Xocova - Use Beyond 5 Days

This medical response contains information in addition to that provided in the Xocova® (ensitrelvir) tablets, for oral use Full Prescribing Information approved by the U.S. Food and Drug Administration (FDA). Shionogi does not recommend the use of Xocova in any manner other than as described in the Full Prescribing Information. **Please read the attached Xocova Full Prescribing Information.**

1. CLINICAL STUDIES

Phase 3 Clinical Studies

- There were **no reports of longer duration of ensitrelvir therapy beyond 5 days observed in the Phase 3 Shionogi clinical trials**: SCORPIO-PEP, SCORPIO-HR, and SCORPIO-SR.[1-3]
  - SCORPIO-PEP and SCORPIO-HR used an ensitrelvir loading dose of 375 mg on day 1 followed by 125 mg once daily on days 2-5, compared with placebo.[2,3]
  - SCORPIO-SR used an ensitrelvir loading dose of 375 mg on day 1 followed by 125 mg once daily on days 2-5, ensitrelvir loading dose of 750 mg on day 1 followed by 250 mg once day on days 2-5, or placebo for 5 days.[1]

Phase 1 Clinical Studies

- **Only one Phase 1 PK study assessed use of ensitrelvir beyond a duration of 5 days while assessing drug-drug interactions (DDIs) between ensitrelvir and midazolam** in one of its study parts.[4]
- Ensitrelvir regimens beyond a duration of 5 days were not evaluated in the other parts of this Phase 1 PK study (which assessed safety, tolerability, PK, including food effect, and other DDIs), nor were they evaluated in any of the other Phase 1 ensitrelvir studies that studied renal impairment, hepatic impairment, DDIs with oral contraceptives, and DDIs with transporter substrates.[4-10]

<u>Phase 1 Study – Use of Ensitrelvir Beyond 5 Days</u>

Shimizu et al. conducted a phase 1, multicenter, double-blind, placebo-controlled study in healthy adults. One of the study parts assessed the DDI potential between ensitrelvir and midazolam in Japanese male participants in an open-label, self-controlled crossover design (N=11; cohort G).[4]

- Participants received ensitrelvir suspension at a loading dose of 750 mg on Day 1 followed by 250 mg once daily on Days 2-6, for a total duration of six days. Midazolam 2 mg syrup was administered in the fasted state alone on Day −2 and coadministered with ensitrelvir on Day 6. Placebo was administered on corresponding days.[4]

Pharmacokinetic Results

- The PK evaluation of midazolam 2 mg when coadministered with ensitrelvir 750/250 mg on Day 6 showed increases in maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing ($AUC_{0\text{-last}}$), and area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-inf}}$) of 2.78-fold, 7.23-fold, and 8.80-fold, respectively, compared to the administration of midazolam alone (see **Table 1**).[4]

- These results indicate that ensitrelvir strongly inhibits CYP3A at this dosing regimen (750/250 mg).[4]

Table 1. Effect of Ensitrelvir on the Pharmacokinetics of Midazolam[4]

	N	GLS mean (Day - 2)	N	GLS mean (Day 6)	GLS mean ratio (90% CI) (Day 6 / Day - 2)
	Midazolam alone		Midazolam with ensitrelvir 750/250 mg[a]		Midazolam with ensitrelvir 750/250 mg[a]/ midazolam alone
C_{max} (ng/mL)	8	16.2	7	44.9	2.7763 (2.3341-3.3022)
$AUC_{0\text{-last}}$ (ng • h/mL)	8	34.70	7	250.8	7.2293 (5.5817-9.3632)
$AUC_{0\text{-inf}}$ (ng • h/mL)	8	35.69	5	314.1	8.8002 (6.7061-11.5484)

Table adapted from Shimizu et al. *Antimicrob Agents Chemotherapy*. 2022.
Abbreviations: $AUC_{0\text{-inf}}$, area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing; CI, confidence interval; C_{max}, maximum plasma concentration; GLS, geometric least square.
[a]Multiple once-daily doses with 750 mg as the loading dose on Day 1 and 250 mg as the maintenance dose on Days 2-6.

Safety Results

- Ensitrelvir was well tolerated. Common treatment-emergent adverse events (TEAEs) included:[4]
  - Decreased high-density lipoprotein (HDL): 7/8 participants
  - Nervous-system disorders: 5/8 participants
  - Diarrhea: 4/8 participants
  - Headache: 4/8 participants
  - Gastrointestinal (GI) disorders: 4/8 participants
  - Somnolence: 3/8 participants (reported after administration of midazolam)
- In the placebo group, 1/3 participants experienced GI disorders and diarrhea.[4]
- Most adverse events were mild in severity, and all adverse events resolved without the need for medical intervention.[4]

<u>Phase 1 Studies – Use of Ensitrelvir for Only Up to 5 Days</u>

The other parts of the Phase 1 PK study assessed the safety, tolerability, PK, and drug-interaction potential of various ensitrelvir regimens in healthy adults, sometimes in comparison to placebo.[4-6]

- In one part, participants were randomized to placebo or single doses of ensitrelvir ranging from 20 to 2,000 mg, and placebo or once-daily regimen of 375 mg on day 1 and 125 mg on days 2-5 or once-daily regimen of 750 mg on day 1 and 250 mg on days 2-5, while also examining food effects and ethnic PK differences.[4]
- Another part assessed drug-drug interaction potential by evaluating how multiple-dose ensitrelvir, given at 750 mg on day 1 and 250 mg on days 2-5 or 375 mg on day 1 and 125 mg on days 2-5, affected the PK of dexamethasone, prednisolone, and midazolam administered alone and again with ensitrelvir.[5]
- Another part examined the ensitrelvir tablet formulation in Japanese females, Japanese elderly participants, and White adults, using 375 mg on day 1 and 125 mg on days 2-5 and 750 mg on

day 1 and 250 mg on days 2-5, alongside placebo, and additionally assessing the effect of food through a single 375 mg fed-versus-fasted crossover.[6]

All other Phase 1 studies evaluating ensitrelvir in participants with renal impairment, hepatic impairment, DDIs with oral contraceptives, and DDIs with transporter substrates assessed ensitrelvir use for only up to 5 days.[7-10]

- Ensitrelvir was assessed in participants with renal impairment and healthy participants:[7]
    - Ensitrelvir was administered as a single oral 375 mg dose to 24 participants with either mild, moderate, or severe renal impairment and 8 matched control participants with normal renal function (participants with severe renal impairment requiring hemodialysis were excluded).[7]
- Ensitrelvir was assessed in participants with mild and moderate hepatic impairment and healthy control participants:[8]
    - Ensitrelvir was administered as a single oral 375 mg dose to 25 participants with either mild or moderate hepatic impairment and 8 matched control participants with normal hepatic function.[8]
- DDIs of ensitrelvir and oral contraceptives were assessed in healthy adult females participants:[9]
    - Participants received multiple oral doses of a combined oral contraceptive (ethinyl estradiol [EE] and drospirenone [DRSP]) once daily for 24 days. Ensitrelvir was administered as a high dose on Day 20 and as a low dose once daily on Days 21–24, all in the fasted state.[9]
- Ensitrelvir was assessed in healthy adult participants using a transporter substrate cocktail containing oral doses of digoxin, rosuvastatin, and metformin administered on Day 1 alone and then again on Day 11 with a one-time oral dose of ensitrelvir 500 mg.[10]

2. RELEVANT PRESCRIBING INFORMATION

INDICATIONS AND USAGE

XOCOVA is indicated 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.[11]

CONTRAINDICATIONS

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[11]

XOCOVA is contraindicated 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.[11]

RECOMMENDED DOSAGE

The recommended dosage of XOCOVA in adults and adolescents 12 years of age and older is 375 mg (three 125-mg tablets taken together) orally on Day 1 and 125 mg (one 125-mg tablet) orally on Days 2 to 5 with or without food.[11]

Begin XOCOVA 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 of XOCOVA 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.[11]

Please read the attached Xocova **Full Prescribing Information**. The use of Xocova in any manner other than as described in the Full Prescribing Information approved by the U.S. Food and Drug Administration (FDA) is not recommended.

3. LITERATURE SEARCH

As of December 2025, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has failed to identify any relevant references regarding ensitrelvir and use beyond 5 days.

Please keep in mind that medical literature databases, while considered a major source of biomedical information, are selective in their sources, and the information derived from them should not be considered all-inclusive.

ABBREVIATIONS

3CL	3-chymotrypsin-like	mITT	Modified Intent-to-Treat
AE	Adverse Event	MHLW	Ministry of Health, Labour, and Welfare
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing	PCC	Post COVID-19 Condition
$AUC_{0\text{-inf}}$	Area under the plasma concentration-time curve from time 0 to infinity	PK	Pharmacokinetic
CI	Confidence Interval	SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
C_{max}	Maximum plasma concentration	SCORPIO-HR	Stopping COVID-19 progression with early protease inhibitor-high risk
COVID-19	Coronavirus disease 2019	SCORPIO-PEP	Stopping COVID-19 progression with early protease inhibitor-post-exposure prophylaxis
DRSP	Drospirenone	SCORPIO-SR	Stopping COVID-19 Progression with early Protease Inhibitor-Standard Risk
EE	Ethinyl estradiol	$TCID_{50}$	50% Tissue Culture Infectious Dose

HDL	High-Density Lipoprotein	TEAE	Treatment-Emergent Adverse Event
HHC	Household Contact	US	United States
LS	Least Squares		

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11. Xocova® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.

ENCLOSURE

Xocova® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.