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Subject: Gonadotropin Releasing Hormone Analogs and Antagonists

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DESCRIPTION:

Leuprolide, histrelin, goserelin and triptorelin are gonadotropin-releasing hormone agonists (GnRH agonist, GnRH–A) that are synthetic peptides modeled after the hypothalamic neurohormone GnRH that interacts with the gonadotropin-releasing hormone receptor to elicit its biologic response (i.e., the release of the pituitary hormones FSH and LH). Agonists do not quickly dissociate from the GnRH receptor and as a result initially there is an increase in FSH and LH secretion. However, after about ten days a profound hypogonadal effect (decrease in FSH and LH) is achieved through receptor downregulation by internalization of receptors. Generally, this induced and reversible hypogonadism is the therapeutic goal.

Degarelix, an injectable gonadotrophin-releasing hormone (GnRH) antagonist, belongs to a class of compounds that are structurally similar to natural GnRH but have an antagonistic effect. Injectable GnRH antagonists are peptide molecules made up multiple, often synthetically produced, amino acids. In December 2020, an oral, non-peptide, small molecule GnRH receptor antagonist for the treatment of advanced prostate cancer, called relugolix (Orgovyx), was approved by the FDA. Relugolix is the second oral GnRH receptor antagonist approved by the FDA, but the first approved for the treatment of prostate cancer. Elagolix (Orilissa) was the first oral GnRH receptor antagonist to be approved; however, it is FDA-approved for the treatment of moderate pain or severe pain associated with endometriosis.

GnRH antagonists compete with natural GnRH for binding to GnRH receptors, thus decreasing or blocking GnRH action in the body. GnRH antagonists competitively bind to GnRH receptors in the pituitary gland, blocking the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. In men, the reduction in LH subsequently leads to rapid suppression of testosterone release from the testes; in women it leads to suppression of estrogen release from the ovaries. Unlike

the GnRH agonists, which cause an initial stimulation of the hypothalamic-pituitary-gonadal axis (HPGA), leading to a surge in testosterone or estrogen levels, GnRH antagonists have an immediate onset of action, rapidly reducing sex hormone levels without an initial surge.

The safety and efficacy of relugolix was assessed in a randomized, open label study in men with advanced prostate cancer requiring at least 1 year of androgen deprivation therapy (HERO, NCT03085095). Eligible patients (median age of 71 years) had evidence of biochemical or clinical relapse after local primary intervention with curative intent (50.2%), newly diagnosed hormone-sensitive metastatic disease (22.7%), or advanced localized disease unlikely to be cured by local primary intervention with curative intent (27.1%). Compared with leuprolide depot injection (n=308), relugolix (n=622) resulted in a significantly greater proportion of patients with sustained testosterone suppression below castrate levels (<50 ng]/dL) from day 29 through 48 weeks (96.7% vs. 88.8%). Relugolix also more rapidly reduced testosterone levels. Relugolix did not meet an important secondary endpoint, that of castration resistance-free survival (CRFS), compared with leuprolide in patients with metastatic disease. CRFS was defined as the time from first dose to PSA progression or death from any cause despite castrate levels of testosterone. Over 48 weeks, 74% of patients with metastatic disease in the relugolix arm had CRFS vs. 75% of those in the leuprolide arm (HR, 1.03; 95% CI, 0.68 to 1.57; p=0.84). The incidence of major adverse cardiovascular events (MACE) after 48 weeks of treatment was reduced with relugolix by 54% (2.9% vs. 6.2%; HR, 0.46 [95% CI, 0.24 to 0.88]). In the subgroup of men with a reported history of MACE, the relugolix group had 80% fewer MACE events (3.6% vs. 17.8%).

POSITION STATEMENT:

NOTE: Coverage for gender-affirming treatment is subject to the member's benefit terms, limitations and maximums. Refer to specific contract language regarding gender reassignment. Coverage may be governed by state or federal regulation.

The following medications **meet the definition of medical necessity** when administered for treatment of an indication listed in Table 1, the medication is not used concomitantly with another GnRH agonist or antagonist, and the condition specific and maximum allowable dose criteria are met:

Table 1

Indications and specific criteria	
Medication	**Condition Specific Criteria**
Leuprolide acetate solution (non-depot formulation)	**INITIATION CRITERIA:** The member is diagnosed with **ANY** of the following, and **ALL** associated criteria are met: 1. Prostate cancer when dosage does not exceed 1 mg daily **Approval Duration: 1 year**

	2. Persistent or recurrent epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer following primary chemotherapy when dosage does not exceed 1 mg daily **Approval Duration: 1 year** 3. Relapsed granulosa cell tumors of the ovary (a type of malignant sex cord-stromal tumor) following primary chemotherapy or radiation therapy when dosage does not exceed 1 mg daily **Approval Duration: 1 year** 4. Salivary gland tumor in members meeting **BOTH** of the following criteria when the dosage does not exceed 1 mg daily: a. **ANY** of the following: • Member has distant metastatic disease • Member has an unresectable locoregional recurrence • Member has a second primary tumor following prior radiation therapy b. Member's disease is androgen receptor (AR) positive **Approval Duration: 1 year** 5. Invasive breast cancer in pre- and peri-menopausal biological females or in biological males* with hormone-receptor positive disease (ER+ and/or PR+) when dosage does not exceed 1 mg daily *For biological males, must be used in combination with aromatase inhibitor therapy **Approval Duration: 1 year** 6. Member has <u>suspected</u> central precocious puberty (CPP) **AND** meets the following: a. Leuprolide acetate is being used as part of a stimulation test to help diagnose CPP b. Only a single dose will be given that does not exceed 20 mcg/kg (up to maximum of 500 mcg) **Approval Duration:** single dose to be given within 1 month of approval

	CONTINUATION CRITERIA: Continuation of leuprolide acetate therapy meets the definition of medical necessity when **ALL** of the following are met: 1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of prostate cancer, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, granulosa cell tumors of the ovary, or salivary gland tumor, **OR** the member previously met all-specific initiation criteria. 2. Member has demonstrated a beneficial response to therapy (exception for prostate cancer in which use can be continued despite disease progression) 3. The dosage does not exceed 1 mg daily **Approval Duration: 1 year**
Leuprolide acetate suspension for intramuscular depot administration [Lupron Depot 1-Month, Lupron Depot 3-Month, Lupron Depot 4-Month, Lupron Depot 6-Month, and leuprolide acetate injection depot 22.5 mg (Lutrate Depot)	**INITIATION CRITERIA:** The member is diagnosed with **ANY** of the following, and **ALL** associated criteria are met: 1. Endometriosis (including adenomyosis, also known as endometriosis interna) when dosage does not exceed 3.75 mg every 4 weeks (28 days) or 11.25 mg every 12 weeks (84 days), **Approval Duration: 6 months** 2. Uterine leiomyomata (fibroids) for **EITHER** of the following when dosage does not exceed 3.75 mg every 4 weeks (28 days) or 11.25 mg every12 weeks (84 days) a. Preoperative treatment for reducing uterine and myoma volume to improve surgical outcomes and/or allow a less invasive surgical procedure b. Prior to surgical treatment (myomectomy or hysterectomy) in individuals with documented anemia **AND** used concomitantly with iron therapy **Approval Duration: 3 months** 3. Preservation (suppression) of ovarian function in premenopausal biological females receiving chemotherapy when dosage does not

	exceed 7.5 mg every 4 weeks (28 days) [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]: **Approval Duration: 1 year** 4. Prostate cancer when dosage does not exceed 7.5 mg every 4 weeks (28 days) [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]: **Approval Duration: 1 year** 5. Persistent or recurrent epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer following primary chemotherapy when dosage does not exceed 7.5 mg every 4 weeks (28 days) [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]. **Approval Duration: 1 year** 6. Relapsed granulosa cell tumors of the ovary (a type of malignant sex cord-stromal tumor) following primary chemotherapy or radiation therapy when dosage does not exceed 7.5 mg every 4 weeks (28 days) [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)] **Approval Duration: 1 year** 7. Salivary gland tumor in members meeting **BOTH** of the following criteria when the dosage does not exceed 7.5 mg every 28 days [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]: a. **ANY** of the following: • Member has distant metastatic disease • Member has an unresectable locoregional recurrence • Member has a second primary tumor following prior radiation therapy b. Member's disease is androgen receptor (AR) positive

	Approval Duration: 1 year 8. Invasive breast cancer in pre- and peri-menopausal biological females or in biological males* with hormone-receptor positive disease (ER+ and/or PR+) when dosage does not exceed 7.5mg every 4 weeks (28 days) [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)] *For biological males, must be used in combination with aromatase inhibitor therapy **Approval Duration: 1 year** 9. Gender dysphoria [previously known as gender identity disorder (GID)] in adults meeting **ALL** of the following criteria: a. The member is 18 years of age or older b. The diagnosis of gender dysphoria (per DSM-V criteria for adolescents and adults) has been confirmed by a licensed mental health professional – documentation must be submitted c. Treatment will be used to reduce the member's levels of endogenous hormones (e.g., testosterone or estrogen) d. The member is determined, by a licensed mental health professional, to have the capacity to make fully informed decisions and provide consent for treatment e. Any significant medical or mental health concerns (if present) are reasonably well-controlled f. Dosage does not exceed 7.5 mg every 4 weeks (28 days) [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]: **Approval Duration: 1 year** **CONTINUATION CRITERIA:** Continuation of leuprolide acetate suspension for intr**a**muscular depot administration (Lupron Depot 1-Month, Lupron Depot 3-Month, Lupron Depot 4-Month, Lupron Depot 6-Month) therapy **meets the definition of medical necessity** when **ALL** of the following are met: 1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the

	treatment of endometriosis, prostate cancer, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, adult gender dysphoria, granulosa cell tumors of the ovary, or salivary gland tumor, **OR** the member previously met all indication-specific initiation criteria. 2. Continuation is **NOT** permitted for uterine leiomyomata (fibroids) or preservation of ovarian function (see initiation criteria if recurrence of leiomyomata following surgery, or if a new line of chemotherapy is started and ovarian preservation is needed) 3. Member has demonstrated a beneficial response to therapy (exception for prostate cancer in which use can be continued despite disease progression) 4. The member's dosage does not exceed any of the following indications-specific dosages: a. Endometriosis - 3.75 mg every 4 weeks (28 days) or 11.25 mg every 12 weeks (84 days) b. Prostate cancer, breast cancer, epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, granulosa cell tumors of the ovary, salivary gland tumor, or gender dysphoria in an adult (≥18 years old) – 7.5 mg every 4 weeks (28 days) [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]: 5. For endometriosis only, at least **ONE** of the following: a. The member has not been previously authorized for continuation of treatment, or has not already received more than 1 year of treatment with leuprolide or goserelin for their endometriosis b. The member is not a candidate for surgery, and requires continuous medical treatment **Approval Duration: 1 year**
Leuprolide acetate and norethindrone acetate kit (Lupaneta Pack)	**INITIATION CRITERIA:** **BOTH** of the following: 1. The member is diagnosed with endometriosis (including adenomyosis, also known as endometriosis interna) 2. The dosage does not exceed 3.75 mg depot suspension of leuprolide acetate and 30 5-mg (150 mg total) norethindrone acetate tablets every month, or 11.25 mg depot suspension of leuprolide acetate and 90 5-mg (450 mg total) norethindrone acetate tablets every 3 months

	Approval Duration: 6 months **CONTINUATION CRITERIA:** Continuation of leuprolide acetate and norethindrone acetate (Lupaneta Pack) therapy **meets the definition of medical necessity** when **ALL** of the following are met: 1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of endometriosis, **OR** the member previously met all indication-specific initiation criteria 2. Member has demonstrated a beneficial response to therapy 3. At least **ONE** of the following: a. The member has not been previously authorized for continuation of treatment, or has not already received more than 1 year of treatment with leuprolide or goserelin for their endometriosis b. The member is not a candidate for surgery, and requires continuous medical treatment 4. Dosage does not exceed 3.75 mg depot suspension of leuprolide acetate and 30 5-mg (150 mg total) norethindrone acetate tablets every month, or 11.25 mg depot suspension of leuprolide acetate and 90 (450 mg) norethindrone acetate tablets every 3 months **Approval Duration: 1 year**
Leuprolide acetate suspension for intramuscular depot administration in children (Lupron Depo-Ped)	**INITIATION CRITERIA:** The member is diagnosed with **EITHER** of the following, all associated criteria are met, and the dosage does not exceed 15 mg every 4 weeks (28 days) [includes 7.5 mg, 11.25 mg, and 15 mg given every 4 weeks (28 days), 11.25 mg and 30 mg given every 12 weeks (84 days), and 45 mg given every 24 weeks (168 days)]: 1. Central Precocious Puberty (CPP) and **ALL** of the following criteria are met. a. Onset of secondary sexual characteristics occurred earlier than age 8 years in females or age 9 years in males b. Confirmed diagnosis by either a pubertal basal level of luteinizing hormone (LH) (based on laboratory reference range) **OR** a pubertal response to a GnRH or leuprolide acetate stimulation test c. Member is less than 13 years of age **Approval Duration: 1 year**

	2. Gender dysphoria [previously known as gender identity disorder (GID)] in children or adolescents meeting **ALL** of the following criteria: a. The member is less than 18 years of age b. The diagnosis of gender dysphoria [per DSM-V criteria for adolescents and adults (ages 12 to 17 years) or criteria for children (ages <12 years)] has been confirmed by a licensed mental health professional – documentation must be submitted c. Treatment will be used for the suppression of puberty d. Member has experienced puberty to at least Tanner stage 2 e. Gender dysphoria emerged or worsened with the onset of puberty f. The member is determined, by a licensed mental health professional, to have the capacity to make fully informed decisions and provide consent for treatment g. Any significant medical or mental health concerns (if present) are reasonably well-controlled h. Treatment is supervised by a board-certified pediatric endocrinologist **Approval Duration: 1 year** **CONTINUATION CRITERIA:** Continuation therapy of leuprolide acetate (Lupron Depo-Ped®) **meets the definition of medical necessity** when **ALL** of the following are met: 1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of CPP or pediatric/adolescent gender dysphoria, **OR** the member previously met all indication-specific initiation criteria 2. Member has demonstrated a beneficial response to therapy 3. **EITHER** of the following: a. CPP - member is less than 13 years old b. Gender dysphoria – member is less than 18 years old

	4. Dosage does not exceed 15 mg every 4 weeks (28 days) [includes 7.5 mg, 11.25 mg, and 15 mg given every 4 weeks (28 days) and 11.25 mg and 30 mg given every 12 weeks (84 days)] **Approval Duration: 1 year**
Leuprolide acetate suspension for subcutaneous depot administration (Eligard)	**INITIATION CRITERIA:** The member is diagnosed with **ANY** of the following, and **ALL** associated criteria are met: 1. Prostate cancer when the dosage does not exceed 7.5 mg every 28 days [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]: **Approval Duration: 1 year** 2. Invasive breast cancer in pre- and peri-menopausal biological females or in biological males* with hormone-receptor positive disease (ER+ and/or PR+) when the dosage does not exceed 7.5 mg every 28 days [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]. *For biological males, must be used in combination with aromatase inhibitor therapy **Approval Duration: 1 year** 3. Persistent or recurrent epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer following primary chemotherapy when the dosage does not exceed 7.5 mg every 28 days [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]. **Approval Duration: 1 year** 4. Relapsed granulosa cell tumors of the ovary (a type of malignant sex cord-stromal tumor) following primary chemotherapy or radiation therapy when the dosage does not exceed 7.5 mg every 28 days [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]: **Approval Duration: 1 year**

	5. Salivary gland tumor in members meeting **BOTH** of the following criteria when the dosage does not exceed 7.5 mg every 28 days [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]: a. **ANY** of the following: • Member has distant metastatic disease • Member has an unresectable locoregional recurrence • Member has a second primary tumor following prior radiation therapy b. Member's disease is androgen receptor (AR) positive **Approval Duration: 1 year** 6. Gender dysphoria [previously known as gender identity disorder (GID)] in adults meeting **ALL** of the following criteria: a. The member is 18 years of age or older b. The diagnosis of gender dysphoria (per DSM-V criteria for adolescents and adults) has been confirmed by a licensed mental health professional – documentation must be submitted c. Treatment will be used to reduce the member's levels of endogenous hormones (e.g., testosterone or estrogen) d. The member is determined, by a licensed mental health professional, to have the capacity to make fully informed decisions and provide consent for treatment e. Any significant medical or mental health concerns (if present) are reasonably well-controlled f. Dosage does not exceed 7.5 mg every 28 days [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)]: **Approval Duration: 1 year** **CONTINUATION CRITERIA:** Continuation of leuprolide acetate (Eligard) therapy **meets the definition of medical necessity** when **ALL** of the following are met: 1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of prostate cancer, breast cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, gender

	dysphoria, granulosa cell tumors of the ovary, or salivary gland tumor, **OR** the member previously met all indication-specific initiation criteria 2. Member has demonstrated a beneficial response to therapy (exception for prostate cancer in which use can be continued despite disease progression) 3. Dosage does not exceed 7.5 mg every 28 days [includes 22.5 mg every 3 months (84 days), 30 mg every 4 months (112 days), and 45 mg every 6 months (168 days)] **Approval Duration: 1 year**
Leuprolide mesylate emulsion for subcutaneous depot administration (Camcevi) [6-month formulation]	**INITIATION AND CONTINUATION CRITERIA:** The member is diagnosed with prostate cancer and the dosage does not exceed 42 mg every 6 months (168 days) **Approval Duration: 1 year**
Leuprolide mesylate emulsion for subcutaneous depot administration (Camcevi ETM) [3-month formulation]	**INITIATION AND CONTINUATION CRITERIA:** The member is diagnosed with prostate cancer and the dosage does not exceed 21 mg every 3 months (84 days) **Approval Duration**: 1 year
Leuprolide acetate suspension for subcutaneous depot administration (Fensolvi)	**INITIATION CRITERIA:** The member is diagnosed with the following and all associated criteria are met: 1. Central Precocious Puberty (CPP) when **ALL** of the following criteria are met. a. Onset of secondary sexual characteristics occurred earlier than age 8 years in females or age 9 years in males b. Diagnosis has been confirmed by either a pubertal basal level of luteinizing hormone (LH) (based on laboratory reference range) **OR** a pubertal response to GnRH or leuprolide acetate stimulation test c. Member is less than 13 years of age d. Dosage of leuprolide acetate suspension does not exceed 45 mg every 6 months **Approval Duration: 1 year** **CONTINUATION CRITERIA:**

	Continuation of leuprolide acetate suspension (Fensolvi) therapy **meets the definition of medical necessity** when **ALL** of the following are met: 1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of CPP, **OR** the member previously met all indication-specific initiation criteria 2. Member has demonstrated a beneficial response to therapy 3. Dosage of leuprolide acetate suspension does not exceed 45 mg every 6 months 4. The member is less than 13 years of age **Approval Duration: 1 year**
Histrelin acetate subcutaneous implant (Supprelin LA)	**INITIATION CRITERIA:** The member is diagnosed with **EITHER** of the following, all associated criteria are met, and the dosage does not exceed 50 mg every 12 months: 1. Central Precocious Puberty (CPP) and **ALL** of the following criteria are met. a. Onset of secondary sexual characteristics occurred earlier than age 8 years in females or age 9 years in males b. Confirmed diagnosis by either a pubertal basal level of luteinizing hormone (LH) (based on laboratory reference range) **OR** a pubertal response to a GnRH or leuprolide acetate stimulation test c. Member is less than 13 years of age **Approval Duration: 1 year** 2. Gender dysphoria [previously known as gender identity disorder (GID)] in children or adolescents meeting **ALL** of the following criteria: a. The member is less than 18 years of age b. The diagnosis of gender dysphoria [per DSM-V criteria for adolescents and adults (ages 12 to 17 years) or criteria for children (ages <12 years)] has been confirmed by a licensed mental health professional – documentation must be submitted c. Treatment will be used for the suppression of puberty

	d. Member has experienced puberty to at least Tanner stage 2 e. Gender dysphoria emerged or worsened with the onset of puberty f. The member is determined, by a licensed mental health professional, to have the capacity to make fully informed decisions and provide consent for treatment g. Any significant medical or mental health concerns (if present) are reasonably well-controlled h. Treatment is supervised by a board-certified pediatric endocrinologist **Approval Duration: 1 year** **CONTINUATION CRITERIA:** Continuation of histrelin acetate (Supprelin® LA) implant therapy **meets the definition of medical necessity** when **ALL** of the following are met: 1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of CPP or gender dysphoria, **OR** the member previously met all indication-specific initiation criteria 2. Member has demonstrated a beneficial response to therapy 3. **EITHER** of the following: a. CPP - member is less than 13 years old b. Gender dysphoria – member is less than 18 years old 4. Dosage does not exceed 50 mg every 12 months **Approval Duration: 1 year**
Goserelin acetate 3.6 mg subcutaneous implant (4 week) (Zoladex)	**INITIATION CRITERIA:** The member is diagnosed with **ANY** of the following, all associated criteria are met, and dosage does not exceed 3.6 mg every 4 weeks (28 days): 1. Endometriosis (including adenomyosis, also known as endometriosis interna) **Approval Duration: 6 months**

	2. Preservation (suppression) of ovarian function in premenopausal biological females receiving chemotherapy **Approval Duration: 1 year** 3. As an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding **Approval Duration: 8 weeks** 4. Uterine leiomyomata (fibroids) and use is for **EITHER** of the following: a. Preoperative treatment for reducing uterine and myoma volume to improve surgical outcomes and/or allow a less invasive surgical procedure b. Prior to surgical treatment (myomectomy or hysterectomy) in individuals with documented anemia AND used concomitantly with iron therapy **Approval Duration: 3 months** 5. Prostate cancer **Approval Duration: 1 year** 6. Invasive breast cancer in pre- or peri-menopausal biological females or in biological males* with hormone-receptor positive disease (ER+ and/or PR+) *For biological males, must be used in combination with aromatase inhibitor therapy **Approval Duration: 1 year** 7. Gender dysphoria [previously known as gender identity disorder (GID)] in adults meeting **ALL** of the following criteria: a. The member is 18 years of age or older b. The diagnosis of gender dysphoria (per DSM-V criteria for adolescents and adults) has been confirmed by a licensed mental health professional – documentation must be submitted

	c. Treatment will be used to reduce the member's levels of endogenous hormones (e.g., testosterone or estrogen) d. The member is determined, by a licensed mental health professional, to have the capacity to make fully informed decisions and provide consent for treatment e. Any significant medical or mental health concerns (if present) are reasonably well-controlled **Approval Duration: 1 year** 8. Gender dysphoria [previously known as gender identity disorder (GID)] in children or adolescents meeting **ALL** of the following criteria: a. The member is less than 18 years of age b. The diagnosis of gender dysphoria [per DSM-V criteria for adolescents and adults (ages 12 to 17 years) or criteria for children (ages <12 years)] has been confirmed by a licensed mental health professional – documentation must be submitted c. Treatment will be used for the suppression of puberty d. Member has experienced puberty to at least Tanner stage 2 e. Gender dysphoria emerged or worsened with the onset of puberty f. The member is determined, by a licensed mental health professional, to have the capacity to make fully informed decisions and provide consent for treatment g. Any significant medical or mental health concerns (if present) are reasonably well-controlled h. Treatment is supervised by a board-certified pediatric endocrinologist **Approval Duration: 1 year** **CONTINUATION CRITERIA:** Continuation of goserelin acetate (Zoladex®) therapy **meets the definition of medical necessity** when **ALL** of the following are met: 1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of endometriosis, prostate cancer, gender dysphoria, or

	breast cancer, **OR** the member previously met all indication-specific initiation criteria 2. Continuation is not permitted for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding, uterine leiomyomata (fibroids), or preservation of ovarian function (see initiation criteria if recurrence of leiomyomata or bleeding following surgery, or if a new line of chemotherapy is started and ovarian preservation is needed) 3. Member has demonstrated a beneficial response to therapy (exception for prostate cancer in which use can be continued despite disease progression) 4. Dosage does not exceed 3.6 mg every 4 weeks (28 days) 5. For endometriosis only, at least **ONE** of the following: a. The member has not been previously authorized for continuation of treatment, or has not already received more than 1 year of treatment with leuprolide or goserelin for their endometriosis b. The member is not a candidate for surgery, and requires continuous medical treatment **Approval Duration: 1 year**
Goserelin acetate 10.8 mg subcutaneous implant (12 week) (Zoladex 3-Month)	**INITIATION CRITERIA:** The member is diagnosed with **EITHER** of the following, all associated criteria are met, and the dosage does not exceed 10.8 mg every 12 weeks (84 days): 1. Prostate cancer **Approval Duration: 1 year** 2. Invasive breast cancer in pre- or peri-menopausal biological females or in biological males* with hormone-receptor positive disease (ER+ and/or PR+) *For biological males, must be used in combination with aromatase inhibitor therapy **Approval Duration: 1 year** 3. Gender dysphoria [previously known as gender identity disorder (GID)] in adults meeting **ALL** of the following criteria: a. The member is 18 years of age or older

	b. The diagnosis of gender dysphoria (per DSM-V criteria for adolescents and adults) has been confirmed by a licensed mental health professional – documentation must be submitted c. Treatment will be used to reduce the member's levels of endogenous hormones (e.g., testosterone or estrogen) d. The member is determined, by a licensed mental health professional, to have the capacity to make fully informed decisions and provide consent for treatment e. Any significant medical or mental health concerns (if present) are reasonably well-controlled **Approval Duration: 1 year** 4. Gender dysphoria [previously known as gender identity disorder (GID)] in children or adolescents meeting **ALL** of the following criteria: a. The member is less than 18 years of age b. The diagnosis of gender dysphoria [per DSM-V criteria for adolescents and adults (ages 12 to 17 years) or criteria for children (ages <12 years)] has been confirmed by a licensed mental health professional – documentation must be submitted c. Treatment will be used for the suppression of puberty d. Member has experienced puberty to at least Tanner stage 2 e. Gender dysphoria emerged or worsened with the onset of puberty f. The member is determined, by a licensed mental health professional, to have the capacity to make fully informed decisions and provide consent for treatment g. Any significant medical or mental health concerns (if present) are reasonably well-controlled h. Treatment is supervised by a board-certified pediatric endocrinologist **Approval Duration: 1 year** **CONTINUATION CRITERIA:** Continuation of goserelin acetate (Zoladex) therapy **meets the definition of medical necessity** when **ALL** of the following are met:

	1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of prostate cancer, breast cancer, or gender dysphoria, **OR** the member previously met all indication-specific initiation criteria 2. Member has demonstrated a beneficial response to therapy (exception for prostate cancer in which use can be continued despite disease progression) 3. Dosage does not exceed 10.8 mg every 12 weeks (84 days) **Approval Duration: 1 year**
Triptorelin extended-release injectable suspension for intramuscular use (Triptodur)	**INITIATION CRITERIA:** The member is diagnosed with the following and all associated criteria are met: 2. Central Precocious Puberty (CPP) when **ALL** of the following criteria are met. e. Onset of secondary sexual characteristics occurred earlier than age 8 years in females or age 9 years in males f. Diagnosis has been confirmed by either a pubertal basal level of luteinizing hormone (LH) (based on laboratory reference range) **OR** a pubertal response to GnRH or leuprolide acetate stimulation test g. Member is less than 13 years of age h. Dosage of triptorelin does not exceed 22.5 mg every 24 weeks (168 days) **Approval Duration: 1 year** **CONTINUATION CRITERIA:** Continuation of triptorelin (Triptodur) therapy **meets the definition of medical necessity** when **ALL** of the following are met: 5. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of CPP, **OR** the member previously met all indication-specific initiation criteria 6. Member has demonstrated a beneficial response to therapy 7. Dosage of triptorelin does not exceed 22.5 mg every 24 weeks (168 days) 8. The member is less than 13 years of age

	Approval Duration: 1 year
Triptorelin pamoate suspension for intramuscular depot administration [Trelstar 3.75 mg (4 week), Trelstar 11.25 mg (12 week), Trelstar 22.5 mg (24 week)]	**INITIATION CRITERIA:** The member is diagnosed with **EITHER** of the following, all associated criteria are met, and dosage does not exceed 3.75 mg every 4 weeks (28 days) [includes 11.25 mg every 12 weeks (84 days) and 22.5 mg every 24 weeks (168 days)]: 1. Prostate cancer **Approval Duration: 1 year** 2. Central Precocious Puberty (CPP) when **ALL** of the following criteria are met. a. Onset of secondary sexual characteristics occurred earlier than age 8 years in females or age 9 years in males. b. Confirmed diagnosis by either a pubertal basal level of luteinizing hormone (LH) (based on laboratory reference range) **OR** a pubertal response to GnRH or leuprolide acetate stimulation test. c. Member is less than 13 years of age **Approval Duration: 1 year** 3. Gender dysphoria [previously known as gender identity disorder (GID)] in adults meeting **ALL** of the following criteria: a. The member is 18 years of age or older b. The diagnosis of gender dysphoria (per DSM-V criteria for adolescents and adults) has been confirmed by a licensed mental health professional – documentation must be submitted c. Treatment will be used to reduce the member's levels of endogenous hormones (e.g., testosterone or estrogen) d. The member is determined, by a licensed mental health professional, to have the capacity to make fully informed decisions and provide consent for treatment e. Any significant medical or mental health concerns (if present) are reasonably well-controlled **Approval Duration: 1 year**

	4. Gender dysphoria [previously known as gender identity disorder (GID)] in children or adolescents meeting **ALL** of the following criteria: a. The member is less than 18 years of age b. The diagnosis of gender dysphoria [per DSM-V criteria for adolescents and adults (ages 12 to 17 years) or criteria for children (ages <12 years)] has been confirmed by a licensed mental health professional – documentation must be submitted c. Treatment will be used for the suppression of puberty d. Member has experienced puberty to at least Tanner stage 2 e. Gender dysphoria emerged or worsened with the onset of puberty f. The member is determined, by a licensed mental health professional, to have the capacity to make fully informed decisions and provide consent for treatment g. Any significant medical or mental health concerns (if present) are reasonably well-controlled h. Treatment is supervised by a board-certified pediatric endocrinologist **Approval Duration: 1 year** **CONTINUATION CRITERIA:** Continuation of triptorelin pamoate (Trelstar) therapy **meets the definition of medical necessity** when **ALL** of the following are met: 1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of prostate cancer, CPP, or gender dysphoria, **OR** the member previously met all indication-specific initiation criteria 2. Member has demonstrated a beneficial response to therapy (exception for prostate cancer in which use can be continued despite disease progression) 3. Dosage does not exceed 3.75 mg every 4 weeks (28 days) [includes 11.25 mg every 12 weeks (84 days) and 22.5 mg every 24 weeks (168 days)]: 4. For CPP only, the member must also be under the age of 13 years **Approval Duration: 1 year**

Relugolix (Orgovyx)	**INITIATION CRITERIA:** The member is diagnosed with advanced prostate cancer, and meets **ALL** of the following criteria: 1. The member meets **ANY** of the following: a. Evidence of biochemical (PSA) or clinical relapse after local primary intervention with curative intent b. Newly diagnosed hormone-sensitive metastatic disease [a.k.a., metastatic castration-sensitive prostate cancer (mCSPC)] c. Advanced localized disease unlikely to be cured by local primary intervention with curative intent 2. The initial dose does not exceed 360 mg on the first day, and subsequent doses do not exceed 120 mg once daily **Approval Duration**: 1 year **CONTINUATION CRITERIA:** Continuation of relugolix (Orgovyx) therapy **meets the definition of medical necessity** when **BOTH** of the following are met: 1. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of advanced prostate cancer, **OR** the member previously met all indication-specific initiation criteria 2. Dosage does not exceed 120 mg once daily **Approval Duration**: 1 year
Degarelix (Firmagon)	**INITIATION CRITERIA:** The member is diagnosed with prostate cancer, and the starting dose does not exceed 240 mg and the maintenance dosage does not exceed 80 mg every 28 days. **Approval Duration: 1 year** **CONTINUATION CRITERIA:** Continuation of degarelix (Firmagon) therapy **meets the definition of medical necessity** when **BOTH** of the following are met: 3. Authorization or reauthorization has been previously approved by Florida Blue or another health plan in the past 2 years for the

	treatment of prostate cancer, **OR** the member previously met all indication-specific initiation criteria 4. Dosage does not exceed 80 mg every 28 days **Approval Duration: 1 year**

Gonadotropin releasing hormone analogs and antagonists are considered **experimental or investigational** when administered for all other indications and specifically those listed below (not an all-inclusive list):

- **In-vitro fertilization** – due to evidence that the effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.
- **Infertility** – there is poor documentation regarding efficacy of leuprolide in this medical condition.
- **PCOS (polycystic ovarian syndrome)** – there is poor documentation regarding efficacy of leuprolide in this medical condition.
- **Premenstrual syndrome** – leuprolide does not have FDA approval for PMS and there are numerous other therapies that are effective for this condition.
- **Prostatic hyperplasia** – there is no documentation in drug references of the use of leuprolide in prostatic hyperplasia.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

ENDOMETRIOSIS

- The recommended dose of Lupron Depot 1 month for endometriosis is 3.75 mg (IM) monthly for a maximum recommended duration of 6 months.
- The recommended dose of Lupron Depot 3 Month is 11.25 mg IM every 3 months for a maximum recommended duration of 6 months.
- Zoladex (goserelin acetate): 3.6 mg administered subcutaneously (SQ) every 28 days into the upper abdominal wall below the navel line with a recommended duration of therapy for 6 months.
- Lupaneta Pack: 11.25 mg of leuprolide acetate by IM injection once every 3 months for up to two injections or 3.75 mg of leuprolide acetate by IM injection once a month for up to six injections (6 months of therapy); 5 mg of norethindrone acetate orally once daily for up to 6 months of therapy If the symptoms of endometriosis recur after the initial course of therapy, consider retreatment for up to another six months.

ENDOMETRIAL THINNING

- Zoladex (goserelin acetate): 3.6 mg for 1 or 2 doses (with each depot given four weeks apart). When one depot is administered, surgery should be performed at four weeks. When two depots are

administered, surgery should be performed within two to four weeks following administration of the second depot.

UTERINE LEIOMYOMATA (FIBROIDS)

- The recommended dose of Lupron Depot for uterine leiomyomata is 3.75 mg IM monthly for a maximum of 3 months.
- The recommended dose of Lupron Depot 3 Month for uterine leiomyomata is 11.25 mg IM given as one intramuscular injection.

PROSTATE CANCER

Implant

- Zoladex (goserelin acetate): 10.8 mg administered SQ every 12 weeks into the anterior abdominal wall below the navel. For Stage B2 to C prostatic carcinoma goserelin is given in combination with radiotherapy and flutamide starting treatment 8 weeks prior to initiating radiotherapy and continue during radiation therapy. Administer 3.6 mg goserelin depot 8 weeks before radiotherapy, followed in 28 days by one 10.8 mg goserelin depot. Alternatively, 4 injections of 3.6 mg depot can be administered at 28-day intervals, 2 depots proceeding and 2 during radiotherapy.

Intramuscular

- Lupron Depot 7.5 milligrams should be administered every 4 weeks as an intramuscular injection.
- The recommended dose of Lupron Depot 3 Month is 22.5 mg to be administered as one injection every 12 weeks.
- The recommended dose of Lupron Depot 4 Month is 30 mg to be administered as one injection every 16 weeks.
- The recommended dose of Lupron Depot 6 Month is 45 mg to be administered as one injection every 24 weeks.
- The recommended dose of Lutrate Depot 3 Month is 22.5 mg to be administered as one injection every 12 weeks.
- The recommended dose of Trelstar (triptorelin pamoate) is 3.75 mg IM every 4 weeks, 11.25 mg every 12 weeks, or 22.5 mg every 24 weeks.

Oral

- Initiate treatment of Orgovyx (relugolix) with a loading dose of 360 mg on the first day and continue treatment with a 120 mg dose taken orally once daily at approximately the same time each day.

Subcutaneous

- The recommended dose of Lupron (leuprolide acetate solution) is 1 mg (0.2 mL or 20-unit mark) administered as a single daily subcutaneous injection
- Eligard should be administered 7.5 mg once a month, 22.5 mg once every 3 months, 30 mg once every 4 months and 45 mg once every 6 months.

- Camcevi is recommend at a dosage of 42 mg given subcutaneously once every 6 months.
- Camcevi ETM is recommend at a dosage of 21 mg given subcutaneously once every 3 months.
- Firmagon injection is administered subcutaneously with a starting dose of 240 mg given as 2 injections of 120 mg at a concentration of 40 mg/ml. The maintenance dose is 80 mg given as one subcutaneous injection at a concentration of 20 mg/ml every 28 days.

BREAST CANCER

- The recommended dose of Lupron Depot for breast cancer is 3.75 mg IM monthly.
- Zoladex (goserelin acetate): 3.6 mg SQ every 28 days into the anterior abdominal wall below the navel line.

CENTRAL PRECOCIOUS PUBERTY (CPP)

Intramuscular

- Supprelin LA implant: The approved dose is one 50-mg implant, surgically inserted subcutaneously into the upper arm once every 12 months.
- Lupron Depo-Ped: 7.5 mg IM once every month in children weighing 25 kg or less; 11.25 mg IM once every month in children weighing more than 25 kg to 37.5 kg; and 15 mg IM once every month in children weighing greater than 37.5 kg; the dose can be titrated upward by to the next available higher dose as needed. Either 11.25 mg or 30 mg IM of the 3-month formulation can be given every 3 months (12 weeks). 45 mg IM of the 6-month formulation can be given every 6 months (24 weeks). Unlike the 1-month formulation, specific dosage recommendations based on weight are not provided for the 3- and 6-month formulations. Must only be administered by a healthcare professional.
- Triptodur: a single intramuscular injection of 22.5 mg once every 24 weeks. Must only be administered by a healthcare provider.

Subcutaneous

- Fensolvi: a single subcutaneous injection of 45 mg once every 6 months. Must only be administered by a healthcare professional.

How supplied:

- Camcevi – 42 mg of leuprolide (equivalent to approximately 48 mg leuprolide mesylate) injectable emulsion supplied in a kit as a single-dose, pre-filled syringe. Store under refrigeration at 2°C - 8°C (36°F - 46°F).
- Camcevi ETM – 21 mg of leuprolide (equivalent to approximately 24 mg leuprolide mesylate) injectable emulsion supplied in a kit as a single-dose, pre-filled syringe. Store under refrigeration at 2°C - 8°C (36°F - 46°F).
- Eligard – 7.5 mg (given every month), 22.5 mg (given every 3 months), 30 mg (given every 4 months), and 45 mg (given every 6 months) as a single use kit of a two syringe-mixing system

- Fensolvi - 45 mg of leuprolide acetate supplied in a kit containing Syringe A prefilled with diluent for reconstitution (ATRIGEL Delivery System) and Syringe B prefilled with 45 mg lyophilized leuprolide acetate powder
- Firmagon – 240 mg Kit Carton (two 120 mg vials for initiation dose) and 80 mg Kit Carton (one 80 mg vial for maintenance doses)
- Lutrate Depot – 22.5 mg (given every 12 weeks). Suppled as a kit of a leuprolide acetate MIXJECT single-dose delivery system consisting of a vial of lyophilized leuprolide acetate microspheres incorporated in a biodegradable polymer, a MIXJECT vial adapter containing the needle, and a pre-filled syringe containing mannitol solution for injection
- Leuprolide acetate solution –14-Day Patient Administration Kit (14 mg/2.8 mL multiple-dose vial, 14 disposable syringes, and 28 alcohol swabs)
- Lupaneta Pack - 1-month co-packaged kit (3.75 mg of leuprolide acetate and 5 mg norethindrone acetate 30-count bottle) and 3-month co-package kit (11.25 mg of leuprolide acetate and 5 mg norethindrone acetate 90-count bottle)
- Lupron Depot (for gynecological indications) – 3.75 mg (given every month) and 11.25 mg (given every 3 months) in prefilled syringes
- Lupron Depot (for prostate cancer indication) – 7.5 mg for 1-Month Administration (given every 4 weeks), 22.5 mg for 3-Month Administration (given every 12 weeks), 30 mg for 4-Month Administration (given every 16 weeks), and 45 mg for 6-Month Administration (given every 24 weeks) in prefilled syringes
- Lupron Depo-Ped – 7.5 mg, 11.25 mg, and 15 mg prefilled syringes (given every month), 11.25 mg and 30 mg prefilled syringes (given every 3 months), and 45 mg prefilled syringe (given every 6 months)
- Orgovyx – 120 mg tablets in either 30-count bottles or a blister pack contain 9 tablets
- Supprelin LA - 50 mg implant in a carton containing 2 inner cartons, one for the implant and one for the Implantation Kit
- Trelstar – 3.75 mg (given every 4 weeks), 11.25 mg (given every 12 weeks), and 22.5 mg (given every 24 weeks) as either a single-dose vial or MIXJECT single-dose delivery system
- Triptodur - 22.5 mg single-use kit containing a single-dose vial of lyophilized powder cake, a 2-mL sterile water for injection syringe, and two needles
- Zoladex – 3.6 mg biodegradable implant in a syringe (given every 4 weeks) and 10.8 mg biodegradable implant in a syringe (given every 12 weeks)

PRECAUTIONS:

Contraindications:

Injectable Products:

- Known hypersensitivity to GnRH, GnRH agonist analogues, or any of the components in the product
- Pregnancy (non-prostate cancer indications, also see Embryo-Fetal Toxicity under Warnings)

- Lupaneta Pack only:
  - Known hypersensitivity to norethindrone acetate
  - Undiagnosed abnormal uterine bleeding
  - Women who are breast-feeding
  - Known, suspected or history of breast or other hormone-sensitive cancer
  - Thrombotic or thromboembolic disorders
  - Liver tumors or liver disease

Relugolix:

- None

Precautions/Warnings:

Injectable Products:

- **Loss of Bone Mineral Density**: Extended treatment with GnRH analogs and antagonists may result in a decrease in bone mineral density (BMD), some of which may not be reversible.
- **Initial Rise of Gonadotropins and Sex Steroid Levels/Initial Agonistic Action/Tumor Flare Phenomenon:** During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug (e.g., increased levels of testosterone in men with prostate cancer, and estrogen in women with breast cancer). For treatment of CPP, an increase in clinical signs and symptoms of puberty including vaginal bleeding may be observed during the first weeks of therapy or after subsequent doses. Instruct patients and caregivers to notify the physician if these symptoms continue beyond the second month after administration. For treatment or cancer, transient worsening of symptoms or the occurrence of additional signs and symptoms of prostate or breast cancer, may occasionally develop during the first few weeks of GnRH treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. Isolated cases of ureteral obstruction and spinal cord compression have been observed in patients treated with GnRH agonists. If spinal cord compression or renal impairment develops, institute standard treatment of these complications. For extreme cases in prostate cancer patients, consider an immediate orchiectomy.
- **Hyperglycemia and Diabetes**: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist.
- **Cardiovascular Diseases**: Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low but should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease.
- **Effect on QT/QTc Interval:** Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent

electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

- **Injection Site Injury**: Extra care should be taken when administering patients with low BMI and/or receiving full anticoagulation medications.
- **Hypercalcemia:** Hypercalcemia has been reported in some prostate and breast cancer patients with bone metastases after starting treatment with GnRH agonists. If hypercalcemia does occur, initiate appropriate treatment measures.
- **Cervical Resistance**: The pharmacologic action of GnRH agonist or antagonist on the uterus and cervix may cause an increase in cervical resistance. Therefore, care should be taken when dilating the cervix for endometrial ablation.
- **Psychiatric Events**: Psychiatric events have been reported in patients taking GnRH agonists. Postmarketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms during treatment.
- **Convulsions**: Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists. Reports have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.
- **Laboratory Testing**: GnRH agonist or antagonist result in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropic and gonadal functions conducted during and after treatment may be affected.
- **Difficulty Locating or Removing Implant**: Loss of or inability to locate or remove an inserted implant has been reported. Caution is recommended.
- **Embryo-Fetal Toxicity**: Based on findings from animal studies and mechanism of action, GnRH agonist or antagonist can cause fetal harm when administered to a pregnant woman Advise pregnant patients and females of reproductive potential of the potential risk to the fetus.
- **Lupaneta Pack only:**
    - Visual Abnormalities: Discontinue in case of sudden loss of vision or onset of proptosis, diplopia or migraine
    - Fluid Retention
    - Clinical Depression: Carefully observe patients with history of depression and discontinue the drug if the depression recurs to a serious degree.

<u>Relugolix</u>**:**

- **Effect on QT/QTc Interval**: Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte

abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

- **Embryo-Fetal Toxicity**: The safety and efficacy of relugolix have not been established in females. Based on findings in animals and mechanism of action, relugolix can cause fetal harm and loss of pregnancy when administered to a pregnant female. In an animal reproduction study, oral administration of relugolix to pregnant rabbits during the period of organogenesis caused embryo-fetal lethality at maternal exposures that were 0.3 times the human exposure at the recommended dose of 120 mg daily based on area under the curve (AUC). Advise males with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of relugolix.
- **Laboratory Testing**: Therapy with relugolix results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropic and gonadal functions conducted during and after treatment may be affected. The therapeutic effect of relugolix should be monitored by measuring serum concentrations of prostate specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.

BILLING/CODING INFORMATION:

HCPCS Coding:

J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg (Lupron Depot)
J1951	Injection, leuprolide acetate for depot suspension (Fensolvi), 0.25 mg
J1952	Leuprolide injectable, Camcevi, 1 mg
J1954	Injection, leuprolide acetate for depot suspension (Lutrate Depot), 7.5 mg
J3315	Injection, triptorelin pamoate, 3.75 mg (Trelstar LA)
J3316	Injection, triptorelin, extended-release, 3.75 mg
J3490	Unclassified drugs [for Lupaneta Pack only]
J8499	Prescription drug, oral, non chemotherapeutic, NOS [for Orgovyx only]
J9003	Leuprolide injectable (Camcevi ETM), 1 mg
J9155	Injection, degarelix, 1mg
J9202	Goserelin acetate implant, per 3.6 mg (Zoladex)
J9217	Leuprolide acetate (for depot suspension), 7.5 mg (Lupron Depot, Eligard)
J9218	Leuprolide acetate, per 1 mg [non-depot formulation]
J9226	Histrelin implant (Supprelin LA), 50mg

ICD-10 Diagnosis Codes That Support Medical Necessity for J3490 [Lupaneta Pack; NDC: 00074-1052-05 (1 month), 00074-1053-05 (3 month)]

N80.0 – N80.9	Endometriosis

ICD-10 Diagnosis Codes That Support Medical Necessity for J1952 and J9003 (Camcevi and Camcevi ETM)

C61	Malignant neoplasm of prostate

ICD-10 Diagnosis Codes That Support Medical Necessity for J1951 (Fensolvi; NDC: 62935-0153-50)

E22.8	Other hyperfunction of pituitary gland [for central precocious puberty diagnosis]

ICD-10 Diagnosis Codes That Support Medical Necessity for J3316 - (triptorelin - Triptodur):

E22.8	Other hyperfunction of pituitary gland [for central precocious puberty diagnosis]

ICD-10 Diagnosis Codes That Support Medical Necessity for J9226 (Supprelin LA):

E22.8	Other hyperfunction of pituitary gland [for central precocious puberty diagnosis]
F64.0	Transsexualism
F64.2	Gender identity disorder of childhood

ICD-10 Diagnosis Codes That Support Medical Necessity for J1950, J1954, J9217, and J9218 [Lutrate Depot, Lupron Depot, Eligard, and Lupron]:

C07	Malignant neoplasm of parotid gland
C08.0	Malignant neoplasm of submandibular gland
C08.1	Malignant neoplasm of sublingual gland
C08.9	Malignant neoplasm of major salivary gland, unspecified
C45.1	Mesothelioma of peritoneum
C48.1 – C48.8	Malignant neoplasm of peritoneum
C50.011 – C50.929	Malignant neoplasm of breast
C56.1 – C56.9	Malignant neoplasm of ovary
C57.00 – C57.4	Malignant neoplasm of fallopian tube, broad ligament, round ligament, parametrium and uterine adnexa
C61	Malignant neoplasm of prostate
D25.0 – D25.9	Leiomyoma of uterus
E22.8	Other hyperfunction of pituitary gland [for central precocious puberty diagnosis]
F64.0	Transsexualism
F64.2	Gender identity disorder of childhood
N80.00 – N80.9	Endometriosis
Z31.84	Encounter for fertility preservation procedure

ICD-10 Diagnosis Codes That Support Medical Necessity for J3315 (triptorelin pamoate - Trelstar):

C61	Malignant neoplasm of prostate
E22.8	Other hyperfunction of pituitary gland [for central precocious puberty diagnosis]

F64.0	Transsexualism
F64.2	Gender identity disorder of childhood

ICD-10 Diagnosis Codes That Support Medical Necessity for J8499 (relugolix – Orgovyx):

C61	Malignant neoplasm of prostate

ICD-10 Diagnosis Codes That Support Medical Necessity for J9202 (goserelin):

C50.011 – C50.929	Malignant neoplasm of breast
C61	Malignant neoplasm of prostate
D25.0 – D25.9	Leiomyoma of uterus
F64.0	Transsexualism
F64.2	Gender identity disorder of childhood
N80.00 – N80.9	Endometriosis
N92.4	Excessive bleeding in the premenopausal period
N92.5	Other specified irregular menstruation
N93.8	Other specified abnormal uterine and vaginal bleeding
Z31.84	Encounter for fertility preservation procedure

ICD-10 Diagnosis Codes That Support Medical Necessity for J9155 (degarelix):

C61	Malignant neoplasm of prostate

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date. The following Local Coverage Determinations (LCDs) were reviewed on the last guideline revised date: Luteinizing Hormone-Releasing Hormone (LHRH) Analogs (L33685), located at fcso.com.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Antineoplastic: preventing the development, growth, or proliferation of malignant cells.

Depot: a body area in which a substance (e.g., a drug) can be accumulated, deposited, or stored and from which it can be distributed.

Follicle-stimulating hormone: hormone produced by the anterior pituitary. It stimulates growth of the follicle in the ovary and spermatogenesis in the testis.

Gender dysphoria - discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth

Gender nonconformity - the extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex. Only some gender-nonconforming people experience gender dysphoria at some point in their lives.

Gonadotropin: hormones produced by the anterior lobe of the hypophysis which includes the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the female and interstitial cell stimulating hormone (ICSH) in the male.

Infertility: Inability of a couple to conceive after one year of unprotected intercourse.

In-vitro fertilization: IVF is a method of assisted reproduction in which the man's sperm and the woman's egg, or oocyte, are combined in a laboratory dish, where fertilization occurs. The resulting embryo is then transferred to the uterus to develop naturally. Usually, two to four embryos are transferred with each cycle.

Luteinizing hormone: hormone secreted by anterior lobe of the hypophysis that stimulates development of the corpus luteum.

PCOS – (polycystic ovarian syndrome): A condition whereby the patient suffers from multiple cysts in her ovaries. Often corresponds with elevated levels of androgens.

Premenstrual syndrome: The physical and psychological symptoms that occur in the week before a woman's menstrual period. Symptoms may include bloating, headache, irritability, anxiety or depression, low self-esteem, difficulty sleeping, changes in appetite, fatigue, and breast swelling and tenderness.

Prostate cancer risk groups: For appropriate treatment selection, patients are divided into risk groups based on the likelihood of the cancer to spread. The NCCN recognized risk groups include: very-low, low, intermediate, high, and very-high risk.

Spinal cord compression: Pressure put upon the spinal cord by a tumor or bony fragment of the spine. If untreated, it can result in permanent paralysis and/or disturbance of bowel and bladder function. Spinal cord compression is one of the indications for emergency radiation therapy.

Steroidogenesis: Production of steroids by living organisms.

Uterine Leiomyomata: These are benign muscle growths of smooth muscle cells along with fibrous tissue from the main body of the uterus.

RELATED GUIDELINES:

None applicable.

OTHER:

DSM-V Criteria for Gender Dysphoria in Children

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least **SIX** of the following (one of which must be Criterion A1):

   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 the 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 the 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 desire 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.

DSM-V Criteria for Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least **TWO** 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 be-cause 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 dif-ferent from one's assigned gender).
6. A strong conviction that one has the typical feelings and reactions of the other gen-der (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.

Tanner Stages

Boys - development of external genitalia

- Stage 1: Prepubertal
- Stage 2: Enlargement of scrotum and testes; scrotum skin reddens and changes in texture
- Stage 3: Enlargement of penis (length at first); further growth of testes
- Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker
- Stage 5: Adult genitalia

Girls - breast development

- Stage 1: Prepubertal
- Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola
- Stage 3: Further enlargement of breast and areola; no separation of their contour
- Stage 4: Areola and papilla form a secondary mound above level of breast
- Stage 5: Mature stage: projection of papilla only, related to recession of areola

Boys and girls - pubic hair

- Stage 1: Prepubertal (can see velus hair similar to abdominal wall)
- Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
- Stage 3: Darker, coarser and more curled hair, spreading sparsely over junction of pubes
- Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
- Stage 5: Adult in type and quantity, with horizontal distribution ("feminine")

Boys Growth

- Stage 1: 5 to 6 cm/year
- Stage 2: 5 to 6 cm/year
- Stage 3: 7 to 8 cm/year

- Stage 4: 10 cm/year
- Stage 5: No further height increase after 17 years

Girls Growth

- Stage 1: 5 to 6 cm/year
- Stage 2: 7 to 8 cm/year
- Stage 3: 8 cm/year
- Stage 4: 7 cm/year
- Stage 5: No further height after 16 years

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/08/25.

GUIDELINE UPDATE INFORMATION:

01/01/05	New Medical Coverage Guideline.
10/15/05	Changed document subject from leuprolide to gonadotropin releasing hormone analogs. Added definitions. Added PCOS to the When Services are not covered section. Added to description, dosage and administration and when services are covered histrelin, triptorelin, and goserelin. Updated ICD-9 codes and HCPCS codes. Updated references.
01/01/06	CPT coding update, deleted expired code 90782, added new code 90772. Annual HCPCS coding update: deleted expired code Q2020, added new codes J1675 and J9225.

10/15/06	Scheduled review; remove “porphyria” from list of covered indications for histrelin; remove ICD-9 code for porphyria.
01/01/07	MCG revised to include Medicare Part D as program exception.
08/15/07	Review and revision; consisting of reformatting guideline, maintain current coverage and limitations, updated dosages, and updated references.
01/01/08	Annual HCPCS coding update: added HCPCS code J9226.
11/15/08	Review and revision; consisting of renaming, updating description, reformatting, adding Plenaxis (abarelix), adding precautions section and updating references.
01/01/09	Annual HCPCS coding update: deleted code 90772; added code 96372.
05/15/09	Revision; consisting of addition of maximum dosages and ICD-9 codes.
07/15/09	Revision; consisting of updating ICD-9 codes.
10/15/09	Revision; consisting of adding new drug Firmagon®, note regarding availability of Plenaxis®, updating description and references.
11/15/09	Review and revision; consisting of updating references.
01/01/10	Annual HCPCS coding update: added HCPCS code J9155.
04/15/10	Revision; consisting of updating ICD-9 codes.
08/01/10	Revision; consisting of updating coding.
09/15/10	Revision; consisting of updating coding.
01/01/11	Review and revision; consisting of removing abarelix, updated coding and references.
02/01/11	Revision; consisting of updating coding.
08/17/11	Revision; ICD-10 codes updated.
01/15/12	Review and revision to guideline; consisting of updating coding and references.
12/15/12	Review and revision to guideline; consisting of reformatting position statement and updating references.
10/15/13	Revision to guideline; consisting of updating coding and program exceptions.
01/15/14	Review and revision to guideline; consisting of updating the description, exceptions and references.
05/15/15	Review and revision to guideline; consisting of revising the position statement by adding continuation criteria.
10/01/15	Revision to guideline consisting of updates to Billing/Coding section and Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.
01/15/16	Review and revision to guideline consisting of updates to position statement, dosage/administration, precautions, coding/billing, and references.
03/15/16	Revision to guideline consisting of updates to the position statement, definitions, and references.
04/15/16	Revision to guideline consisting of update to the position statement.
10/01/16	Revision: ICD-10 code updates
01/15/17	Review and revision to guideline consisting of updates to the position statement, dosage/administration section, coding/billing, and references.
09/15/17	Revision to guideline consisting of update to the position statement, dosage/administration, coding/billing, and references based on the FDA approval of Triptodur.

01/01/18	Annual HCPCS coding update: added HCPCS code C9016
01/15/18	Review and revision to guideline consisting of updating the position statement, precautions, and references.
08/15/18	Revision to guideline consisting of updating the position statement to clarify the maximum dosage limits.
01/01/19	Revision: HCPCS code updates. Added J3316, and removed C9016 and J3490.
01/15/19	Review and revision to guideline consisting of updating the position statement, billing/coding, and references based on a new NCCN-recommended indication.
09/15/19	Revision: HCPCS code updates.
01/15/20	Review and revision to guideline consisting of updating the position statement, dosage/administration, precautions, billing/coding, and references.
06/15/20	Revision to guideline consisting of updating the position statement.
08/15/20	Revision to guideline consisting of update to the position statement, dosage/administration, precautions, coding/billing, and references based on the FDA approval of Fensolvi.
03/15/21	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and references.
07/01/21	Revision: Added HCPCS code J1951.
09/15/21	Revision to guideline consisting of updating the position statement, dosage/administration, precautions, billing/coding, and references.
01/01/22	Revision: Added HCPCS code J1951 ands removed code J9999.
10/01/22	10/01/22 Revision: ICD-10 code updates.
01/01/23	Revision: Newly launched leuprolide acetate injection depot 22.5 mg (Cipla) added. Added HCPCS code J1954 that is associated with this new product.
04/15/23	Revision to guideline consisting of updating the position statement, dosage/administration, billing/coding, and references. Clarified use in biological males with breast cancer. Updated ICD-10 code for preservation of ovarian function during chemotherapy. Vantas criteria removed as it has been removed from the US market.
05/01/25	Revision. Added the Lupron Depot-Ped 45 mg for 6-month administration to the list of available products for CPP. Added that Lupron Depo-Ped 45 mg given every 24 weeks (6 months) is within the acceptable maximum dosage for CPP.
07/01/25	Revision: Revised description of HCPCS code J1954. Cipla product is now Lutrate Depot from Avyxa Pharma.
01/01/26	Revision to guideline consisting of updating the position statement, dosage/administration, and references. Newly approved product, Camcevi ETM, added for the treatment of prostate cancer. A note has been added to the position statement that coverage for gender-affirming treatment is subject to the member's benefit terms, limitations and maximums.
04/01/26	Revision: Added HCPCS code J9003.