Clinical Policy: Nirmatrelvir and Ritonavir (Paxlovid)

Reference Number: CP.PMN.288
Effective Date: 09.01.23
Last Review Date: 08.24
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

Co-packaged nirmatrelvir and ritonavir (Paxlovid ™) consist of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor.

FDA Approved Indication(s)

Paxlovid is approved for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitation(s) of use: Paxlovid is not approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

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 Paxlovid is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. COVID-19 (must meet all)**:**

1. Diagnosis of COVID-19;
2. Age ≥ 18 years;
3. Onset of COVID-19 symptom(s) (e.g., cough, fever, diarrhea, sore throat) is within 5 days;
4. Member has ≥ 1 risk factor for progression to severe COVID-19 (*see Appendix D*);
5. A second course of Paxlovid is not prescribed for the treatment of COVID-19 due to the continuation of symptoms after an initial course of Paxlovid therapy (e.g., rebound symptoms, long-COVID, post-acute sequelae of SARS-CoV-2);
6. Dose does not exceed 600 mg nirmatrelvir (4 tablets) with 200 mg ritonavir (2 tablets) per day for 5 days.

Approval duration: 5 days

B. 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. COVID-19
1. Re-authorization for extension of an initial course of therapy is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

B. 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;

B. Pre-exposure prophylaxis for prevention of COVID-19;

C. Post-exposure prophylaxis for prevention of COVID-19.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CDC: Centers for Disease Control
COVID-19: coronavirus disease 2019
CPAP: continuous positive airway pressure
FDA: Food and Drug Administration
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

- Contraindication(s): history of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components; co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions; co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance
- Boxed warning(s): risk of serious adverse reactions due to drug interactions due to ritonavir component, a strong CYP3A inhibitor; this may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events

Appendix D: Risk factors for progression to severe COVID-19

Per the EPIC-HR pivotal trial inclusion criteria and Centers for Disease Control (CDC), the following are health factors and underlying medical conditions known to increase the risk of developing severe COVID-19. This is not a comprehensive list.

- Age ≥ 50 years
- Diabetes
- Overweight Status (BMI ≥ 25)
- Smoking, current and former
- Pregnancy and recent pregnancy
- Physical inactivity
- Hypertension
- Mental health conditions (e.g., depression, schizophrenia)
- Chronic lung disease (e.g., asthma)
- Chronic kidney disease
- Chronic liver disease
- Cerebrovascular disease
- Cardiovascular disease
- Primary immunodeficiencies
- Solid organ or blood stem cell transplantation
- Immunosuppressive disease or immunosuppressive treatment
- Sickle cell disease
- Neurodevelopmental disorders (e.g., Down syndrome)
- Cystic fibrosis
- Active cancer
- HIV

- Dementia
- Tuberculosis
- Substance use disorders

Appendix E: COVID Re-treatment

- According to the CDC, COVID-19 reinfection occurs when a patient is infected, recovers, and then gets infected again. Data regarding the timing of re-infection are evolving and likely vary depending on the circulating variant.
- According to the CDC, COVID-19 rebound has been reported to occur between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative. A brief return of symptoms may be part of the natural history of SARS-CoV-2 infection in some persons, independent of treatment with Paxlovid and regardless of vaccination status. To date, the recurrence of COVID-19 symptoms and virus detection following the use of antiviral therapies has not been associated with progression to severe COVID-19. Longer treatment courses of Paxlovid are not currently authorized, and there are insufficient data on the efficacy of administering a second course.
    - There is an ongoing phase 2 study (NCT05567952) to learn about the safety and effects of Paxlovid for the potential treatment of COVID-19 rebound.
- Per the NIH COVID-19 Treatment Guidelines, some patients report persistent, new, or recurrent symptoms and conditions (e.g., cardiopulmonary injury, neurocognitive impairment, new-onset diabetes) more than 4 weeks after the initial COVID-19 diagnosis. The nomenclature for this phenomenon is evolving; no clinical terminology has been established. The terminology used includes long-COVID, post-COVID-19 condition, post-COVID-19 syndrome, and post-acute sequelae of SARS-CoV-2. Patients who have these symptoms or conditions have been called "long haulers."
- U.S. Government Patient Assistance Program (PAP) operated by Pfizer is available for eligible patients (Note: additional information on the U.S. Government PAP and Paxlovid co-pay savings program can be found on Pfizer's Paxlovid website):
    - Through December 31, 2024, individuals covered under federal programs, such as Medicare or Medicaid, and uninsured patients are eligible for the PAP and can receive Paxlovid at no cost. Health care providers and dispensing locations can provide information to patients regarding eligibility and how eligible patients can enroll in the PAP to obtain free product. Through this program, participating PAP dispensing sites will be reimbursed for any product dispensed, along with a dispensing fee. Retail pharmacies that would like to learn more about participating in the U.S. Government PAP, can contact the program vendor at PharmacyNetworkContract102101@assistrx.com.
    - Pfizer is also operating a Paxlovid co-pay savings program for eligible commercially insured patients.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
COVID-19	300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all 3 tablets taken together BID daily for 5 days	600 mg nirmatrelvir + 200 mg ritonavir per day

VI. Product Availability

Tablets, co-packaged: nirmatrelvir 150 mg, ritonavir 100 mg

VII. References

1. Paxlovid Prescribing Information. New York, NY: Pfizer/BioNTech; May 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217188s000lbl.pdf?utm_medium=email&utm_source=govdelivery. Accessed May 14, 2024.
2. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. Last updated February 29, 2024. Accessed June 6, 2024.
3. CDC. Underlying medical conditions associated with higher risk for severe COVID-19: information for healthcare professionals. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Last updated April 12, 2024. Accessed June 6, 2024.
4. Interim clinical considerations for COVID-19 treatment in outpatients. CDC; last updated January 17, 2024. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/outpatient-treatment-overview.html. Accessed January 26, 2024.
5. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med. 2022;386(15):1397-1408.
6. Paxlovid (nirmatrelvir co-packaged with ritonavir). HHS, Administration for Strategic Preparedness and Response (ASPR). Available at: https://aspr.hhs.gov/COVID-19/Therapeutics/Products/Paxlovid/Pages/default.aspx. Accessed January 26, 2024.
7. U.S. Department of Health & Human Services. Sunsetting the U.S. Government COVID-19 Therapeutics Distribution Program. Last Updated December 20, 2023. https://aspr.hhs.gov/COVID-19/Therapeutics/Pages/COVID19-Tx-Transition-Guide.aspx. Accessed January 26, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	06.06.23	08.23
Removed criterion to exhaust U.S. government supplies; added appendix information on patient assistance program offered for eligible patients under federal programs.	01.26.24	
3Q 2024 annual review: no significant changes; updated the list of the CDC's risk factors for progression to severe disease in Appendix D; references reviewed and updated.	05.14.24	08.24

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.

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