

Ensirelvir (XOCOVA) in COVID-19 Postexposure Prophylaxis

National Drug Monograph

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VA Pharmacy Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA PRESCRIBING INFORMATION¹

Description / MOA	Ensirelvir is an inhibitor of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M ^{pro}), also referred to as 3C-like protease (3CL ^{pro}) or nonstructural protein 5 (nsp5) protease. Inhibition of M ^{pro} renders it incapable of processing viral polyproteins pp1a and pp1ab, preventing viral replication.
Indication Under Review	Post-exposure prophylaxis (PEP) 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.
Dosage Regimen	375 mg (three 125-mg tablets taken at the same time) orally on Day 1 and 125 mg (one 125-mg tablet) orally on Days 2 to 5, taken with or without food. Treatment should be initiated as soon as possible and within 72 hours following contact with an individual who has COVID-19.
Dosage Forms Under Review	Tablets: 125 mg of ensirelvir
Pretreatment Procedures	Verify pregnancy/lactation status of females of reproductive potential prior to initiating ensirelvir.

EFFICACY CONSIDERATIONS

Trial	SCORPIO-PEP²
Design	Phase 3, multinational, double-blind, randomized, placebo-controlled trial.
Population	N= 2041 (mITT). Eligible participants were ≥12 years of age, had a negative reverse transcriptase-polymerase chain reaction (RT-PCR) test for SARS-CoV-2, and were enrolled within 72 hours after symptom onset of the index patient. <u>Definition of index patient:</u> 1 st person with documented COVID-19 in a household <u>Definition of COVID-19:</u> Positive RT-PCR test for SARS-CoV-2 (baseline screening for index patients could also use Ag test) and the presence of at least 1 of 14 prespecified COVID-19 symptoms lasting for at least 48 hours <u>Key Exclusions:</u> Fever or COVID-19 symptoms at screening, documented SARS-CoV-2 infection or receipt of SARS-CoV-2 vaccine within the previous 6 months, pregnancy <u>Demographics:</u> Mean age 42 years; 59% female; 61% White, 32% Asian, 5% Black; 37% had at least one risk factor for severe illness (e.g., obesity, smoking, age >65 years); 70% had history of COVID-19 vaccination; >99% had seropositive SARS-CoV-2 antibody test
Intervention	Ensirelvir – 375 mg on Day 1 and 125 mg daily on Days 2 through 5 (n=1030)
Comparator	Matched placebo (n=1011)
Results	Primary and Key Secondary Endpoints

Outcome (Day 10)	Ensirelvir (n/N)	Placebo (n/N)	Risk Ratio (95% CI)	p-value
Incidence of COVID-19, mITT ^a	2.9% (30/1030)	9.0% (91/1011)	0.33 (0.22, 0.49)	<0.0001
Incidence of COVID-19, ITT ^b	4.4% (52/1194)	10.2% (122/1193)	0.43 (0.32, 0.59)	<0.0001
Lab-confirmed SARS-CoV-2, mITT ^b	14% (144/1030)	21.5% (217/1011)	0.66 (0.55, 0.79)	N/A

^a Primary endpoint ^b Secondary endpoint

Safety

- Similar incidence of adverse events between the two groups (15.1% in ensirelvir, 15.5% in placebo).
- Similar incidence of serious adverse events (0.2% in each group).
- Reversible, dose-related decrease in HDL cholesterol in ensirelvir group (approximately 27% decline by Day 6, returning to baseline by Day 15).
- No COVID-19-related hospitalizations or deaths reported during trial.

SAFETY CONSIDERATIONS^{1,2}

Boxed Warnings	None
Contraindications	History of clinically significant hypersensitivity to ensirelvir or any other components of XOCOVA. Co-administration with drugs primarily metabolized by CYP3A for which elevated concentrations may be associated with serious and/or life-threatening reactions. Co-administration with strong CYP3A inducers because they may significantly reduce ensirelvir plasma concentrations, leading to the potential loss of virologic response.

Other Warnings	Embryofetal Toxicity: May cause fetal harm based on animal reproduction studies. Advise pregnant women and females of reproductive potential that ensirelvir may cause fetal harm. Advise females of reproductive potential to use effective contraception during ensirelvir use and for 2 weeks after the final dose. Drug Interactions: Significant potential for interactions; consult the full prescribing information prior to and during treatment for potential drug interactions. Hypersensitivity Reactions including anaphylaxis, anaphylactic shock, and angioedema have been reported with ensirelvir. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue ensirelvir and initiate appropriate treatment.
Top AEs	Headache (2.9%), diarrhea (1.8%), nasopharyngitis (1.3%), cough (1.2%), fatigue (1.1%), influenza (1.1%)
Drug Interactions	Ensirelvir is a strong CYP3A inhibitor and an inhibitor of P-gp and BCRP – concomitant administration of ensirelvir and substrates of these enzymes and transporters may result in increased plasma concentrations of the substrates and increased risk of adverse events. Initiation of ensirelvir should be considered only after careful evaluation of relevant clinical and pharmacokinetic factors. Ensirelvir is a CYP3A substrate – coadministration with strong CYP3A4 inducers are contraindicated as they may reduce ensirelvir plasma concentrations and lead to loss of virologic response. No dose adjustment is recommended with moderate or weak CYP3A inducers.
Pregnancy	May cause fetal harm. Verify pregnancy status before use. Advise effective contraception during treatment and for 2 weeks after the final dose in females of reproductive potential. In animal studies, embryofetal toxicity (including skeletal malformations and embryofetal lethality), fetal growth retardation, and low fetal body weight was observed at ensirelvir exposures 7-9 times the recommended human dose (RHD).
Lactation	Insufficient human data. Ensirelvir was present in the milk of lactating rats. Advise lactating women not to breastfeed during treatment and for 2 weeks after the final dose due to potential adverse effects in the breastfed child.
Renal Impairment	No dosage adjustment is recommended for patients with mild, moderate, or severe renal impairment. It has not been studied in patients with kidney failure receiving dialysis.
Hepatic Impairment	No dosage adjustment is recommended for patients with mild or moderate (Child-Pugh Class A or B) hepatic impairment. Not studied in severe hepatic impairment (Child-Pugh Class C).

POTENTIAL PLACE IN THERAPY¹⁻⁴

1. Ensirelvir is the first oral antiviral to receive FDA approval for the prevention of COVID-19 and was found to be effective if administered within 72 hours of household or close contact with an individual with COVID-19. In the SCORPIO-PEP trial, ensirelvir demonstrated a 67% relative risk reduction in confirmed, symptomatic COVID-19 disease by Day 10 compared to placebo and results were consistent regardless of risk factors for severe disease.
2. Ensirelvir currently has FDA approval exclusively for post-exposure prophylaxis (PEP) and is not indicated for the treatment of active SARS-CoV-2 infection in the United States. In two Phase 3 trials evaluating standard-risk and high-risk patients (SCORPIO-SR, SCORPIO-HR), ensirelvir did not meet its primary clinical endpoint for treatment of symptomatic COVID-19 despite potent antiviral activity.
3. Ensirelvir is not meant to be an alternative or replacement for COVID-19 vaccination but can potentially provide acute, exposure-specific risk reduction in some cases (e.g., household contacts of a patient with COVID-19, managing outbreaks in vulnerable settings such as a Community Living Center [CLC] or transplant unit). In SCORPIO-PEP, 70% of participants had a history of COVID-19 vaccination and more than 99% were seropositive for SARS-CoV-2 antibodies at the time of screening, exhibiting a high level of background immunity in the participants. Despite this, ensirelvir was still able to demonstrate a 67% reduction in symptomatic COVID-19 rate compared to placebo. However, investigators did note differences in background immunity, amongst other factors, may have contributed to varying incidence of COVID-19 across trial sites as placebo-group event rates were lower in the United States compared to Japan. This demonstrates that ensirelvir PEP can potentially provide additive protection on top of vaccination, rather than serving as a substitute for it, particularly in patients who are unlikely to mount an adequate immune response to vaccination.

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References

1. XOCOVA (ensirelvir) tablets, for oral use [prescribing information online]. Florham Park, NJ: Shionogi, Inc. May 2026. Available at: <https://www.shionogi.com/content/dam/shionogi/si/products/pdf/xocova.pdf>.
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3. Yotsuyanagi, H., et al. "Efficacy and Safety of 5-Day Oral Ensirelvir for Patients with Mild to Moderate COVID-19: The SCORPIO-SR Randomized Clinical Trial." *JAMA Network Open*, vol. 7, no. 2, 2024, e2354991, <https://doi.org/10.1001/jamanetworkopen.2023.54991>.
4. Luetkemeyer, A. F., et al. "Ensirelvir for the Treatment of Nonhospitalized Adults with COVID-19: Results from the SCORPIO-HR, Phase 3, Randomized, Double-blind, Placebo-Controlled Trial." *Clinical Infectious Diseases*, vol. 80, no. 6, 2025, pp. 1235–1244, <https://doi.org/10.1093/cid/ciaf029>.