XOCOVA®
(ensitrelvir) 125 mg tablets

Drug Interaction Reference Guide

An overview of drug interactions and associated prescribing considerations for XOCOVA

XOCOVA (ensitrelvir) is indicated for 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.

CONTRAINDICATIONS

XOCOVA is contraindicated when administered with drugs primarily metabolized by CYP3A for which elevated concentrations may be associated with serious and/or life-threatening reactions or when administered with strong CYP3A inducers because they may significantly reduce XOCOVA plasma concentrations leading to potential loss of virologic response.

Please see additional Important Safety Information on page 8 and full Prescribing Information.

Drug interaction considerations with XOCOVA[1]

Risk of serious adverse reactions due to drug interactions

XOCOVA is a strong CYP3A inhibitor and an inhibitor of P-gp and BCRP. In patients receiving or initiating medications metabolized by CYP3A or transported by P-gp or BCRP, XOCOVA may increase plasma concentrations of those medications and may potentially lead to severe, life-threatening, or fatal events from increased exposure of concomitant medications. In addition, medications that induce CYP3A may decrease concentrations of XOCOVA, leading to loss of therapeutic effect.

Potential for XOCOVA to affect other drugs

XOCOVA is a strong inhibitor of CYP3A and an inhibitor of P-gp and BCRP. Co-administration of XOCOVA with drugs that are primarily 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. For drugs that are CYP3A substrates and contraindicated with XOCOVA, initiation of XOCOVA should be considered only after careful evaluation of relevant clinical and pharmacokinetic factors related to the concomitant medication. In addition, re-initiation of contraindicated CYP3A substrates should be considered based on an assessment of the duration of CYP3A inhibition and patient-specific considerations. Refer to individual drug prescribing information for additional information.

Potential for other drugs to affect XOCOVA

XOCOVA is a CYP3A substrate; therefore, drugs that induce CYP3A may decrease XOCOVA plasma concentrations and reduce XOCOVA therapeutic effect. Therefore, **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. Refer to individual drug prescribing information for additional information.

Established and other potentially significant drug interactions

The table on pages 4 to 7 provides examples of drugs that are contraindicated with XOCOVA. It is provided as a guide consistent with Section 7 of the XOCOVA Prescribing Information. It is not a comprehensive list of all possible drugs that may interact with XOCOVA. The healthcare provider should consult other appropriate resources, such as the prescribing information for the interacting drug, for comprehensive information on dosing and monitoring with concomitant use of a strong CYP3A inhibitor, like XOCOVA.

Please see additional Important Safety Information on page 8 and full Prescribing Information.

XOCOVA® (ensitrelvir) tablets

Drug interaction considerations with XOCOVA[1] (cont'd)

Drug initiation considerations

For drugs that are CYP3A substrates and contraindicated with XOCOVA, initiation of XOCOVA should be considered only after careful evaluation of relevant clinical and pharmacokinetic factors related to the concomitant medication. Reinitiation of contraindicated CYP3A substrates should be considered based on an assessment of the duration of CYP3A inhibition and patient-specific considerations.

Prior to prescribing XOCOVA, review all concomitant medications taken by the patient to assess for potential drug-drug interactions and determine whether dose adjustment, interruption, and/or additional monitoring is required. Consider the benefit of XOCOVA and whether the risk of potential drug-drug interactions can be appropriately managed.

Before prescribing

- ☐ Review patient's full medication list, including prescription and non-prescription medications, and over-the-counter vitamins and supplements
- ☐ Assess for potential drug interactions or contraindications
- ☐ Evaluate if concomitant medications may require interruption, dose adjustment, and/or additional monitoring
- ☐ Consult additional appropriate resources, including the Prescribing Information for XOCOVA and other interacting drugs

The table on pages 4 to 7 provides examples of drugs that are contraindicated with XOCOVA.

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Drugs contraindicated with XOCOVA due to risk of potentially serious or fatal interactions[1]

The table on pages 4 to 7 provides examples of drugs that are contraindicated with XOCOVA. It is provided as a guide consistent with Section 7 of the XOCOVA Prescribing Information. It is not a comprehensive list of all possible drugs that may interact with XOCOVA. Not all drug interactions can be managed.

↑ = increase in effect on drug concentration ↓ = decrease in effect on drug concentration

Drug class	Drug example(s) within class	Effect on drug concentration	Clinical comment
Antiarrhythmics	quinidine	↑ antiarrhythmic	Co-administration is contraindicated due to potential for cardiac arrhythmias
Anticancer drugs	apalutamide, enzalutamide	↓ ensitrelvir	Co-administration is contraindicated due to potential loss of virologic response
Anticonvulsants	carbamazepine,* phenytoin	↓ ensitrelvir	Co-administration is contraindicated due to potential loss of virologic response
Antigout agents	colchicine	↑ colchicine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment

*Strong CYP3A4 inducers: co-administration with the strong CYP3A inducer carbamazepine (titrated from 100 mg twice daily to 300 mg twice daily over 1 week and then maintained at a 300-mg twice-daily dose for 11 days, with some subjects requiring dose reduction) decreased the AUC of ensitrelvir by approximately 40% to 45%.[1]

AUC=Area Under Curve.

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XOCOVA® (ensitrelvir) tablets

Drugs contraindicated with XOCOVA due to risk of potentially serious or fatal interactions[1] (cont'd)

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Drug class	Drug example(s) within class	Effect on drug concentration	Clinical comment
Antimycobacterials	rifampin	↓ ensitrelvir	Co-administration is contraindicated due to potential loss of virologic response
Antipsychotics	lurasidone, pimozide	↑ lurasidone, pimozide	Co-administration is contraindicated due to serious and/or life-threatening reactions, such as cardiac arrhythmias
Cardiovascular drugs	eplerenone, ivabradine	↑ eplerenone, ivabradine	Co-administration is contraindicated
Cystic fibrosis transmembrane conductance regulator potentiators	lumacaftor/ivacaftor	↓ ensitrelvir	Co-administration is contraindicated due to potential loss of virologic response

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XOCOVA® (ensitrelvir) tablets

Drugs contraindicated with XOCOVA due to risk of potentially serious or fatal interactions[1] (cont'd)

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Drug class	Drug example(s) within class	Effect on drug concentration	Clinical comment
Ergot derivatives	dihydroergotamine, ergotamine, methylergonovine	↑ dihydroergotamine, ergotamine, methylergonovine	Co-administration is contraindicated due to potential for acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues, including the central nervous system
Herbal products (for depression)	St John's wort	↓ ensitrelvir	Co-administration is contraindicated due to potential loss of virologic response
HMG-CoA reductase inhibitors (statins)	simvastatin	↑ simvastatin	Co-administration is contraindicated. Discontinue use of simvastatin at least 12 hours prior to initiation of XOCOVA

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XOCOVA® (ensitrelvir) tablets

Drugs contraindicated with XOCOVA due to risk of potentially serious or fatal interactions[1] (cont'd)

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Drug class	Drug example(s) within class	Effect on drug concentration	Clinical comment
Immunosuppressants	voclosporin	↑ voclosporin	Co-administration is contraindicated due to potential for acute and/or chronic nephrotoxicity
Microsomal triglyceride transfer protein (MTTP) inhibitors	lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions
Mineralocorticoid receptor antagonists	finerenone	↑ finerenone	Co-administration is contraindicated due to potential for serious adverse reactions, including hyperkalemia, hypotension, and hyponatremia
Sedatives	triazolam	↑ triazolam	Co-administration is contraindicated

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XOCOVA® (ensitrelvir) tablets

Indication and Important Safety Information

INDICATION

XOCOVA (ensitrelvir) is indicated for 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.

IMPORTANT SAFETY INFORMATION

Contraindications

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to XOCOVA or any of its components. XOCOVA is also contraindicated when administered with drugs primarily metabolized by CYP3A for which elevated concentrations may be associated with serious and/or life-threatening reactions or when administered with strong CYP3A inducers because they may significantly reduce XOCOVA plasma concentrations leading to potential loss of virologic response.

Embryofetal Toxicity

Based on animal data, 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 before initiating XOCOVA and advise using effective contraception during XOCOVA use and for 2 weeks after the final dose.

Risk of Serious Adverse Reactions Due to Drug Interactions

XOCOVA is a strong CYP3A inhibitor and an inhibitor of P-gp and BCRP. In patients receiving or initiating medications metabolized by CYP3A or transported by P-gp or BCRP, XOCOVA may increase plasma concentrations of those medications and may potentially lead to severe, life-threatening, or fatal events from increased exposure. CYP3A inducers may decrease concentrations of XOCOVA, leading to loss of therapeutic effect.

Please see full Prescribing Information.

Before prescribing XOCOVA, review all concomitant medications to assess potential drug-drug interactions and determine if those medications require a dose adjustment, interruption, and/or additional monitoring. Consider the benefit of XOCOVA and whether risk of potential drug-drug interactions can be managed.

Hypersensitivity Reactions Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, anaphylactic shock, and angioedema have been reported. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue XOCOVA and initiate appropriate treatment.

Lactation

There are no data on the presence of XOCOVA in human milk, effects on breastfed infants, or effects on milk production. XOCOVA was present in the milk of lactating rats. Advise women not to breastfeed while on XOCOVA and for 2 weeks after the final dose.

Adverse Reactions

The most common adverse events occurring in ≥1% of XOCOVA patients and at greater frequency than placebo, respectively, were headache (2.9% vs 2.6%), diarrhea (1.7% vs 1.3%), and cough (1.1% vs 0.6%).

Laboratory Abnormalities

Asymptomatic hemoglobin declines from baseline of >2 g/dL occurred in XOCOVA and placebo patients (3% vs 1%, respectively).

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Read full **Prescribing Information**

Learn more at **XocovaHCP.com**

Reference: 1. XOCOVA [package insert]. Florham Park, NJ: Shionogi Inc.

SHIONOGI

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