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Policy Number: C21100-A

Orgovyx (relugolix), Myfembree (relugolix, estradiol, and norethindrone)

PRODUCTS AFFECTED

Orgovyx (relugolix), Myfembree (relugolix, estradiol, and norethindrone)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Advanced prostate cancer, Uterine fibroids, Endometriosis

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. ADVANCED PROSTATE CANCER (ORGOVYX ONLY):
   1. Documentation of a diagnosis of advanced prostate cancer
      AND

2. Documentation the utilization of a Gonadotropin- Releasing Hormone Antagonist is recommended for the members stage and disease per NCCN updated guidelines for prostate cancer.
   AND
3. Documentation of trial, failure or labeled contraindication to Eligard (leuprolide acetate), Lupron (leuprolide) or Zoladex (goserelin)
   AND
4. Provider attestation that member has been advised to use effective contraception during treatment and for 2 weeks following the last dose of Orgovyx if member has a female partner of reproductive potential.

B. UTERINE FIBROIDS (MYFEMBREE ONLY):
1. Documentation of uterine leiomyomas confirmed with pelvic imaging
   AND
2. Documentation member is symptomatic as evidenced by heavy or prolonged menstrual bleeding, bulk- related symptoms, such as pelvic pressure and pain, or reproductive dysfunction (i.e., infertility or obstetric complications)
   AND
3. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Myfembree (relugolix, estradiol, and norethindrone) include: High risk of arterial, venous thrombotic or thromboembolic disorder, Pregnancy, Known osteoporosis, Current or history of breast cancer or other hormone-sensitive malignancies, Known hepatic impairment or disease, Undiagnosed abnormal uterine bleeding, Known hypersensitivity to components of Myfembree, and do not use in women with uncontrolled hypertension]
   AND
4. (a) Documentation member is naïve to Myfembree (relugolix, estradiol, and norethindrone)
   OR
   (b) Start date is provided and does not exceed a total lifetime duration of 24 months
   AND
5. Prescriber attests that member has not had a greater than the lifetime maximum of GnRH therapy
   AND
6. Prescriber attests member is premenopausal
   AND
7. Prescriber attestation of the following baseline tests completed prior to initiation of treatment and plan for continued monitoring as clinically appropriate: pregnancy test in a woman of childbearing potential, liver function tests, bone mineral density in a woman with risk factors for bone loss or risk factors for osteoporosis

C. MODERATE TO SEVERE PAIN ASSOCIATED WITH ENDOMETRIOSIS (MYFEMBREE ONLY):
1. Documentation of a diagnosis of endometriosis either surgically confirmed OR Clinically diagnosed and failed a three-month trial of analgesics and/or combined oral estrogen progesterone contraceptives within the last year
   AND
2. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Myfembree (relugolix, estradiol, and norethindrone) include: High risk of arterial, venous thrombotic or thromboembolic disorder, Pregnancy, Known osteoporosis, Current or history of breast cancer or other hormone-sensitive Malignancies, Known hepatic impairment or disease, Undiagnosed abnormal uterine bleeding, Known hypersensitivity to components of Myfembree, or women with uncontrolled hypertension]
   AND
3. (a) Documentation member is naïve to Myfembree (relugolix, estradiol, and norethindrone)

OR
(b) Start date is provided and does not exceed a total duration lifetime duration of 24 months
AND

4. Prescriber attests that member has not had a greater than the lifetime maximum of GnRH therapy
AND
5. Prescriber attests member is premenopausal
AND
6. Prescriber attestation of the following baseline tests completed prior to initiation of treatment and plan for continued monitoring as clinically appropriate: pregnancy test in a woman of childbearing potential, liver function tests, bone mineral density in a woman with risk factors for bone loss or risk factors for osteoporosis
AND
7. Documentation member has tried/failed or has an absolute contraindication to ALL of the following:
   (a) One formulary NSAID (i.e., Ibuprofen, naproxen)
   AND
   (b) One formulary preferred oral estrogen-progestin contraceptive, or medroxyprogesterone, or norethindrone acetate

CONTINUATION OF THERAPY:

A. ADVANCED PROSTATE CANCER (ORGOVYX ONLY):
   1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history (Review Rx history for compliance)
   AND
   2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
   3. Documentation of positive clinical response as demonstrated by low disease activity or stabilization of disease due to Orgovyx therapy

B. UTERINE FIBROIDS (MYFEMBREE ONLY):
   1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history (Review Rx history for compliance)
   AND
   2. Documentation member has experienced a clinically significant improvement with less menstrual blood loss
   AND
   3. Documentation member has not exceeded a total lifetime duration of 24 months of GnRH therapy
   AND
   4. Prescriber attests to continued monitoring as clinically appropriate: pregnancy test in woman of childbearing potential, liver function tests, bone mineral density in a woman with risk factors for bone loss or risk factors for osteoporosis.
   AND
   5. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

C. MODERATE TO SEVERE PAIN ASSOCIATED WITH ENDOMETRIOSIS (MYFEMBREE ONLY):
   1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history (Review Rx history for compliance)
   AND
   2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND

3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms
   AND
4. Documentation that member's treatment has not exceeded the lifetime maximum of 24 months
   AND
5. Prescriber attests to continued monitoring as clinically appropriate: pregnancy test in woman of childbearing potential, liver function tests, bone mineral density in a woman with risk factors for bone loss or risk factors for osteoporosis.

DURATION OF APPROVAL:
Orgovyx: Initial authorization: 6 months, Continuation of Therapy: 12 months
Myfembree: Initial authorization: 3 months, Continuation of Therapy: 3 months - cannot exceed lifetime max of 24 months
MOLINA REVIEWER NOTE: For Illinois Marketplace, Kentucky Marketplace, Mississippi Marketplace, Ohio Marketplace, and Kentucky Medicaid please see Appendix.

PRESCRIBER REQUIREMENTS:
Orgovyx (relugolix): Prescribed by or in consultation with a urologist or oncologist [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

Myfembree (relugolix, estradiol, and norethindrone): Prescribed by or in consultation with a board-certified endocrinologist or gynecologist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
Orgovyx (relugolix): Loading dose of 3 x 120mg tablets (360mg) once; Maintenance: 120mg daily
Myfembree (relugolix, estradiol, and norethindrone): 1 tablet per day

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Estrogen-Progestin-GnRH Antagonist; Gonadotropin Releasing Hormone Antagonist

FDA-APPROVED USES:
Orgovyx (relugolix) is indicated for the treatment of adult patients with advanced prostate cancer

Myfembree (relugolix, estradiol, and norethindrone) is indicated in premenopausal women for the: management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids), and management of moderate to severe pain associated with endometriosis.
Limitations of Use: Use of MYFEMBREE should be limited to 24 months due to the risk of continued bone loss which may not be reversible.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

State Specific Information
State Marketplace
Illinois (Source: Illinois General Assembly)
"(215 ILCS 200/60) Sec. 60. Length of prior authorization approval. *A prior authorization approval shall be valid for the lesser of 6 months after the date the health care professional or health care provider receives the prior authorization approval or the length of treatment as determined* by the patient's health care professional or the renewal of the plan, and the *approval period shall be effective regardless of any changes, including any changes in dosage for a prescription drug* prescribed by the health care professional. All dosage increases must be based on established evidentiary standards and nothing in this Section shall prohibit a health insurance issuer from having safety edits in place. This Section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids. Except to the extent required by medical exceptions processes for prescription drugs set forth in Section 45.1 of the Managed Care Reform and Patient Rights Act, nothing in this Section shall require a policy to cover any care, treatment, or services for any health condition that the terms of coverage otherwise completely exclude from the policy's covered benefits without regard for whether the care, treatment, or services are medically necessary. (Source: P.A. 102-409, eff. 1-1-22.)"
"(215 ILCS 200/65) Sec. 65. Length of prior authorization approval for *treatment for chronic or long-term conditions*. If a health insurance issuer requires a prior authorization for a recurring health care service or maintenance medication for the treatment of a chronic or long-term condition, *the approval shall remain valid for the lesser of 12 months from the date the health care professional or health care provider receives the prior authorization approval or the length of the treatment as determined by the patient's health care professional*. This Section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids. Except to the extent required by medical exceptions processes for prescription drugs set forth in Section 45.1 of the Managed Care Reform and Patient Rights Act, nothing in this Section shall require a policy to cover any care, treatment, or services for any health condition that the terms of coverage otherwise completely exclude from the policy's covered benefits without regard for whether the care, treatment, or services are medically necessary. (Source: P.A. 102-409, eff. 1-1-22.)"

Kentucky (Source: Kentucky Revised Statutes)
KY304.17A-167 Time span of authorizations
(Subsection 2) "Unless otherwise provided in subsection (3) of this section or prohibited by state or federal law, if a provider receives a prior authorization for a drug prescribed to a covered person with a condition that requires ongoing medication therapy, and the provider continues to prescribe the drug, and the drug is used for a condition that is within the scope of use approved by the United States Food and Drug Administration or has been proven to be a safe and effective form of treatment for the patient's specific underlying condition based on clinical practice guidelines that are developed from peer-reviewed publications, the prior authorization received shall: (a) Be valid for the lesser of: 1. One (1) year from the date the provider receives the prior authorization; or 2. Until the last day of coverage under the covered person's health benefit plan during a single plan year; and (b) Cover any change in dosage prescribed by the provider during the period of authorization." (Subsection 3) "Except as provided in paragraph (b) of this subsection, the provisions of subsection (2) of this section shall not apply to: 1. Medications that are prescribed for a non-maintenance condition; 2. Medications that have a typical treatment period of less than twelve (12) months; 3. Medications where there is medical or scientific evidence that does not support a twelve (12) month approval; or 4. Medications that are opioid analgesics or benzodiazepines. (b) Paragraph (a) of this subsection shall not apply to any medication that is prescribed to a patient in a community-based palliative care program."
Re-authorization (approved authorization previously issued by Molina Healthcare) for maintenance

medications within this policy shall be approved for a 12 month duration when request meets policy requirements, unless exceptions noted above have been met.

Mississippi (Source: Mississippi Legislature)
"SECTION 13. Length of approvals. (1) A prior authorization approval shall be valid for the lesser of six (6) months after the date the health care professional or health care provider receives the prior authorization approval or the length of treatment as determined by the patient's health care professional or the renewal of the policy or plan, and the approval period shall be effective regardless of any changes, including any changes in dosage for a prescription drug prescribed by the health care professional. Notwithstanding the foregoing, a health insurer and an enrollee or his/her health care professional may extend a prior authorization approval for a longer period, by agreement. All dosage increases must be based on established evidentiary standards, and nothing in this section shall prohibit a health insurance issuer from having safety edits in place. This section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids.
(2) Nothing in this section shall require a policy or plan to cover any care, treatment, or services for any health condition that the terms of coverage otherwise completely exclude from the policy's or plan's covered benefits without regard for whether the care, treatment or services are medically necessary.
SECTION 14. Approvals for chronic conditions. (1) If a health insurance issuer requires a prior authorization for a recurring health care service or maintenance medication for the treatment of a chronic or long-term condition, including, but not limited to, chemotherapy for the treatment of cancer, the approval shall remain valid for the lesser of twelve (12) months from the date the health care professional or health care provider receives the prior authorization approval or the length of the treatment as determined by the patient's health care professional. Notwithstanding the foregoing, a health insurer and an enrollee or his or her health care professional may extend a prior authorization approval for a longer period, by agreement. This section shall not apply to the prescription of benzodiazepines or Schedule II narcotic drugs, such as opioids.
(2) Nothing in this section shall require a policy or plan to cover any care, treatment or services for any health condition that the terms of coverage otherwise completely exclude from the policy's or plan's covered benefits without regard for whether the care, treatment, or services are medically necessary."

Ohio (Source: Ohio Revised Code)
Chapter 3923 Sickness And Accident Insurance Section 3923.041 Policies with prior authorization requirement provisions "(B)(6)(a) For policies issued on or after January 1, 2017, *for a prior approval related to a chronic condition*, the insurer or plan shall honor a prior authorization *approval for an approved drug for the lesser of the following from the date of the approval: (i) Twelve months*; (ii) The last day of the covered person's eligibility under the policy or plan. (b) The duration of all other prior authorization approvals shall be dictated by the policy or plan."

State Medicaid
Kentucky (Source: Kentucky Revised Statutes)
KY304.17A-167 Time span of authorizations
(Subsection 2) "Unless otherwise provided in subsection (3) of this section or prohibited by state or federal law, if a provider receives a prior authorization for a drug prescribed to a covered person with a condition that requires ongoing medication therapy, and the provider continues to prescribe the drug, and the drug is used for a condition that is within the scope of use approved by the United States Food and Drug Administration or has been proven to be a safe and effective form of treatment for the patient's specific underlying condition based on clinical practice guidelines that are developed from peer-reviewed publications, the prior authorization received shall: (a) Be valid for the lesser of: 1. One (1) year from the date the provider receives the prior authorization; or 2. Until the last day of coverage under the covered person's health benefit plan during a single plan year; and (b) Cover any change in dosage prescribed by the provider during the period of authorization." (Subsection 3) "Except as provided in paragraph (b) of this subsection, the provisions of subsection (2) of this section shall not apply to: 1. Medications that are prescribed for a non-maintenance condition; 2. Medications that have a typical treatment period of less than twelve (12) months; 3. Medications where there is medical or scientific evidence that does not support a twelve (12) month approval; or 4. Medications that are opioid analgesics or benzodiazepines. (b) Paragraph

(a) of this subsection shall not apply to any medication that is prescribed to a patient in a community-based palliative care program."

Re-authorization (approved authorization previously issued by Molina Healthcare) for maintenance medications within this policy shall be approved for a 12 month duration when request meets policy requirements, unless exceptions noted above have been met.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

The American Cancer Society estimates that in 2020, there will have been more than 190,000 cases of prostate cancer in the U.S. One of the treatment options for advanced prostate cancer is androgen deprivation therapy, which uses drugs to lower levels of the hormones that help prostate cancer cells grow. Current FDA-approved treatments of this type are injected or placed as small implants under the skin. Orgovyx is an orally administered treatment that works by blocking the pituitary gland from making hormones called luteinizing hormone and follicle-stimulating hormone, thereby reducing the amount of testosterone the testicles are able to make.

The safety and efficacy of Orgovyx was evaluated in a randomized, open-label trial in men with advanced prostate cancer. The patients randomly received either Orgovyx once daily or injections of leuprolide, another hormone-targeting drug, every three months for 48 weeks. The objective was to determine if Orgovyx achieved and maintained low enough levels of testosterone (castrate levels), by day 29 through end of the treatment course. In the 622 patients who received Orgovyx, the castration rate was 96.7%.

The most common side effects of Orgovyx include hot flush, increased glucose, increased triglycerides, musculoskeletal pain, decreased hemoglobin, fatigue, constipation, diarrhea, and increased levels of certain liver enzymes. Androgen deprivation therapies such as Orgovyx may affect the heart's electrical properties or cause electrolyte abnormalities, therefore healthcare providers should consider periodic monitoring of electrocardiograms and electrolytes. Based on findings in animals and the mechanism of action, Orgovyx can cause fetal harm and loss of pregnancy when administered to a pregnant female; it is advised that males with female partners of reproductive potential use effective contraception during treatment and for two weeks after the last dose of Orgovyx. Due to the drug's suppression of the pituitary gonadal system, diagnostic test results of the pituitary gonadotropic and gonadal functions conducted during and after taking Orgovyx may be affected.

Myfembree is a fixed-dose combination of relugolix, estradiol and norethindrone. Relugolix is an oral gonadotropin-releasing hormone used for the medical management of heave menses associated with uterine fibroids. Myfembree was studied in two phase III randomized trials, which looked at the reduction in menstrual blood loss in patients treated for 24 weeks. The product also has hormonal add-back therapy (estradiol and norethindrone).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Orgovyx (relugolix) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Orgovyx (relugolix) include: Known hypersensitivity to relugolix or to any of the product components.

All other uses of Myfembree (relugolix, estradiol, and norethindrone) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Myfembree (relugolix, estradiol, and norethindrone) include: High risk of arterial, venous thrombotic or thromboembolic disorder, Pregnancy, Known osteoporosis, Current or history of breast cancer or other hormone- sensitive malignancies, Known hepatic impairment or disease, Undiagnosed abnormal uterine bleeding, Known hypersensitivity to components of Myfembree, and do not use in women with uncontrolled hypertension.

OTHER SPECIAL CONSIDERATIONS:

Myfembree (relugolix, estradiol, and norethindrone) has a Black Box Warning for thromboembolic disorders and vascular events.

Myfembree changes menstrual bleeding patterns and reduces the ability to recognize pregnancy. Women should be advised to use non-hormonal contraception during treatment with and one week following discontinuation of Myfembree. Myfembree may delay the ability to recognize the occurrence of pregnancy because it alters menstrual bleeding.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Orgovyx TABS 120MG
Myfembree TABS 40-1-0.5MG

REFERENCES

1. Orgovyx (relugolix) [prescribing information]. Brisbane, CA: Movant Sciences; August 2023.
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4. Myovant. Myovant Sciences Announces Results of Additional Secondary Endpoint of Castration Resistance-Free Survival from Phase 3 HERO Study of Relugolix in Advanced Prostate Cancer. Published online September 29, 2020. Accessed February 7, 2021. https://investors.myovant.com/news-releases/news-release-details/myovant-sciences-announces-results-additional-secondary-endpoint
5. National Institutes of Health. In NIH trial, A Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer (HERO, NCT03085095). www.clinicaltrials.gov. Published March 2017. Updated October 2020.
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7. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med*. 2020;382(23):2187-2196. doi: 10.1056/NEJMoa2004325
8. Al-Hendy A, Lukes AS, Poindexter AN 3rd, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. N Engl J Med. 2021;384(7):630-642. doi:10.1056/NEJMoa2008283
9. National Comprehensive Cancer Network. 2023. Prostate Cancer (Version 1.2023). [online] Available at: <prostate.pdf (nccn.org)> [Accessed 17 May 2023].
10. National Comprehensive Cancer Network. 2024. Prostate Cancer (Version 4.2024). [online] Available at: <prostate.pdf (nccn.org)> [Accessed 27 June 2024].

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval References	Q3 2024
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Prescriber Requirements Drug Class FDA-Approved Uses Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q3 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval References	Q4 2022
Q2 2022 Established tracking in new format	Historical changes on file