I. Description

Leuprolide acetate (Lupron) is an injectable drug and belongs to a class of drugs called gonadotropin-releasing hormone (GnRH) agonists. It is used to decrease the body’s production of specific hormones, natural chemicals that influence the behavior of certain cells. Because leuprolide acetate can reduce the production of both male and female hormones, it is used to treat specific conditions in men, women and children.

Histrelin acetate (Supprelin LA) is a GnRH agonist indicated for the treatment of children with central precocious puberty (CPP). The recommended dose of Supprelin LA is one subcutaneous implant every 12 months. The implant is inserted subcutaneously in the inner aspect of the upper arm and provides continuous release of histrelin for 12 months of hormonal therapy.

II. Criteria/Guidelines

A. Leuprolide acetate is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the following indications:

1. Prostate cancer – for palliative treatment for advanced prostate cancer
2. Anemia due to uterine leiomyomas
   a. The patient must have been diagnosed with iron deficiency anemia secondary to vaginal bleeding associated with; leiomyomas and
   b. The patient’s hemoglobin is less than 11 or hematocrit less than 33; and
   c. The patient is scheduled for surgery to remove the, leiomyomas and the physician feels that it is necessary to increase the hematocrit prior to surgery; and
   d. A course of treatment is limited to three months.
3. Endometriosis
   a. The patient is 18 years of age or older; and
   b. The patient is symptomatic.
   c. A course of treatment is limited to six months.

4. Breast cancer
   a. The patient has advanced breast cancer; and
   b. The patient is premenopausal or perimenopausal; and
   c. The patient has tried and failed other treatment (e.g. tamoxifen).

B. Leuprolide acetate and histrelin acetate (subcutaneous implant) are covered (subject to Limitations/Exclusions and Administrative Guidelines) for CPP:
   1. Initial Therapy: Onset of secondary sexual characteristics before the age of eight in girls and age nine in boys, and bone age is one year beyond chronological age.
   2. Extension of therapy beyond age 11 in girls and 12 or older in boys: There is continued need to delay puberty beyond the normal age of onset (e.g. extreme short stature with height below the mean by more than two standard deviations and open growth plates).

III. Limitations/Exclusions
   A. Either leuprolide acetate or histrelin acetate (subcutaneous implant) may be covered for the treatment of CPP. HMSA reserves the right to approve the least costly treatment for this condition.
   B. Leuprolide acetate as a treatment prior to surgery for leiomyoma in patients without anemia is not covered as it is not FDA-approved.
   C. Leuprolide acetate or histrelin acetate (subcutaneous implant) as a treatment for CPP should be discontinued before the age of 11 in females or the age of 12 in males except as specified in II.B.2.
   D. Leuprolide acetate as a treatment of endometriosis should have a duration of initial treatment or retreatment limited to six months each. Reliable evidence shows that further studies or clinical trials are necessary to determine maximum tolerated dose, toxicity and safety. Treatment for this indication is limited to females age 18 or older.

IV. Administrative Guidelines
   A. Precertification is required for the following indications. To precertify, complete the Drug Review Request and mail or fax the form as indicated.
      1. Uterine leiomyomomas
         When therapy will extend beyond one course of treatment (three months), documentation must be submitted clearly indicating cause for delay in surgery.
      2. Central precocious puberty
         When therapy will extend beyond age 11 in girls and 12 or older in boys, documentation must be submitted (e.g. clinical notes, growth charts, imaging studies) supporting the continued need to delay puberty.
3. **Retreatment for endometriosis**  
   When therapy will extend beyond one course of treatment (six months), documentation must be submitted clearly stating reasons for retreatment.

4. **Palliative treatment of breast cancer**  
   Documentation must be submitted supporting the diagnosis of advanced breast cancer, that the patient is pre- or peri-menopausal, and indicating what treatments have been tried and failed.

B. Leuprolide acetate used in conjunction with an HMSA-approved in vitro fertilization procedure during the approval period, is covered without precertification.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1950</td>
<td>Injection, leuprolide acetate (for depot suspension), per 3.75 mg (use this code for Lupron Depot)</td>
</tr>
<tr>
<td>J9217</td>
<td>Leuprolide acetate (for depot suspension), 7.5 mg (use this code for Lupron Depot, Eligard)</td>
</tr>
<tr>
<td>J9218</td>
<td>Leuprolide acetate, per 1 mg (use this code for Lupron, Eligard)</td>
</tr>
<tr>
<td>J9219</td>
<td>Leuprolide acetate implant, 65 mg (use this code for Lupron implant)</td>
</tr>
<tr>
<td>J9226</td>
<td>Histrelin implant (Supprelin LA), 50 mg</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>ICD-9-CM Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>174.0-174.9</td>
<td>Malignant neoplasm of female breast</td>
</tr>
<tr>
<td>185</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>218.0-218.9</td>
<td>Uterine leiomyoma (fibroids)</td>
</tr>
<tr>
<td>259.1</td>
<td>Other endocrine disorders, precocious sexual development and puberty, not elsewhere classified</td>
</tr>
<tr>
<td>617.0-617.9</td>
<td>Endometriosis</td>
</tr>
</tbody>
</table>

ICD-10 codes are provided for your information. These will not become effective until 10/1/2014:

<table>
<thead>
<tr>
<th>ICD-10-CM Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C61</td>
<td>Malignant neoplasm of prostate</td>
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<tr>
<td>D25.0 – D25.9</td>
<td>Leiomyoma of uterus</td>
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<tr>
<td>E30.1</td>
<td>Precocious puberty</td>
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<tr>
<td>E30.8</td>
<td>Other disorders of puberty</td>
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<tr>
<td>N80.0 – N80.9</td>
<td>Endometriosis</td>
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</tbody>
</table>
Leuprolide Acetate (Lupron) and Histrelin Acetate (Supprelin LA) Subcutaneous Implant

<table>
<thead>
<tr>
<th>C50.011 – C50.019</th>
<th>Malignant neoplasm of nipple and areola, female</th>
</tr>
</thead>
<tbody>
<tr>
<td>C50.111 – C50.119</td>
<td>Malignant neoplasm of central portion of breast, female</td>
</tr>
<tr>
<td>C50.211 – C50.219</td>
<td>Malignant neoplasm of upper-inner quadrant of breast, female</td>
</tr>
<tr>
<td>C50.311 – C50.319</td>
<td>Malignant neoplasm of lower-inner quadrant of breast, female</td>
</tr>
<tr>
<td>C50.411 – C50.419</td>
<td>Malignant neoplasm of upper-outer quadrant of breast, female</td>
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<tr>
<td>C50.511 – C50.519</td>
<td>Malignant neoplasm of lower-outer quadrant of breast, female</td>
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<tr>
<td>C50.611 – C50.619</td>
<td>Malignant neoplasm of axillary tail of breast, female</td>
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<tr>
<td>C50.811 – C50.819</td>
<td>Malignant neoplasm of overlapping sites of breast, female</td>
</tr>
<tr>
<td>C50.911 – C50.919</td>
<td>Malignant neoplasm of breast of unspecified site, female</td>
</tr>
</tbody>
</table>

V. **Scientific Background**

**Prostatic carcinoma**

Isolated short-term worsening of neurologic symptoms may contribute to paralysis with or without fatal complications in patients with vertebral metastases. For patients at risk, therapy may be initiated with daily leuprolide injection for the first two weeks to observe patient reaction, since worsening of symptoms occasionally requires discontinuation of therapy and possible surgical intervention. Patients receiving leuprolide should be under supervision of a physician experienced in cancer chemotherapy.

**Anemia due to uterine fibroids**

According to the Agency for Healthcare Research and Quality (AHRQ) Evidence Report/Technology Assessment: Number 34, Management of Uterine Fibroids, there is insufficient data to allow conclusions about the most appropriate therapy for a given symptomatic patient. The majority of randomized clinical trials identified which used gonadotropin-releasing hormone (GnRH) agonists were done as adjunctive treatment prior to uterine surgery. The remainder of citations were uncontrolled case series, case series with historical or nonrandomized controls, case-control studies, or in a few instances, prospective cohort studies. The principal findings of the report included the finding that there is good evidence based on randomized trials that use of GnRH agonists prior to myomectomy or hysterectomy reduces estimated blood loss and may facilitate certain surgical approaches. There is also no information on long-term clinical significance of these effects. Also, there is no data supporting prophylactic hysterectomy or myomectomy in women with asymptomatic fibroids.

In clinical trials, GnRH agonists reduced fibroid size and were useful as a pre-operative adjunct with rapid regrowth of fibroids following discontinuation. Available literature states only short-term treatment is recommended (i.e., one to three months) especially to prevent bone loss after menopause.
According to DrugDex, dosing information, therapy for anemia due to uterine leiomyomas should continue uninterrupted for three months. Therapy should be given concomitantly with iron. Retreatment is not recommended. If retreatment is contemplated, bone density should be assessed prior to beginning treatment to verify that values are in the normal range.

Central precocious puberty
Leuprolide acetate dosage must be individualized for each patient and titrated upward until the patient’s pituitary-gonadal axis is suppressed, according to clinical and/or laboratory parameters. Usually the dose that adequately suppresses the pituitary-gonadal axis is appropriate for the entire therapy. However, there are insufficient data to guide dosage adjustments as a child’s weight changes, a special concern for children who started therapy at a very early age at a low dose. Careful monitoring for suppression of the pituitary-gonadal axis is required, especially one or two months after treatment initiation or following changes in dose.

If the patient responds and tolerates leuprolide acetate or histrelin acetate (subcutaneous implant) therapy, treatment should continue until resumption of puberty is desired. Discontinuation of leuprolide therapy should be considered before the age of 11 years in females and 12 years in males. Normal function of pituitary-gonadal axis is restored within 4 to 12 weeks after treatment discontinuation.

Endometriosis
Therapy with leuprolide acetate should continue uninterrupted for six months. Retreatment is not recommended. However, if retreatment is contemplated, bone density should be assessed prior to beginning treatment to verify that values are in the normal range. Studies of leuprolide acetate for endometriosis indicate that six months is an appropriate length for therapy. There is a lack of safety data with long-term use as well as concerns in the available literature regarding effects on bone density.

VI. 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
HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any
supporting documentation.

VII. References

1. BCBSA. Combined Androgen Blockade for the Treatment of Metastatic Prostate Cancer.
   March 27, 2013.
3. Jasonni VM, D’Anna R, et al. Randomized double-blind study evaluating the efficacy on uterine
   fibroids shrinkage and on intra-operative blood loss of different length of leuprolide acetate
   Research and Quality, Rockville, MD.
   34. AHRQ Publication No. 01-E051, January 2001. Agency for Healthcare Research and Quality,
   Rockville, MD.
6. Hornstein MD, Surrey ES, et al. Leuprolide acetate depot and hormonal add-back in
8. Supprelin LA (histrelin acetate) subcutaneous implant prescribing information April 2013.