Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
GnRH analogs for non-oncology and oncology-related indications	MP-RX-FP-34-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of of gonadotropin releasing hormone (GnRH) analogs for the treatment of non-oncology and oncology-related indications.

The GnRH analogs included in the document for the treatment of oncology indications include: Firmagon (degarelix), Zoladex (goserelin acetate), Camcevi, (leuprolide mesylate) Eligard (leuprolide acetate), Lupron Depot (leuprolide acetate), and Trelstar (triptorelin pamoate).

GnRH analogs included in this review for the treatment of non-oncologic indication are: Fensolvi (leuprolide acetate), Lupron Depot, Lupron Depot-Ped (leuprolide acetate), Supprelin LA 12 month implant (histrelin acetate), Synarel Nasal Spray (nafarelin acetate), Triptodur (triptorelin pamoate extended-release),Vantas (Histrelin) and Zoladex (goserelin acetate).

B vs D Criteria: Drugs included in this protocol are subject to B vs D evaluation. Medication is eligible to be evaluated through part B if furnished "incident to" physician service provided. If not, medication must be evaluated through part D."

Background Information

GnRH analogs are a group of hormonal drugs consisting of GnRH agonists and antagonists, both of which suppress pituitary hormones. GnRH agonists typically act over several days and GnRH antagonists act quickly within several hours. Affecting the pituitary gland in the brain, GnRH analogs suppress function of the ovaries and testes, blocking the production of testosterone in males and estrogen in females. Repeated administration of these drugs will cause gonadal hormone dependent tissues/organs to reduce or cease activity, such as the normal prostate gland that is dependent on testosterone for growth and function. This effect is reversible on discontinuation of the drug therapy.

- **GnRH analogs for non-oncology related indications**

Central Precocious Puberty (CPP) is defined as the full activation of the hypothalamic-pituitary-gonadal (HPG) axis before 8 years of age in girls and before 9 years of age in boys. The diagnosis may be considered in girls who have progressive breast development and who cross percentiles upward on the linear growth chart. CPP is far less common in boys but may be considered if there is evidence of both testicular and penile enlargement before 9

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years of age (Kaplowitz 2016). The diagnostic evaluation of suspected CPP will typically include a bone age determination, which is often useful in predicting adult height. Baseline laboratory testing may include FSH, LH, and either estradiol or testosterone. The decision as to when to stop therapy is complex but typically occurs when it is apparent that continued pubertal suppression is no longer beneficial to the child. Thus, if the child is able to cope with puberty, and the predicted adult height is within the normal range, treatment may be stopped early; it often takes a year or more after cessation for menses to start. Some endocrinologists will end therapy in girls by 10 years of age, and others will continue it until 11 or 12 years of age, depending on clinical circumstances.

Gender dysphoria or gender incongruence is a condition wherein an individual's experienced gender is the opposite of his or her natal gender (usually assigned at birth based on anatomic sex). This can result in distress associated with persistent feelings, such as being "Trapped in the wrong body." Gender dysphoria is distinct from cross dressing (transvestitism), inability to accept homosexual orientation, psychotic delusions or personality disorders. Most individuals who express gender dysphoria in adolescence and later are thought to sustain the experienced gender. Guidance from the 2009 and 2017 Endocrine Society Clinical Practice Guidelines for the endocrine treatment of Gender-Dysphoric/Gender Incongruence Persons and “Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (WPATH)” were utilized in this guideline.
GnRH analogs for oncologic indications

- **GnRH analogs for oncology related indications**

The GnRH analogs included in the document include: Firmagon (degarelix), Zoladex (goserelin acetate), Camcevi, (leuprolide mesylate) Eligard (leuprolide acetate), Lupron Depot (leuprolide acetate), and Trelstar (triptorelin pamoate).

Breast Cancer

Breast cancer is the most common cancer diagnosed in women today with the exception of skin cancer. Suppression of ovarian function with the use of luteinizing hormone-releasing hormone (LHRH) agonists has been shown to be effective in the treatment of hormone receptor positive breast cancer in pre- or peri-menopausal women. LHRH agonists currently available in the United States include goserelin acetate and leuprolide acetate.

Breast cancer in men is a relatively rare disease. Due to this rarity, studies are limited in number and size. However, several authors (Giordano, 2002; Hotko, 2013) report that additive hormonal therapy has been shown to have substantial response rates in metastatic breast carcinoma in men.

The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium and Clinical Practice Guidelines for Breast Cancer indicate that leuprolide acetate and goserelin acetate may be used to treat premenopausal women with hormone receptor- positive disease in combination with adjuvant endocrine therapy for recurrent or metastatic disease. Additionally, NCCN notes that men with breast cancer should be treated similarly to postmenopausal women, except that use of an aromatase inhibitor is ineffective without concomitant suppression of testicular steroidogenesis. These recommendations are NCCN category 1 and 2A.

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Two randomized phase III clinical trials) (TEXT and SOFT) (Pagani, 2014) demonstrated that the aromatase inhibitor exemestane plus ovarian suppression significantly reduced breast cancer recurrences as compared to tamoxifen plus ovarian suppression. The primary analysis combined data from 4690 subjects from the two trials. The rate of disease-free survival at 5 years was 91.1% (95% confidence interval [CI], 89.7 to 92.3) for subjects assigned to exemestane plus ovarian suppression, compared to 87.3% (95% CI, 85.7-88.7) for those in the tamoxifen plus ovarian suppression group. A GnRH analog was used for ovarian suppression in both groups. Based on results of these trials, NCCN included ovarian suppression plus an aromatase inhibitor for 5 years as adjuvant endocrine therapy option for premenopausal women with hormone receptor positive breast cancer at a higher risk of recurrence. Factors indicating a higher risk of recurrence include young age, high-grade tumor and lymph node involvement. One trial investigated whether or not 3-month depot was reliable as 6 cycles of CMF. In the trial, Lupron 11.25 mg subcutaneously was administered once every 3 months for 2 years in 589 patients. Leuprolide was compared to 6 cycles of CMF (cyclophosphamide, methotrexate, and fluorouracil) as adjuvant treatment in premenopausal patients with node-positive breast cancer (TABLE study) and was shown to be non-inferior for 2-year relapse free survival (63.9% vs. 63.4%; p=0.83). There are no trials currently comparing monthly injections to a 3-month depot injection.

Ovarian Cancer

Leuprolide acetate is a viable option for treatment of ovarian cancer under certain circumstances (Rao, 2006; Yokoyama, 2013). Fishman (1996) evaluated 6 women with recurrent or persistent ovarian granulosa cell tumor who were treated with monthly leuprolide acetate injections. Cessation of disease progression was noted in 5 subjects. The 6th subject remained disease free after her primary cytoreductive surgery while on adjuvant therapy with leuprolide acetate for 24 months. There were no major side effects noted and the treatment was well tolerated. The authors concluded that a reasonable disease progression-free interval occurred, and leuprolide treatment should be considered for further trials of therapy. Balbi (2004) reported on a study in which 12 women with advanced ovarian cancer previously treated with paclitaxel were administered leuprolide on days 1, 8, and 28. Progression-free survival was 6 months, and the treatment was well tolerated. The authors noted: “the high tolerability and the results obtained with leuprolide versus platinum in second-line therapy might permit a better use of the analogs for advanced ovarian cancer.”

The NCCN Drugs and Biologics Compendium and Clinical Practice Guidelines for Ovarian Cancer indicate that leuprolide acetate may be used for hormonal therapy as a single agent for persistent disease or recurrence of ovarian cancer (epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer) and for clinical relapse of stage II-IV granulosa cell tumors (2A recommendations).

Prostate Cancer

Prostate cancer is the most common form of cancer, other than skin cancer, among men. Wilt and colleagues (2008) report that approximately 90% of men with prostate cancer have disease confined to the prostate gland (clinically localized disease). GnRH analogs are commonly used in the treatment of prostate cancer under specific conditions as indicated by current FDA approved labels and NCCN.

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Men with prostate cancer are categorized according to their recurrence risk into those with clinically localized disease at low, intermediate and high risk of recurrence, or those with locally advanced disease at very high risk of recurrence, or those with metastatic disease. The NCCN Clinical Practice Guidelines for Prostate Cancer include the following additional information defining prostate cancer recurrence risk categories:

Very low risk category includes individuals with tumors stage T1c, biopsy Gleason score (less than or equal to 6)/Gleason grade group 1 and serum PSA below 10 ng/ml, presence of disease in fewer than 3 biopsy cores, 50% or less prostate involvement in any core and PSA density less than 0.15 ng/ml/g.

Low risk category includes individuals with tumors stage T1-T2a, Gleason score 6/Gleason grade group 1, and serum PSA level below 10 ng/ml.

Intermediate risk category includes individuals with clinical stage T2b to T2c cancer, Gleason score 7/Gleason grade group 2-3, or PSA value of 10-20 ng/mL. Those with multiple adverse factors may be shifted into the high risk category.

High risk category includes individuals with prostate cancer that is stage T3a, Gleason score 8-10/Gleason grade group 4-5, or PSA level greater than 20 ng/mL.

Very high risk of recurrence (locally advanced) includes individuals with stage T3b to T4 disease, primary Gleason pattern 5, or more than 4 biopsy cores with Gleason score 8-10/Gleason grade group 4-5.

Neoadjuvant androgen deprivation therapy (ADT) (which includes GnRH analogs) may be used to shrink the prostate to an acceptable size prior to brachytherapy, however increased toxicity would be expected from ADT and prostate size may not decline in some men (NCCN Clinical Practice Guidelines for Prostate Cancer). The American Academy of Urology (2008) indicates that there is evidence of benefit from hormone therapy prior to cryosurgery for downsizing purposes.

Salivary Gland Tumors

Salivary gland tumors can be found in the major salivary glands (for example, parotid, submandibular, sublingual) or in the minor salivary glands. Salivary gland carcinoma is rare and accounts for 6% of head and neck cancers in the United States (Dalin, 2017).

Fushimi and colleagues (2017) performed the first prospective, phase II, open-label, single-arm study of a combined androgen blockade for androgen receptor-positive salivary gland carcinoma. A total of 36 subjects were included (33 with recurrent/metastatic disease and 3 with locally advanced disease). Inclusion criteria included: ≥ 20 years of age, ECOG performance status of 0-2, adequate organ function, measurable lesions, and at least a 3-month life expectancy. The researchers administered leuprorelin (another name for leuprolide) 3.75 mg every 4 weeks and bicalutamide 80 mg daily until the subjects' disease progressed or they had unacceptable toxicities. Tumor response was assessed every 6 weeks using computed tomography or magnetic resonance imaging. The

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best overall response rate was 41.7% (n=15; 95% CI, 25.5% to 59.2%) and the clinical benefit rate was 75% (n=27, 95% CI, 57.8% to 87.9%). The median progression-free survival was 8.8 months (95% CI, 6.3 to 12.3) and median overall survival was 30.5 months (95% CI, 16.8 to not reached). Serious adverse events included elevated grade 3 liver transaminases and increased serum creatinine. The authors concluded that a combined androgen blockade may have antitumor activity in androgen-positive salivary gland carcinoma.

The NCCN Drugs and Biologics Compendium and Clinical Practice Guidelines for Head and Neck Cancers indicate that leuprolide acetate may be used for salivary gland tumors for androgen receptor positive (AR+) recurrent disease with distant metastases and a PS of 0-3 (2A recommendation). NCCN also recommends leuprolide to treat salivary gland tumors that are AR+, locally advanced, and unresectable (2A recommendation).

Definitions and Measures

- Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.
- Advanced prostate cancer: Disease that has spread beyond the prostate to surrounding tissues or distant organs.
- Androgen deprivation therapy (also known as androgen ablation or androgen suppression): Treatment to suppress or block the production or action of male hormones. This is done by having the testicles removed, by taking female sex hormones, or by taking drugs called antiandrogens or GnRH analogs.
- Brachytherapy (also known as internal radiation): A type of radiation treatment used to stop the growth of cancer cells by implanting radioactive material directly into the tumor or into the surrounding tissues.
- Cancer staging: The process of determining how much cancer there is in the body and where it is located; describes the extent or severity of an individual's cancer based on the extent of the original (primary) tumor and the extent of spread in the body.
- Clinically localized prostate cancer: Cancer presumed to be confined within the prostate based on pre-treatment findings such as physical exam, imaging, and biopsy findings.
- Cryosurgery (also called cryotherapy or cryosurgical ablation): Is the use of extreme cold produced by liquid nitrogen (or argon gas) to destroy abnormal tissue. Cryosurgery may be used to treat tumors on the skin (external tumors), such as basal cell carcinoma, or tumors inside the body (internal tumors), such as prostate cancer.
- ECOG Performance Status: A scale used to determine the individual's level of functioning. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:
    - 0= Fully active, able to carry on all pre-disease performance without restriction
    - 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
    - 2= Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

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- 3= Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- 4= Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
- 5= Dead

- External beam radiation therapy (EBRT) (also known as teletherapy): A form of therapy using radiation to stop the growth of cancer cells. A linear accelerator directs a photon or electron beam from outside the body through normal body tissue to reach the cancer and the radiation is given 5 days per week for a period of 3 to 8 weeks.

- Gleason Grade Group: Assigns grade groups from 1-5, derived from the Gleason score. Gleason grade group 1: Gleason score 6 and only individual discrete well-formed glands.
  - Gleason grade group 2: Gleason score 3+4=7 and predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands.
  - Gleason grade group 3: Gleason score 4+3=7 and predominantly poorly formed/fused/cribriform glands with lesser component of well- formed glands.
  - Gleason grade group 4: Gleason score 4+4=8; 3+5=8; 5+3=8
    - Only poorly formed/fused/cribriform glands; or
    - Predominantly well-formed glands and lesser component lacking glands[1]; or
    - Predominantly lacking glands and lesser component of well-formed glands[1].
  - Gleason grade group 5: Gleason score 9-10 and lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands[2].

  [1] Poorly formed/fused/cribriform glands can be a more minor component

  [2]For cases with more than 95% poorly formed/fused/cribriform glands or lack of glands on a core or at RP, the component of less than 5% well-formed glands is not factored into the grade.

- Gleason Grading System: A prostate cancer grading system. A primary and secondary pattern, the number range of each is from 1 to 5, are assigned and then summed to yield a total score.
- Gleason score: Represents the sum of the two most common Gleason grades observed by the pathologist on a specimen, the first number is the most frequent grade seen.
- Locally advanced disease (prostate cancer): Cancer that has spread from where it started to nearby tissue or lymph nodes.
- Metastatic: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
- Second primary cancer: a new primary cancer that occurs in a person who has had cancer in the past, second primary cancers may occur months or years after the original (primary) cancer was diagnosed and treated.

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Approved Indications

Oncology-related approved indications of each product are described in the following table:

Product	FDA approved Indication
Camcevi (leuprolide injectable emulsion)	For the treatment of adult patients with advanced prostate cancer
Eligard (leuprolide acetate)	For palliative treatment of advanced prostate cancer
Firmagon (degarelix)	For the treatment of patients with advanced prostate cancer
Lupron	For the treatment of patients with advanced prostate cancer Used as a single agent for persistent disease or recurrence of ovarian cancer (epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer) and for clinical relapse of stage II-IV granulosa cell tumors (NCCN 2A recommendations)
Trelstar (triptorelin pamoate)	For the treatment of advanced prostate cancer
Zoladex (goserelin implant)	Use in combination with flutamide for the management of locally confined carcinoma of the prostate [Stage T2b-T4 (Stage B2-C)]
	Palliative treatment of advanced carcinoma of the prostate
	Palliative treatment of advanced breast cancer in pre- and perimenopausal women

Summary of FDA-approved Non-Oncology related indications and commercially available GnRH Agents:

Agent	Endo	IET	CPP	UL
Lupron Depot (leuprolide acetate) 1 month, 3 month, 6-month	x			x
Zoladex (goserelin acetate) 1 month	x	x		
Synarel (nafarelin acetate) 1 month	x		x	
Lupron Depot-Ped (leuprolide acetate) 1 month, 3 month, 6-month			x	
Supprelin LA (histrelin acetate) 12 month			x	
Triptodur (triptorelin) 6 month			x	
Fensolvi (leuprolide acetate) injectable suspension 45 mg kit			x	

Endo = Endometriosis, IET = Induce Endometrial Thinning, CPP = Central Precocious Puberty, UL = Uterine Leiomyomata (fibroids)

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Other Uses

The uses of GnRH analogs considered to be medically necessary for the treatment of oncology conditions in this document (as described in the background section) have sufficient published evidence available to support them. However, there is a lack of scientific evidence found from which conclusions could be made concerning the safety and efficacy of treating various other oncologic indications, including, but not limited to cancers of the endometrium and liver. Currently there is a lack of evidence to support the use of leuprolide as monotherapy to treat salivary gland tumors.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

- **Non-oncology related indications**

HCPCS	Description
J1675	Injection, histrelin acetate, 10 micrograms
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg [Lupron Depot, Lupron Depot-Ped, Lupaneta Pack]
J1951	Injection, leuprolide acetate for depot suspension (Fensolvi), 0.25 mg
J1954	Injection, leuprolide acetate for depot suspension (Lutrate), 7.5 mg
J3315	Injection, triptorelin pamoate, 3.75 mg [Trelstar, Trelstar Depot, Trelstar LA]
J3316	Injection, triptorelin, extended-release, 3.75 mg [Triptodur]
J9202	Goserelin acetate implant, per 3.6 mg [Zoladex]
J9217	Leuprolide acetate (for depot suspension), 7.5 mg [Eligard, Lupron Depot, Lupron Depot-Ped, Lupaneta Pack]
J9226	Histrelin implant (Supprelin LA), 50 mg
S9560	Home injectable therapy; hormonal therapy (e.g., leuprolide, goserelin), including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10	Description
All diagnoses excluding oncologic diagnoses	

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- **Oncology-related indications**

Breast Cancer Treatment

HCPCS	Description
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg [Lupron Depot 3.75]
J9202	Goserelin acetate implant, per 3.6 mg [Zoladex]
J9218	Leuprolide acetate, per 1 mg [Lupron]
S9560	Home injectable therapy; hormonal therapy (e.g.; leuprolide, goserelin), including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10	Description
C50.011-C50.929	Malignant neoplasm of breast
Z85.3 N95.9	Personal history of malignant neoplasm of breast Menopausal and other premenopausal disorders
C50.011-C50.929	Malignant neoplasm of breast

Ovarian Cancer Treatment

HCPCS	Description
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg [Lupron Depot 3.75, Lupron Depot 3-month 11.25]
J9218	Leuprolide acetate, per 1 mg [Lupron]
S9560	Home injectable therapy; hormonal therapy (e.g.; leuprolide, goserelin), including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10	Description
C48.1-C48.8	Malignant neoplasm of peritoneum
C56.1-C56.9	Malignant neoplasm of ovary
C57.00-C57.9	Malignant neoplasm of other and unspecified female genital organs
Z85.4	Personal history of malignant neoplasm of ovary
N95.9	Menopausal and other premenopausal disorders

Prostate Cancer Treatment

HCPCS	Description
J3315	Injection, triptorelin pamoate, 3.75 mg [Trelstar, Trelstar LA]
J9155	Injection, degarelix, 1 mg [Firmagon]
J9202	Goserelin acetate implant, per 3.6 mg [Zoladex]

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J9217	Leuprolide acetate (for depot suspension), 7.5 mg [Eligard, Lupron Depot 7.5, including 22.5 mg (3-month), 30 mg (4-month), 45 mg (6-month)]
J9218	Leuprolide acetate, per 1 mg [Lupron]
J1952	Leuprolide injectable, [Camcevi], 1 mg
S9560	Home injectable therapy; hormonal therapy (e.g.; leuprolide, goserelin), including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10	Description
C61	Malignant neoplasm of prostate
Z85.46	Personal history of malignant neoplasm of prostate

Salivary Gland Tumor Treatment

HCPCS	Description
J9217	Leuprolide acetate (for depot suspension), 7.5 mg [Eligard 7.5 mg (1 Month), 22.5 mg (3 Month); Lupron Depot 7.5 mg (1 Month), 22.5 mg (3 Month)]
S9560	Home injectable therapy; hormonal therapy (e.g.; leuprolide, goserelin), including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10	Description
C08.0-C08.9	Malignant neoplasm of other and unspecified major salivary glands
Z85.818-Z85.819	Personal history of malignant neoplasm of lip, oral cavity and pharynx

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

For the treatment of non-oncology related conditions: GnRH analogs (Firmagon (degarelix), Zoladex (goserelin acetate), Camcevi, (leuprolide mesylate) Eligard (leuprolide acetate), Lupron Depot (leuprolide acetate), and Trelstar (triptorelin pamoate).

A. Criteria For Initial Approval

Central Precocious Puberty: Fensolvi, Lupron Depot-Ped (leuprolide acetate), Synarel Nasal Spray (nafarelin acetate), Supprelin LA (histrelin acetate subcutaneous implant), and Triptodur (triptorelin pamoate intramuscular extended release) in Central Precocious Puberty (CPP)- Requests may be approved if the following criteria are met:

i. Individual is 14 years of age or younger (clinical judgement; Kaplowitz, et al. 2016); **AND**
ii. Documentation is provided that individual has a diagnosis of central precocious puberty (defined as the beginning of secondary sexual characteristics before age 8 in girls and 9 in boys) (Kaplowitz, et al. 2016); **AND**
iii. Documentation is provided that the diagnosis of CPP has been confirmed by one of the following:
    A. A pubertal response to a gonadotropin hormone (GnRH) agonist test; **OR**
    B. A pubertal level of a third-generation luteinizing hormone (LH) assay; **OR**
    C. A pubertal level of an ultra-sensitive luteinizing hormone (LH) assay; **OR**
    D. A pubertal level on a luteinizing hormone (LH) assay that can detect levels less than 0.2; **AND**
iv. The diagnosis has been confirmed by assessment of bone age versus chronological age.

Gynecologycal Uses: Zoladex (goserelin acetate), Lupron Depot or Lupron Depot-Ped (leuprolide acetate), or Synarel Nasal Spray (nafarelin acetate) in Gynecological uses- Requests may be approved if the following criteria are met:

i. Individual has a diagnosis of chronic pelvic pain (defined as "pain symptoms perceived to originate from pelvic organs or structures typically lasting more than six months…with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor, myofascial, or gynecological dysfunction") (ACOG 2020); **OR**

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ii. Individual is using to induce amenorrhea (such as but not limited to menstruating women diagnosed with severe thrombocytopenia or aplastic anemia);

Requests for Zoladex (goserelin acetate) may be approved if the following criteria are met:

i. Individual is using for treatment of endometriosis and duration of treatment is limited to 6 months; **OR**
ii. Individual is using for dysfunctional uterine bleeding; **OR**
iii. Individual is using for endometrial thinning prior to endometrial ablation for dysfunctional uterine bleeding (3.6 mg implant only).

Requests for Lupron Depot or Lupron Depot-Ped (leuprolide acetate) may be approved if the following criteria are met:

i. Individual is using for initial treatment or retreatment of endometriosis; **OR**
ii. Individual is using for preoperative treatment as adjunct to surgical treatment of uterine fibroids (leiomyoma uteri), such as but not limited to reducing the size of fibroids to allow for a vaginal procedure (AHFS); **OR**
iii. Individual is using prior to surgical treatment (myomectomy or hysterectomy) in those with a diagnosis of confirmed anemia (Letheby et al. 2001, 2017); **OR**
iv. Individual is using for endometrial thinning prior to endometrial ablation for dysfunctional uterine bleeding.

Synarel (nafarelin acetate)

i. Requests for Synarel (nafarelin acetate) may be approved if the following criteria are met:
    a. Individual is using for endometriosis; **AND**
    b. Duration of treatment with agent is limited to 6 months

Gender Dysphoria/Incongruence in Adolescents: Zoladex (goserelin acetate), Supprelin LA (histrelin acetate), Fensolvi, Lupron Depot or Lupron Depot-Ped (leuprolide acetate), Synarel Nasal Spray (nafarelin acetate), and Triptodur (triptorelin pamoate intramuscular extended release)

i. Individual has a diagnosis of gender dysphoria/incongruence (Coleman 2022).

B. Criteria For Continuation of Therapy

i. Continuation requests for chronic pelvic pain may approved if the following criterion is met:
    a. Individual has confirmation of symptomatic relief.
    b. Requests for continuation for chronic pelvic pain may not be approved if the patient has no symptomatic relief of chronic pelvic pain.

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ii. Continuation requests for leuprolide (up to 12 months) for endometriosis may be approved if the following criterion is met:
   a. Patient experienced recurrence of symptoms

C. Authorization Duration

i. For Chronic Pelvic Pain:
   A. Initial Approval Duration: 3 months
   B. Reauthorization Approval Duration: 3 months

ii. For Endometriosis:
   A. Initial Approval Duration: 6 months
   B. Reauthorization Approval Duration: A single additional course of leuprolide acetate may be approved for 6 months (total duration of therapy should not exceed 12 months). For Synarel and Zoladex, the total duration of therapy should not exceed 6 months.

iii. For uterine fibroids (leiomyoma uteri): Total Therapy should not exceed 3 months.

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Requests for Fensolvi, Lupron Depot-Ped (leuprolide acetate), Synarel Nasal Spray (nafarelin acetate), Supprelin LA (histrelin acetate subcutaneous implant), or Triptodur (triptorelin pamoate intramuscular extended release) may not be approved if the following criteria are met:
   a. Individual is diagnosed with peripheral precocious puberty; **OR**
   b. Individual is diagnosed with benign or non-progressive precocious puberty

For the treatment of oncology-related conditions: GnRH analogs (Firmagon (degarelix), Zoladex (goserelin acetate), Camcevi, (leuprolide mesylate) Eligard (leuprolide acetate), Lupron Depot (leuprolide acetate), and Trelstar (triptorelin pamoate).

A. Criteria For Initial Approval

Firmagon (degarelix)

Requests for Firmagon (degarelix) may be approved if the following criteria are met:

i. Individual is using for the treatment of prostate cancer and any of the following are met:
   A. Used as androgen deprivation therapy as a single agent or in combination with an antiandrogen; **OR**

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B. Used for clinically localized disease with intermediate (T2b to T2c cancer, Gleason score of 7/Gleason grade group 2-3, or prostate specific antigen (PSA) value of 10-20 ng/mL) or higher risk of recurrence as neoadjuvant therapy with radiation therapy or cryosurgery; **OR**
C. Used for progressive castration-naïve disease; **OR**
D. Used for castration-recurrent disease; **OR**
E. Other advanced, recurrent, or metastatic disease;

OR

ii. Individual is using in the preservation of fertility in pre-menopausal women; **AND**
iii. Individual currently has a cancer diagnosis; **AND**
iv. Individual meets one of the following:
A. Individual will receive chemotherapy for cancer with a curative intent; **OR**
B. Individual will receive radiation therapy for cancer with a curative intent.

Trelstar (triptorelin pamoate)

Requests for Trelstar (triptorelin pamoate) may be approved if the following criteria are met:

i. Individual is using for the treatment of prostate cancer and any of the following are met:
A. Used as androgen deprivation therapy as a single agent or in combination with an antiandrogen; **OR**
B. Used for clinically localized disease with intermediate (T2b to T2c cancer, Gleason score of 7/Gleason grade group 2-3, or prostate specific antigen (PSA) value of 10-20 ng/mL) or higher risk of recurrence as neoadjuvant therapy with radiation therapy or cryosurgery; **OR**
C. Used for progressive castration-naïve disease; **OR**
D. Used for castration-recurrent disease; **OR**
E. Other advanced, recurrent, or metastatic disease.

OR

ii. Individual is using for the treatment of men and pre-, or peri-menopausal women with hormone receptor positive breast cancer (Pagani, 2014);

OR

iii. Individual is using in the preservation of fertility in pre-menopausal women; **AND**
iv. Individual currently has a cancer diagnosis; **AND**
v. Individual meets one of the following:
A. Individual will receive chemotherapy for cancer with a curative intent; **OR**
B. Individual will receive radiation therapy for cancer with a curative intent.

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Zoladex (goserelin acetate)

Requests for Zoladex (goserelin acetate) may be approved if the following criteria are met:

i. Individual has a diagnosis of breast cancer, men and pre-, or peri-menopausal women with hormone receptor positive breast cancer;

OR

ii. Individual is using for the treatment of prostate cancer and any of the following are met:
   A. Used as androgen deprivation therapy as a single agent or in combination with an antiandrogen; **OR**
   B. Used for clinically localized disease with intermediate (T2b to T2c cancer, Gleason score of 7/Gleason grade group 2-3, or prostate specific antigen (PSA) value of 10-20 ng/mL) or higher risk of recurrence as neoadjuvant therapy with radiation therapy or cryosurgery; **OR**
   C. Used for progressive castration-naïve disease; **OR**
   D. Used for castration-recurrent disease; **OR**
   E. Other advanced, recurrent, or metastatic disease.

OR

iii. Individual is using in the preservation of fertility in pre-menopausal women; **AND**
iv. Individual currently has a cancer diagnosis; **AND**
v. Individual meets one of the following:
   A. Individual will receive chemotherapy for cancer with a curative intent; **OR**
   B. Individual will receive radiation therapy for cancer with a curative intent.

Leuprolide acetate (Eligard, Lupron Depot), leuprolide acetate (immediate release), and leuprolide mesylate (Camcevi)

Requests for leuprolide acetate (Eligard, Lupron Depot) may be approved if the following criteria are met:

i. Individual is using for the treatment of salivary gland tumors (NCCN 2A); **AND**
   A. Individual has androgen receptor positive recurrent disease with distant metastases; **AND**
   B. Individual has a current Easter Cooperative Oncology Group (ECOG) performance status of 0-3.

Requests for leuprolide acetate (Eligard, Lupron Depot), *leuprolide acetate (immediate release),* or leuprolide mesylate (Camcevi) may be approved if the following criteria are met:

i. Individual is using for the treatment of prostate cancer and any of the following are met:
   A. Used as androgen deprivation therapy as a single agent or in combination with an antiandrogen; **OR**
   B. Used for clinically localized disease with intermediate (T2b to T2c cancer, Gleason score of 7/Gleason grade group 2-3, or prostate specific antigen (PSA) value of 10-20 ng/mL) or higher risk of recurrence as neoadjuvant therapy with radiation therapy or cryosurgery; **OR**

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C. Used for progressive castration-naïve disease; **OR**
D. Used for castration-recurrent disease; **OR**
E. Other advanced, recurrent, or metastatic disease.

<u>Requests for leuprolide acetate (Lupron Depot and Eligard) may be approved if the following criteria are met:</u>

i. Individual is using for the treatment of ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) and the following are met:
   A. Hormonal therapy for clinical relapse in individuals with stage II-IV granulosa cell tumors; **OR**
   B. Hormonal therapy for treatment of epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer as a single agent for persistent disease or recurrence;

OR

ii. Individual is using for the treatment of men and pre-, or peri-menopausal women with hormone receptor positive breast cancer.

<u>Requests for leuprolide acetate (Eligard, Lupron Depot), leuprolide acetate (immediate release) may be approved if the following criteria are met:</u>

i. Individual is using in the preservation of fertility in pre-menopausal women; **AND**
ii. Individual currently has a cancer diagnosis; **AND**
iii. Individual meets one of the following:
   A. Individual will receive chemotherapy for cancer with a curative intent; **OR**
   B. Individual will receive radiation therapy for cancer with a curative intent.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of GnRH therapy medically necessary in members requesting reauthorization for an oncology-related indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen. The following information should be submitted for reauthorization:
   A. A current oncology note documenting the patient's response to treatment showing no progression of disease.
   Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results (every six months)

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

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D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

Requests for leuprolide acetate (Lupron, Lupron Depot) may not be approved for the following:

ii. Individual is pre-menopausal and diagnosed with non-invasive ductal carcinoma in situ (DCIS) of the breast.

Limits or Restrictions

A. Therapeutic Alternatives

This medical policy may be subject to Step Therapy. Please refer to the document published on the MMM Website: https://www.mmm-pr.com/planes-medicos/formulario-medicamentos

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

- **For the treatment of non-oncology related conditions:**

Drug	Limit
Fensolvi (leuprolide acetate) 45 mg kit	1 kit per 24 weeks (6 months)
Lupron Depot (leuprolide acetate) 3.75 mg, 7.5 mg	1 kit per 4 weeks
Lupron Depot (leuprolide acetate) 11.25 mg, 22.5 mg	1 kit per 12 weeks
Lupron Depot (leuprolide acetate) 30 mg	1 kit per 16 weeks
Lupron Depot (leuprolide acetate) 45 mg	1 kit per 24 weeks (6 months)
Lupron Depot Ped (leuprolide acetate) (1-month kit) 7.5, 11.25 or 15 mg	1 kit per 4 weeks
Lupron Depot Ped (leuprolide acetate) (3-month kit) 11.25 or 30 mg	1 kit per 12 weeks
Lupron Depot Ped (leuprolide acetate) 45 mg	1 kit per 24 weeks
Supprelin LA (histrelin acetate) 50 mg	1 implant per year
Synarel (nafarelin acetate) 2 mg/mL (60 sprays/bottle)	5 bottles per 30 days
Triptodur (triptorelin) 22.5mg kit	1 kit per 24 weeks (6 months)
Zoladex (goserelin acetate) 3.6 mg Implant	1 per 4 weeks
Zoladex (goserelin acetate) 10.8 mg Implant	1 per 12 weeks

- **For the treatment of oncology-related conditions:**

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Product	*FDA-approved Indication*	*Recommended Dosage*
Camcevi (leuprolide injectable emulsion)	Advanced prostate cancer	• 42 mg administered subcutaneously once every 6 months
Eligard (leuprolide acetate)	Advanced prostate cancer	• 7.5 mg every month • 22.5 mg every 3 months • 30 mg every 4 months • 45 mg every 6 months
Firmagon (degarelix)	Advanced prostate cancer	Starting Dose: 240 mg given as two subcutaneous injections of 120 mg at a concentration of 40 mg/mL Maintenance dose: (28 days after the starting dose) 80 mg given as one subcutaneous injection at a concentration of 20 mg/mL •
Lupron	Advanced prostate cancer	• 7.5 mg for 1-month administration, given as a single intramuscular injection every 4 weeks. • 22.5 mg for 3-month administration, given as a single intramuscular injection every 12 weeks. • 30 mg for 4-month administration, given as a single intramuscular injection every 16 weeks. • 45 mg for 6-month administration, given as a single intramuscular injection every 24 weeks.
Trelstar (triptorelin pamoate)	Advanced prostate cancer	• 3.75 mg every 4 weeks • 11.25 mg every 12 weeks • 22.5 mg every 24 weeks
Zoladex (goserelin implant)	Use in combination with flutamide for the management of locally confined carcinoma of the	Treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy.

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	prostate [Stage T2b-T4 (Stage B2-C)]	• A treatment regimen using a Zoladex 3.6 mg depot 8 weeks before radiotherapy, followed in 28 days by the Zoladex 10.8 mg depot, can be administered. • Alternatively, four injections of 3.6 mg depot can be administered at 28-day intervals, two depots preceding and two during radiotherapy.
	Advanced Prostate Cancer	3.6 mg should be administered subcutaneously every 28 days
	Advanced breast cancer in pre- and perimenopausal women	3.6 mg should be administered subcutaneously every 28 days
Exceptions		
** Firmagon has a starting dose package of 240 mg given as two subcutaneous injections of 120 mg at a concentration of 40 mg/mL. Maintenance dose (administered 28 days after starting dose) is 80 mg given as one subcutaneous injection at a concentration of 20 mg/mL		

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T	MPCC

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