POLICY NUMBER UM_1041	**SUBJECT** Luteinizing Hormone Releasing Hormone (LHRH) Agonists and Antagonist		**DEPT/PROGRAM** UM	**PAGE 1 OF 5**
DATE REVIEWED 01/12/11, 03/13/13, 02/11/14, 06/09/15, 10/12/15, 12/09/15, 08/22/16, 10/20/16, 08/10/17, 08/02/18, 07/05/19, 08/08/19	**APPROVAL DATE** August 14, 2019	**EFFECTIVE DATE** August 14, 2019	**REVISION DATES** (latest version listed last) 01/12/11, 03/13/13, 02/12/14, 06/10/15, 10/12/15, 08/25/16, 11/08/16, 08/08/18, 07/10/19, 08/14/19	
PRIMARY BUSINESS OWNER: UM **APPROVED BY:** Dr. Andrew Hertler		**COMMITTEE/BOARD APPROVAL** Utilization Management Committee		
URAC STANDARDS HUM 1		**ADDITIONAL AREAS OF IMPACT**		
CMS REQUIREMENTS	**STATE/FEDERAL REQUIREMENTS**		**APPLICABLE LINES OF BUSINESS** Oncology	

I. PURPOSE

To define and describe the accepted indications for Luteinizing Hormone Releasing Hormone (LHRH) agonists and antagonist usage in the treatment of cancer.

II. DEFINITIONS

Luteinizing Hormone Releasing Hormone (LHRH) agonists: are also known as gonadotropin releasing hormone (GnRH) agonists. LHRH agonists initially stimulate the release of luteinizing hormone resulting in a transient elevation in testosterone in men and estrogen in women. However, chronic administration can cause down-regulation of the LHRH receptors, thus inhibiting the secretion of LH and ultimately the sex hormones (testosterone, estrogen). By decreasing the testicular production of testosterone in men, LHRH agonists can inhibit the growth of androgen-dependent prostate cancer. Similarly, LHRH agonists reduce the ovarian secretion of estrogen and progesterone in women, leading to inhibition of estrogen-dependent breast cancer.

Luteinizing Hormone Releasing Hormone (LHRH) antagonist: is also known as GnRH receptor antagonist. LHRH antagonist is different from LHRH agonists in that it immediately, competitively, and reversibly binds to and blocks GnRH receptors in the pituitary, which reduces the release of luteinizing hormone, follicle stimulating hormone, and consequently testosterone without causing an associated testosterone surge or clinical flare.

LHRH agonists and antagonist are FDA approved for the palliative treatment of advanced prostate cancer and/or advanced breast cancer. To date, there are four LHRH agonists commercially available for use: Lupron (Leuprolide), Zoladex (Goserelin), Trelstar (Triptorelin), and Vantas (Histrelin). The only LHRH antagonist commercially available is Firmagon (Degarelix).

Leuprolide is available as the following dosage formulations:

- Lupron injection: 14 mg multidose vial (14 daily SC injections)
- Lupron Depot: 3.75/7.5 mg (1 month IM injection), 11.25/22.5 mg (3 months IM injection), 30 mg (4 months IM injection), 45 mg (6 months IM injection).
- Eligard: 7.5 mg (1 month SC injection), 22.5 mg (3 months SC injection), 30 mg (4 months SC injection), 45 mg (6 months SC injection).
- Viadur: 65 mg implant (12 months SC injection).

Goserelin is available as Zoladex in 3.6 mg (1 month SC injection) and 10.8 mg (3 months SC injection).

Triptorelin is available as Trelstar in 3.75 mg (1 month IM injection), 11.25 mg (3 months IM injection), and 22.5 mg (6 months IM injection).

Histrelin is available as Vantas in 50 mg implant (12 months SC injection).

Degarelix is available as Firmagon in 80 mg and 240 mg (box of 120 mg x 2) SC injection .

III. POLICY

New Century Health is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century Health may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: LHRH agonists and antagonist may be considered medically necessary when any of the following selection criteria is met

1. **Prostate Cancer**
    a. LHRH agonist or antagonist is being used in the treatment of prostate cancer for any of the following conditions
        i. Adjuvant treatment if positive lymph nodes were found during pelvic lymph node dissection
        ii. Initial short-term, in combination with radiation therapy for one of the following
            a. With unfavorable intermediate risk of recurrence
        iii. Initial long-term, in combination with radiation therapy for one of the following
            a. With high or very high risk of recurrence
            b. For regional disease.
        iv. Initial treatment for very high risk group who are not candidates for definitive therapy, regional, or metastatic disease
        v. For postprostatectomy recurrence with one of the following
            a. With radiation therapy in member without distant metastases
            b. In member with distant metastases.
        vi. Salvage therapy following radiation therapy in member with positive digital rectal examination with one of the following
            a. Negative biopsy and no distant metastatic disease
            b. In member who is not a candidate for local therapy
        vii. Used for progressive castration-naive disease for any of the following:
    b. In combination with a first generation antiandrogen (not for Degarelix)

c. As a single agent for M0 or M1 disease

d. In combination with docetaxel with concurrent steroid for M1 disease.

e. In combination with abiraterone and prednisone/methylprednisolonefor M1 disease

f. As a single agent or in combination with a first-generation antiandrogen and external beam radiation therapy (EBRT) to the primary tumor for low volume M1 disease.

g. Used in combination with secondary hormone therapy apalutamide or enzalutamide for M1 disease.

i. Used for M0 and M1 castration resistant disease to maintain castrate serum levels of testosterone (<50 ng/dL).

2. **Breast Cancer**

a. Zoladex (Goserelin), Trelstar (triptorelin), or Lupron (Leuprolide) is being used in e early or late stage breast cancer in pre- and perimenopausal women for the following conditions

i. Hormone receptor-positive (ER and/or PR positive) disease and one of the following

a. As adjuvant therapy in combination with endocrine therapy (i.e. Tamoxifen or aromatase inhibitor) or
b. Endocrine therapy for recurrent or metastatic disease.

3. **Infertility**

a. The member is undergoing controlled ovarian hyperstimulation and subsequent in vitro fertilization (IVF) or other assisted reproductive technology (ART) for the treatment of infertility (Leuprolide and Tripterolin only).

Exclusion Criteria: LHRH agonists and antagonist are not considered medically necessary when any of the following selection criteria is met

1. Vantas (Histrelin) or Firmagon (Degarelix) is being used for breast cancer.
2. LHRH agonists or antagonist is being used in male breast cancer (use is considered experimental).
3. Zoladex (Goserelin), Trelstar (triptorelin), or Lupron (leuprolide) is being used in postmenopausal female member.
4. Zoladex (Goserelin), Trelstar (triptorelin), or Lupron (Leuprolide) is being used in member with hormone receptor negative (ER and/or PR negative) breast cancer.
5. Dosing exceeds single dose limit of Leuprolide 65 mg, Goserelin 10.8 mg, Triptorelin 22.5 mg, Histrelin 50 mg and Degarelix 240 mg.
6. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

IV. PROCEDURE

Requests for LHRH agonists and antagonist shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia

1. **Dosing and administration**

a. Lupron (Leuprolide)

Prostate Cancer:

i. Subcutaneous (SQ) injection: 1 mg SQ once daily.

ii. Depot 6-month IM injection: 45 mg IM every 6 months.

iii. Depot 4-month IM injection: 30 mg depot IM every 4 months.

iv. Depot 3-month IM injection: 22.5 mg depot IM every 3 months.

v. Depot IM injection: 7.5 mg depot IM every 4 weeks.

vi. Depot 1-month injection: 7.5 mg Eligard SQ depot injection every 4 weeks.

vii. Depot 3-month injection: 22.5 mg Eligard SQ depot injection every 4 weeks .

viii. Depot 4-month injection: 30 mg Eligard SQ depot injection every 4 weeks .

ix. Depot 6-month injection: 45 mg Eligard SQ depot injection every 4 weeks.

x. 12-month implant: 65 mg (one Viadur implant) inserted SQ in inner area of upper arm every 12 months.

Breast Cancer: 3.75 mg IM once monthly or 11.25 mg IM every 3 months.

Infertility: started on day 21 to 24 of the menstrual cycle prior to the ovarian stimulation cycle; dosages vary but typically range 0.5 to 1 mg/day subcutaneous.

b. Zoladex (Goserelin): Breast and Prostate Cancers

i. Breast cancer: 3.6 mg SQ every 28 days for long-term therapy or 10.8 mg every 12 weeks.

ii. Prostate cancer: 3.6 mg SQ every 28 days **OR** 10.8 mg SQ every 12 weeks for long-term therapy.

iii. Prostate cancer (in combination with flutamide): 3.6 mg followed in 28 days 10.8 mg. This regimen should begin 8 weeks prior to radiotherapy and be used in combination with flutamide. Therapy should continue during the radiation therapy. Alternatively, the 3.6 mg depot may be given every 28 days with 2 depot injections before and 2 injections during radiotherapy.

c. Trelstar (Triptorelin): Prostate Cancer

i. Trelstar Depot: 3.75 mg IM every 4 weeks

ii. Trelstar LA: 11.25 mg IM every 3 months

iii. Trelstar: 3.75 mg IM every 4 weeks

iv. Trelstar: 11.25 mg IM every 12 weeks

v. Trelstar: 22.5 mg IM every 24 weeks

Infertility: A single 3.75 mg IM dose has been given 15 days prior to initiation of ovarian stimulation therapy

d. Vantas (Histrelin): Prostate Cancer- one 50mg implant inserted SQ every 12 months.

e. Firmagon (Degarelix) Prostate Cancer- 240 mg given as two subcutaneous abdominal injections of 120 mg each. The maintenance dose, to be given 28 days after the starting dose, is 80 mg administered as a single subcutaneous abdominal injection every 28 days.

2. **Dosage Adjustments**: Specific guidelines for dosage adjustments in renal or hepatic impairment are not available.

3. **Monitoring**

a. Serum calcium levels after starting LHRH agonists in member with bone metastases.

b. Signs and symptoms of possible development of cardiovascular disease.

a. Significant bone mineral density loss and fracture risk.

b. Hyperglycemia with onset of diabetes or worsening glycemic control.

c. Firmagon (Degarelix): concomitant use with Class IA (i.e., quinidine, procainamide) or Class III (i.e. amiodarone, sotalol) antiarrhythmic medications or electrolyte abnormalities may increase risk of prolonged QT/QTc interval.

V. APPROVAL AUTHORITY

1. Review – UM Department
2. Final Approval – UMQI Committee

VI. ATTACHMENTS

None

VII. REFERENCES

1. Lupron prescribing information. AstraZeneca Pharmaceuticals LP, Wilmington, DE. 2018.
2. Trelstar prescribing information. Watson Pharma, Inc. Morristown, NJ. 2018.
3. Zoladex prescribing information. AstraZeneca Pharmaceuticals LP, Wilmington, DE. 2018.
4. Vantas prescribing information. Endo Pharmaceuticals Solutions Inc. Chadds Ford, PA. 2017.
5. Firmagon prescribing information. Ferring Pharmaceuticals Inc. Parsippany, NJ. 2018.
6. Clinical Pharmacology Elsevier Gold Standard. 2019.
7. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Co. 2019.
8. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium. 2019.