Clinical Policy: Relugolix (Orgovyx), Relugolix/Estradiol/Norethinedrone (Myfembree)

Reference Number: CP.PHAR.529
Effective Date: 06.01.21
Last Review Date: 05.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Relugolix (Orgovyx®) is a gonadotropin-releasing hormone (GnRH) receptor antagonist.

Relugolix/estradiol/norethinedrone (Myfembree®) is a combination of a GnRH receptor antagonist with an estrogen and progestin.

FDA Approved Indication(s)

Orgovyx is indicated for the treatment of adult patients with advanced prostate cancer.

Myfembree is indicated in premenopausal women for the

- Management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids)
- Management of moderate to severe pain associated with endometriosis

Limitation(s) of use: Use of Myfembree should be limited to 24 months due to the risk of continued bone loss, which may not be reversible.

Policy/Criteria

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

It is the policy of health plans affiliated with Centene Corporation® that Orgovyx and Myfembree are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Prostate Cancer (must meet all)**:**

1. Diagnosis of prostate cancer;
2. Request is for Orgovyx;
3. Prescribed by or in consultation with an oncologist or urologist;
4. Age ≥ 18 years;
5. For brand Orgovyx requests, member must use generic relugolix, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. Request meets one of the following (a, b, or c):*
   a. Initial dose does not exceed 360 mg (3 tablets) given on the first day of treatment as a loading dose;
   b. Maintenance dose does not exceed (i or ii):
      i. 120 mg (1 tablet) per day;

ii. 240 mg (2 tablets) per day if prescribed with rifampin and combination use is unavoidable;

c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

B. Heavy Menstrual Bleeding Associated with Uterine Fibroids (must meet all)**:**

1. Diagnosis of uterine leiomyomas (fibroids) confirmed by ultrasound;
2. Request is for Myfembree;
3. Prescribed by or in consultation with a gynecologist or reproductive endocrinologist;
4. Age ≥ 18 years;
5. Member has experienced heavy menstrual bleeding for at least 2 consecutive cycles;
6. Failure of a 3-month trial of a combination estrogen-progestin contraceptive agent (*see Appendix B for examples*);*
   **For Illinois HIM requests, the step therapy requirements above do not apply as of 1/1/2026 per IL HB 5395*
7. Member has not already received ≥ 24 cumulative months of Myfembree therapy;
8. Dose does not exceed 40 mg of relugolix (1 tablet) per day.

Approval duration: 12 months

Total duration of therapy should not exceed 24 months.

C. Endometriosis Pain (must meet all)**:**

1. Diagnosis of pain due to endometriosis;
2. Request is for Myfembree;
3. Prescribed by or in consultation with a gynecologist or reproductive endocrinologist;
4. Age ≥ 18 years;
5. Failure of a 3-month trial within the last year of an agent from one of the following drug classes, unless clinically significant adverse effects are experienced or all are contraindicated (a or b):*
   **For Illinois HIM requests, the step therapy requirements below do not apply as of 1/1/2026 per IL HB 5395*
   a. Non-steroidal anti-inflammatory drug *(see Appendix B for examples)*;
   b. Oral or depot injectable progestin or progestin-containing contraceptive *(see Appendix B for examples)*;
6. Member has not already received ≥ 24 cumulative months of Myfembree therapy;
7. Dose does not exceed 40 mg of relugolix (1 tablet) per day.

Approval duration: 12 months

Total duration of therapy should not exceed 24 months.

D. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Prostate Cancer (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Orgovyx for a covered indication and has received this medication for at least 30 days;
2. Request is for Orgovyx;
3. Member is responding positively to therapy;
4. For brand Orgovyx requests, member must use generic relugolix, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. New dose does not exceed 120 mg (1 tablet) per day;
   b. New dose does not exceed 240 mg (2 tablets) per day if combined with rifampin and combination use is unavoidable;
   c. New dose is supported by practice guideline or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

B. Heavy Menstrual Bleeding Associated with Uterine Fibroids (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Request is for Myfembree;
3. Member is responding positively to therapy as evidenced by reduced menstrual blood loss;
4. Member has not already received ≥ 24 cumulative months of Myfembree therapy;
5. If request is for a dose increase, new dose does not exceed 40 mg of relugolix (1 tablet) per day.

Approval duration: up to 12 months

Total duration of therapy should not exceed 24 months.

C. Endometriosis Pain (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Request is for Myfembree;
3. Member is responding positively to therapy as evidenced by improvement in dysmenorrhea, dyspareunia, pelvic pain/induration/tenderness, or size of endometrial lesions;
4. Member has not already received ≥ 24 cumulative months of Myfembree therapy;
5. If request is for a dose increase, new dose does not exceed 40 mg of relugolix (1 tablet) per day.

Approval duration: up to 12 months
Total duration of therapy should not exceed 24 months.

D. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
GnRH: gonadotropin-releasing hormone
NCCN: National Comprehensive Cancer Network

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Heavy Menstrual Bleeding associated with Uterine Fibroids, Endometriosis Pain		
NSAIDs: ibuprofen, naproxen, fenoprofen, ketoprofen, mefenamic acid, meclofenamate, indomethacin, tolmetin, diclofenac, etodolac, diflunisal, meloxicam, piroxicam	Varies – refer to specific prescribing information	Varies – refer to specific prescribing information
Progestin-containing oral contraceptives: norethindrone, ethinyl estradiol + (desogestrel, ethynodiol diacetate, drospirenone, etonogestrel, levonorgestrel, norelgestromin, norethindrone, norgestimate, or norgestrel); estradiol valerate + dienogest; mestranol + norethindrone	1 tablet PO QD	1 tablet/day
Depot injection progestin contraceptives: medroxyprogesterone acetate (Depo-Provera®, Depo-SubQ Provera 104®)	IM: 150 mg every 13 weeks SC: 104 mg every 12 to 14 weeks	IM: 150 mg/3 months SC: 104 mg/3 months
Combination estrogen-progestin contraceptive agent: ethinyl estradiol + (desogestrel, ethynodiol diacetate, drospirenone, etonogestrel, levonorgestrel, norelgestromin, norethindrone, norgestimate, or norgestrel)	1 tablet PO QD	1 tablet/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Orgovyx: known hypersensitivity to relugolix or to any of the product components
  - Myfembree only:
    - High risk of arterial, venous thrombotic, or thromboembolic disorder
    - Pregnancy
    - Known osteoporosis
    - Current or history of breast cancer or other hormone-sensitive
    - Known hepatic impairment or disease
    - Undiagnosed abnormal uterine bleeding
    - Known hypersensitivity to components of Myfembree

- Boxed warning(s):
  - Orgovyx: none reported
  - Myfembree: thromboembolic disorders and vascular events

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Relugolix (Orgovyx)	Prostate cancer	A loading dose of 360 mg PO on the first day of treatment followed by 120 mg PO QD Avoid use with combined P-gp and strong CYP3A inducers (e.g., rifampin). If unavoidable, increase Orgovyx dose to 240 mg PO QD	First dose: 360 mg/day Maintenance dose: 240 mg/day (if co-administration with combined P-gp and strong CYP3A inducers)
Relugolix/estradiol/ norethinedrone (Myfembree)	Heavy menstrual bleeding due to uterine fibroids, endometriosis pain	1 tablet PO QD for up to 24 months	1 tablet/day

VI. Product Availability

Drug Name	Product Availability
Relugolix (Orgovyx)	Tablet: 120 mg
Relugolix/estradiol/ norethinedrone (Myfembree)	Tablet: fixed-dose combination containing relugolix 40 mg, estradiol 1 mg, norethindrone acetate 0.5 mg

VII. References

1. Myfembree Prescribing Information. Marlborough, MA: Sumitomo Pharma America, Inc.; July 2024. Available at www.myfembreehcp.com. Accessed January 24, 2025.
2. Orgovyx Prescribing Information. Marlborough, MA: Sumitomo Pharma America, Inc.; October 2024. Available at www.orgovyx.com. Accessed January 24, 2025.
3. Relugolix. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed February 3, 2025.
4. National Comprehensive Cancer Network. Prostate Cancer Version 1.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed February 3, 2025.
5. American College of Obstetricians and Gynecologists. Practice bulletin: Clinical management guidelines for obstetrician-gynecologist: Management of endometriosis. Am J Obstet Gynecol 2010 Jul (reaffirmed 2016); 116(1):223-236.
6. American College of Obstetricians and Gynecologists. Practice bulletin: Clinical management guidelines for obstetrician-gynecologist: Alternatives to hysterectomy in the management of leiomyomas. Am J Obstet Gynecol. 2008; 112(2):387-400.

7. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins–Gynecology. Management of Symptomatic Uterine Leiomyomas: ACOG Practice Bulletin, Number 228. Obstet Gynecol. 2021 Jun 1;137(6):e100-e115.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01.25.21	05.21
RT4: Criteria added following prior clinical guidance for new FDA-approved combination product and its indication: Myfembree for management of heavy menstrual bleeding due to uterine fibroids.	06.23.21	
2Q 2022 annual review: for prostate cancer added generic oral oncology redirection if available per template; for heavy menstrual bleeding continuation of therapy added requirement that member has not received ≥ 24 months of Myfembree therapy to reemphasize existing notations for approval duration; references reviewed and updated.	02.15.22	05.22
RT4: criteria added for endometriosis pain; for bleeding associated with fibroids added criterion that member has not received ≥ 24 months of Myfembree therapy for initial therapy and reproductive endocrinologist as a prescriber option for alignment. Template changes applied to other diagnoses/indications and continued therapy section.	08.29.22	
2Q 2023 annual review: for prostate cancer, removed specific diagnosis characteristic requirements to align with current approach for the other GnRH agents (all are recommended for use in the same place in therapy per NCCN); references reviewed and updated.	01.23.23	05.23
2Q 2024 annual review: no significant changes; updated Appendix C to include new hypersensitivity contraindication for Orgovyx per updated PI; references reviewed and updated.	02.08.24	05.24
2Q 2025 annual review: no significant changes; references reviewed and updated.	02.03.25	05.25
Added step therapy bypass for IL HIM per IL HB 5395.	06.25.25	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.