermediate- or high-risk stratification groups
      iii. Members risk stratification group is very high risk
   c. Member has locally advanced disease, recurrent disease, biochemical failure from previous therapy, progressive castration-naïve disease, castration-recurrent disease, or regional/metastatic disease.

4. **Breast cancer (Lupron Depot 3.75 mg)**
   Authorization of 12 months may be granted for premenopausal adult female members with hormone receptor-positive breast cancer who meet either of the following:
   a. Lupron Depot is used in combination with endocrine therapy for recurrent or metastatic breast cancer
   b. Lupron Depot is used in combination with adjuvant endocrine therapy

5. **Serous/Endometrioid epithelial carcinoma (Lupron Depot 3.75 mg, 11.25 mg)**
   Authorization of 12 months may be granted for adult female members who are prescribed Lupron Depot as adjuvant hormone therapy as a single agent for pathologic stage IC-IV low-grade disease.

6. **Epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer (Lupron Depot 3.75 mg, 11.25 mg)**
   Authorization of 12 months may be granted for adult female members who are prescribed Lupron Depot as a single agent for persistent or recurrent disease.

7. **Malignant sex-cord stromal tumors (Lupron Depot 3.75, 11.25 mg)**
   Authorization of 12 months may be granted for adult female members who are prescribed Lupron Depot 3.75 mg or 11.25 mg for clinical relapse of stage II-IV granulosa cell tumors.

8. **Central precocious puberty (Leuprolide [generic]; Lupron Depot-PED)**
   Authorization for use up to 12 years of age may be granted for female members when the following criteria are met:
   a. Member has a diagnosis of CPP confirmed by a GnRH test or third-generation basal LH assay
b. Member has advanced bone age (bone age at least 1 year greater than chronological age)
c. Intracranial tumor has been excluded with diagnostic imaging of the brain
d. Onset of secondary sexual characteristics occurred at age < 8 years

Authorization for use up to 13 years of age may be granted for male members when the following criteria are met
   a. Member has a diagnosis of CPP confirmed by a GnRH test or third-generation basal LH assay
   b. Member has advanced bone age (bone age at least 1 year greater than chronological age)
c. Intracranial tumor has been excluded with diagnostic imaging of the brain
d. Onset of secondary sexual characteristics occurred at age < 8 years

9. Puberty suppression therapy for gender dysphoria (leuprolide [generic]; Lupron Depot; Lupron Depot-PED)
Puberty suppression therapy is covered for 12 months when all of the following criteria are met:
   a. The patient has been diagnosed with persistent, well-documented gender dysphoria as defined by the current Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (see Appendix A) and gender identity disorder as defined by the current International Classification of Diseases (ICD) criteria by a qualified mental health professional (see Appendix B);
   b. The patient has exhibited the first physical changes of puberty, indicated by a minimum Tanner stage of 2 or 3;
   c. The patient has completed at least three months of successful continuous full time real-life experience in their gender identity across a wide span of life experiences and events (e.g., holidays, vacations, season-specific school and/or work experience, family events);
   d. Clinical records document that the patient assents to treatment and the parent/guardian has made a fully informed decision and consents to treatment;
   e. The patient’s comorbid medical and mental health conditions (if present) are reasonably well-controlled; and
   f. Puberty suppression therapy will be administered in a safe, appropriate, medically supervised manner.

E. CONTINUATION OF THERAPY
1. Uterine Fibroids
   - No previous authorization/precertification:
     ○ All members (including new members and members currently receiving treatment without prior authorization) must meet initial criteria for approval in section D.
   - Reauthorization
     ○ Authorization of 3 months (one additional treatment course; maximum of 2 courses total) may be granted for retreatment of uterine fibroids when all initial criteria have been met in addition to the following:
       ▪ There has been a delay in leiomyoma removal surgery and appropriate documentation is provided.

2. Endometriosis
   - No previous authorization/precertification:
All members (including new members and members currently receiving treatment without prior authorization) must meet initial criteria for approval in section D.

- Reauthorization
  - Authorization of 6 months (one additional treatment course; maximum of 2 courses total) may be granted to members requesting retreatment of endometriosis when all initial criteria have been met, retreatment is deemed clinically necessary, and appropriate documentation is provided.

3. **Prostate cancer**
   - No previous authorization/precertification:
     - All members (including new members and members currently receiving treatment without prior authorization) must meet criteria for initial approval in section D.
   - Reauthorization:
     - Authorization of 12 months may be granted for members requesting authorization for continuation of therapy who were previously authorized by HMSA/CVS, who show no progression of the cancer being treated, and who provide appropriate documentation.
       - A current oncology note documenting the patient’s response to treatment showing no progression of disease
       - Current imaging studies and other objective measures showing no progression of disease when compared with previous results
     - For members with prostate cancer who have evidence of disease progression (eg, increase in serum prostate-specific antigen [PSA], new metastases, progression of existing metastases) while being managed with androgen deprivation therapy (ADT), authorization for 12 months can be granted if ADT is to be used with any following agents: abiraterone, enzalutamide, taxane chemotherapy, sipuleucel-t, radium-223.

4. **Breast cancer, serous/endometrioid epithelial carcinoma, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, malignant sex-cord stromal tumors**
   - No previous authorization/precertification:
     - All members (including new members and members currently receiving treatment without prior authorization) must meet criteria for initial approval in section D.
   - Reauthorization:
     - Authorization of 12 months may be granted for members requesting authorization for continuation of therapy who were previously authorized by HMSA/CVS, who show no progression of the cancer being treated, and who provide appropriate documentation.
       - A current oncology note documenting the patient’s response to treatment showing no progression of disease
       - Current imaging studies and other objective measures showing no progression of disease when compared with previous results

5. **Central precocious puberty**
   - No previous authorization/precertification:
     - All members (including members currently receiving treatment without prior authorization) must meet criteria for initial approval in section D.
   - Reauthorization beyond 12 years of age in females or 13 years of age in males:
Authorization of a 12 month extension may be granted for members (until the age of 18 years old) when there is a continued need to delay puberty (such as extreme short stature), and appropriate documentation is provided.

6. Puberty suppression therapy for gender dysphoria
   - No previous authorization/precertification:
     o All members (including members currently receiving treatment without prior authorization) must meet criteria for initial approval in section D.
   - Reauthorization:
     o Authorization of 12 months may be granted for members requesting authorization of continuation of therapy who have been previously authorized by HMSA/CVS, there is a continued need to delay puberty (until the age of 18 years old), and appropriate documentation is provided.

F. DOSAGE AND ADMINISTRATION
   Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

G. ADMINISTRATIVE GUIDELINES
   Precertification is required. Please refer to the HMSA medical policy web site for the fax form.

H. IMPORTANT REMINDER
   The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that CVS/Caremark reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

I. APPENDICES
   Appendix A: Diagnostic Statistical Manual of Mental Disorders (DSM-5) Criteria for Gender Dysphoria
   Adults and Adolescents
   A. A marked incongruence between one’s experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by two or more of the following:
      1. A marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics (or, in young adolescents, the anticipated secondary sex characteristics).
2. A strong desire to be rid of one’s primary and/or secondary sex characteristics because of a marked incongruence with one’s experienced/expressed gender (or, in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).

3. A strong desire for the primary and/or secondary sex characteristics of the other gender.

4. A strong desire to be of the other gender (or some alternative gender different from one’s assigned gender).

5. A strong desire to be treated as the other gender (or some alternative gender different from one’s assigned gender).

6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one’s assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Children

A. A marked incongruence between one’s experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by six or more of the following (one of which must be criterion A.1.):

1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender, different from one’s assigned gender).

2. In boys (assigned gender), a strong preference for cross dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to wearing of typical feminine clothing.

3. A strong preference for cross-gender roles in make-believe play or fantasy play.

4. A strong preference for toys, games, or activities stereotypically used or engaged in by the other gender.

5. A strong preference for playmates of the other gender.

6. In boys (assigned gender), a strong rejection of typically masculine toys, games and activities and a strong avoidance of rough and tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games and activities.

7. A strong dislike of one’s sexual anatomy.

8. A strong dislike for the primary and/or secondary sex characteristics that match one’s experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Appendix B: Characteristics of a Qualified Mental Health Professional

A. A master’s degree or its equivalent in a clinical behavioral science field. This degree, or a more advanced one, should be granted by an institution accredited by the appropriate national or regional accrediting board. The mental health professional should have documented credentials from a relevant licensing board or equivalent for that country;

B. Competence in using the Diagnostic Statistical Manual of Mental Disorders and/or the International Classification of Diseases for diagnostic purposes;

C. Ability to recognize and diagnose coexisting mental health concerns and to distinguish these from gender dysphoria;

D. Documented supervised training and competence in psychotherapy or counseling;
E. Knowledgeable about gender-nonconforming identities and expressions, and the assessment and treatment of gender dysphoria;
F. Continuing education in the assessment and treatment of gender dysphoria. This may include attending relevant professional meetings, workshops, or seminars; obtaining supervision from a mental health professional with relevant experience; or participating in research related to gender nonconformity and gender dysphoria.

J. REFERENCES
4. Lupron Depot 7.5 mg, 22.5 mg, 30 mg, 45 mg [package insert]. North Chicago, IL: AbbVie Inc.; June 2016.

Document History

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