New Drug Overview

Xocova (ensitrelvir)

PDL Category: COVID-19 Agents

Introduction

Disease Background:

- A global pandemic resulted at the end of 2019 as coronavirus spread, with the virus labeled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus disease 2019 (COVID-19) is described as an acute respiratory condition due to infection with SARS-CoV-2 (*Lennox et al 2026, Cohen and Gebo 2026*).
- In adults, COVD-19 can range from asymptomatic infection to mild respiratory tract symptoms or to pneumonia with acute respiratory distress syndrome (*Cohen and Gebo 2026*).
  - As of May 2025, there have been more than 777 million COVID-19 cases, including more than 7 million deaths, globally (*Lennox et al 2026)*.
- SARS-CoV-2 is transmitted from person-to-person, with many cases happening due to exposure to respiratory fluids that contain the virus (*Lennox et al 2026)*.
- Symptoms that can range from mild to severe may occur 2 to 14 days after being exposed to the virus. They may include fever or chills, cough, fatigue, myalgia, headache, new loss of smell or taste, sore throat, congestion or runny nose, nausea/vomiting, diarrhea, and shortness of breath, among others (*Lennox et al 2026)*.
- Treatment as inpatient or outpatient should be individualized, as mild disease quite frequently does not require hospitalization (*Lennox et al 2026)*.
- Xocova was FDA approved in 2026.

Pharmacology/Usage

- Xocova (ensitrelvir), an antiviral, is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M-pro) inhibitor, also referred to as 3C-like protease (3CL-pro) or nonstructural protein 5 (nsp5) protease. Inhibition of SARS-CoV-2 M-pro renders it incapable of processing the viral polyproteins pp1a and pp1ab, preventing viral replication.
  - Ensitrelvir exhibited antiviral activity against infection of the SARS-CoV-2 Delta and Omicron BA.1, BE.1, and XBB.1.5 variants in primary human nasal or bronchial epithelial cells.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Xocova (ensitrelvir)
• For post-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19.	✔

(Prescribing information: Xocova 2026)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Xocova (ensitrelvir)	Tablets: 125mg	PO	375mg (three 125mg tablets taken together) PO on day 1 and 125mg PO on days 2 to 5, with or without food.	• Begin as soon as possible and within 72 hours following contact with an individual who has COVID-19. The tablets should be taken at approximately the same time each day. • If a dose is missed, take the missed dose as soon as possible on the same day, and then take the next dose as scheduled the following day. • Verify pregnancy status of females of reproductive potential prior to starting Xocova. • The impact of severe hepatic impairment on the pharmacokinetics of ensitrelvir is not known.

See the current prescribing information for full details.

Clinical Efficacy Summary

- Trial SCORPIO-PEP was a randomized, double-blind, placebo-controlled multinational post-exposure prophylaxis trial in 5 countries that assessed Xocova in asymptomatic standard- or high-risk adult and adolescent subjects considered not to have SARS-CoV-2 infection.
  - Eligible subjects were 12 years of age or older, had a negative screening test for SARS-CoV-2, and lived in a household with the index patient for the duration of the study.
  - The trial excluded individuals who were using or were anticipating use of any medications prohibited with Xocova.
  - Subjects (N=2387) were randomized to Xocova 375mg on day 1 followed by 125mg on days 2-5 or matching placebo on days 1-5 and enrolled within 72 hours of symptom onset in an index patient of COVID-19 within their household.
    - In the modified intention-to-treat (mITT) analysis population of 2041 subjects (including 118 adolescents), the mean age was 42 years (range 12 to 91 years), 59% were female, 61% were White, 70% had a history of COVID-19 vaccination, and more than 99% had a seropositive SARS-CoV-2 antibody test at screening. In addition, 37% had at least one risk factor associated with severe COVID-19, including 2 subjects who were considered immunocompromised. Baseline demographic and disease characteristics were balanced between the Xocova and placebo arms.

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- The primary endpoint was the incidence of COVID-19 (defined as the onset of COVID-19 symptoms with duration for at least 48 hours and RT-PCR-confirmed SARS-CoV-2 infection) within 10 days of randomization in the modified intention-to-treat (mITT) population.
  - A key secondary endpoint, which was the same as the primary endpoint but analyzed in the intention-to-treat (ITT) population, was assessed in all subjects (including those subsequently found to be RT-PCR positive at baseline by central laboratory testing).
    - The primary and key secondary endpoints were met. A 67% reduction in confirmed symptomatic COVID-19 (with symptom duration of at least 48 hours) on day 10 (primary endpoint) was achieved with Xocova (relative risk ratio 0.33, $p < 0.0001$).
    - For the key secondary endpoint (day 10 [ITT population]), the risk reduction with Xocova was 57% (relative risk ratio 0.43, $p < 0.0001$).
    - Results were consistent regardless of risk factors, and are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy results

	Xocova n (%)	Placebo n (%)	Risk Ratio Estimate
Primary endpoint: Confirmed symptomatic SARS-CoV-2 infection through day 10, mITT population	N=1030 30 (2.9%)	N=1011 91 (9%)	0.33 ($p < 0.0001$)
Key secondary endpoint: Confirmed symptomatic SARS-CoV-2 infection through day 10, ITT population	N=1194 52 (4.4%)	N=1193 122 (10.2%)	0.43 ($p < 0.0001$)

Clinical guidelines

- There are currently no published guidelines found addressing the use of Xocova.
- **Infectious Diseases Society of America (IDSA): Guidelines on the treatment and management of patients with COVID-19** (*IDSA updated 2025*).
  - Nirmatrelvir/ritonavir:
    - The IDSA panel recommends nirmatrelvir/ritonavir rather than no antiviral treatment for adults with mild to moderate COVID-19 who are at high risk or with numerous factors associated with increased risk for progression to severe disease.
    - Nirmatrelvir/ritonavir use is suggested rather than no antiviral treatment for adults with mild to moderate COVID-19 at increased risk but not high risk for progressing to severe disease.
    - It is suggested against routine use of nirmatrelvir/ritonavir in adults with no risk factors for progressing to severe disease.
  - Remdesivir:
    - The IDSA panel recommends IV remdesivir rather than no antiviral treatment for adults with mild to moderate COVID-19 at high risk or with numerous factors associated with increased risk for progressing to severe disease.
    - Remdesivir use is suggested rather than no antiviral treatment for adults with mild to moderate COVID-19 at increased but not high risk for progressing to severe disease.
    - It is suggested against routine use of remdesivir in adults with no risk factors for progressing to severe disease.
  - Post-exposure prophylaxis
    - The IDSA panel recommends against hydroxychloroquine use in persons exposed to COVID-19.
    - The IDSA panel recommends against post-exposure prophylaxis with lopinavir/ritonavir in those exposed to COVID-19.

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Safety summary

- **Contraindications:**
  - In patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.
  - In patients taking drugs that are:
    - Primarily metabolized by CYP3A for which elevated concentrations may be associated with serious and/or life-threatening reactions, and
    - Strong CYP3A inducers because they may significantly reduce ensitrelvir plasma concentrations, leading to the potential loss of virologic response.

- **Box Warning:** None.

- **Warnings and precautions:**
  - Based on animal reproduction studies, Xocova may cause fetal harm when administered to a pregnant woman.
    - Advise pregnant women and females of reproductive potential that Xocova may cause fetal harm.
    - Verify pregnancy status of females of reproductive potential prior to starting Xocova.
    - Advise females of reproductive potential to use effective contraception during Xocova use and for 2 weeks after the final dose.
  - Prior to prescribing Xocova, review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring (eg, calcineurin inhibitors). Consider the benefit of Xocova and whether the risk of potential drug-drug interactions can be appropriately managed.
  - Hypersensitivity reactions, including anaphylaxis, anaphylactic shock, and angioedema, have been reported with Xocova. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue Xocova and start appropriate treatment.

- **Common adverse drug reactions**:
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (Xocova) minus reported % incidence for placebo.
    - The most frequently reported adverse events included headache (0.3%), diarrhea (0.4%), and cough (0.5%).

- **Drug interactions:**
  - Xocova is a strong inhibitor of CYP3A and an inhibitor of P-gp and BCRP. Co-administration of Xocova with drugs that are mainly metabolized by CYP3A or are transported by P-gp or BCRP may result in increased plasma concentrations of such drugs and increase the risk of adverse events.
  - Xocova is a CYP3A substrate; thus, drugs that induce CYP3A may decrease ensitrelvir plasma concentrations and reduce Xocova therapeutic effect. Thus, use of Xocova with strong CYP3A4 inducers is contraindicated. No dose adjustment is recommended when Xocova is used concomitantly with moderate or weak CYP3A inducers.
  - The following are examples of drugs that are contraindicated with Xocova:
    - Antiarrhythmics (quinidine)
    - Anticancer drugs (apalutamide, enzalutamide)
    - Anticonvulsants (carbamazepine, phenytoin)
    - Antigout agents (colchicine)
    - Antimycobacterial (rifampin)
    - Antipsychotics (lurasidone, pimozide)

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- Cardiovascular drugs (eplerenone, ivabradine)
- Cystic fibrosis transmembrane conductance regulator potentiators (lumacaftor/ivacaftor)
- Ergot derivatives (dihydroergotamine, ergotamine, methylergonovine)
- Herbal products (St. John's wort)
- HMG-CoA reductase inhibitors (statins; simvastatin)
- Immunosuppressants (voclosporin)
- Microsomal triglyceride transfer protein (MTTP) inhibitors (lomitapide)
- Mineralocorticoid receptor antagonists (finerenone)
- Sedatives (triazolam)

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that based on animal reproduction studies, Xocova may cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential that Xocova may cause fetal harm. The available clinical data on use during pregnancy are not sufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.
    - Verify pregnancy status of females of reproductive potential prior to starting Xocova.
    - Advise females of reproductive potential to use effective contraception during use and for 2 weeks after the final Xocova dose.
  - The safety and efficacy of use in the pediatric population less than 12 years of age have not been established.

Conclusion

- A global pandemic resulted at the end of 2019 as coronavirus spread, with the virus labeled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus disease 2019 (COVID-19) is described as an acute respiratory condition due to infection with SARS-CoV-2 (*Lennox et al 2026, Cohen and Gebo 2026*).
- Xocova, a SARS-CoV-2 main protease inhibitor, is indicated for post-exposure prophylaxis of COVID-19 in adults and adolescents 12 years of age and older following contact with an individual who has COVID-19.
  - Begin Xocova as soon as possible and within 72 hours following contact with an individual who has COVID-19.
  - Verify pregnancy status of females of reproductive potential prior to starting Xocova.
- Prior to prescribing Xocova, review all medications taken by the patient to assess potential drug-drug interactions and determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring.
- Its efficacy was assessed in a randomized, double-blind, placebo-controlled study that assessed Xocova in asymptomatic standard- or high-risk adult and adolescent subjects considered not to have SARS-CoV-2 infection.
  - The primary endpoint was the incidence of COVID-19 within 10 days of randomization in the modified intention-to-treat (mITT) population.
    - The primary endpoint was met. A 67% reduction in confirmed symptomatic COVID-19 (with symptom duration of at least 48 hours) on day 10 was achieved with Xocova (relative risk ratio 0.33, $p < 0.0001$).
- Guidelines do not currently include discussion on Xocova for post-prophylaxis exposure as it was FDA approved after the guidelines were published. Xocova is the first prescription tablet FDA approved for use in patients 12 years and older to help prevent getting sick after being exposed to COVID-19. Note that Xocova treatment should begin as soon as possible and within 72 hours following contact with an individual who has COVID-19.

- It is recommended that Xocova should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

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- **PDL Placement:**
  - ☐ Preferred
  - ☒ Non-Preferred

References

- Cohen P, Gebo K. Covid-19: Evaluation and management of adults with acute infection in the outpatient setting. UpToDate website. Last updated September 11, 2026. Accessed September 14, 2026. www.uptodate.com.
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