Xocova - Use in Hepatic Impairment

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). This document is being provided in response to an unsolicited request for medical information from a healthcare professional. 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. SUMMARY

- No dosage adjustment for XOCOVA is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The impact of severe hepatic impairment on the pharmacokinetics (PK) of ensitrelvir is unknown.[1]
- A Phase 1 study to assess safety, tolerability, and PK of ensitrelvir in healthy participants and in participants with mild to moderate hepatic impairment was conducted in the US. Ensitrelvir was well tolerated by participants with mild to moderate hepatic impairment, and no dose adjustment for ensitrelvir use was deemed required[2]
- Details about hepatic impairment representation in ensitrelvir clinical trials can be found below in the **Appendix**.
- **Yamato et al** conducted a single-center, retrospective chart review assessed the outcomes of patients treated with ensitrelvir for SARS-CoV-2, including three patients with hepatic impairment (hepatitis, liver failure, and liver metastasis from cancer of the sigmoid colon). After 5 days of treatment, all three patients with hepatic impairment experienced clinical improvement as assessed by the investigator, and all three patients had achieved viral clearance at final measurement[3,4]

2. PHASE 1 HEPATIC IMPAIRMENT STUDY

Study Design

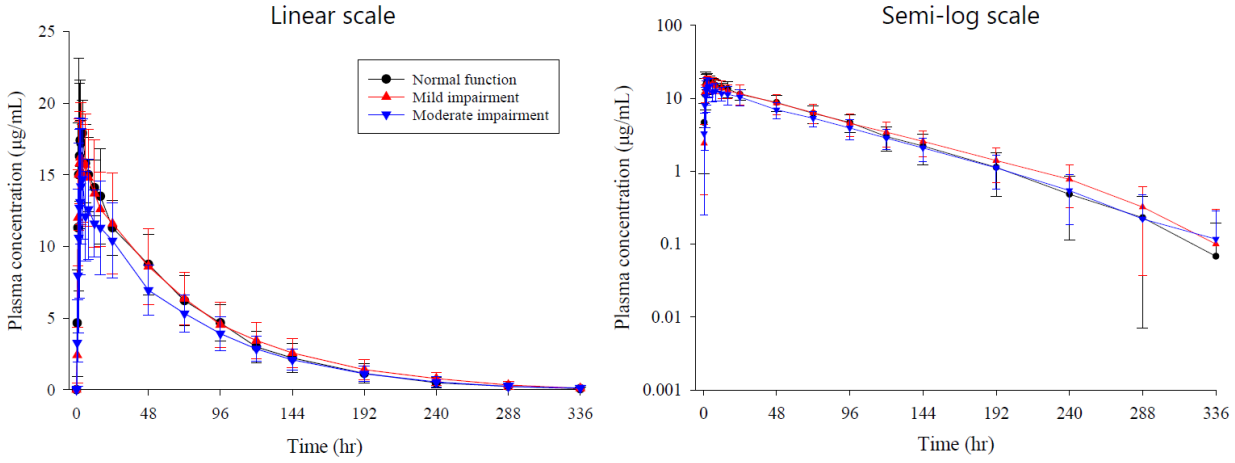
- A Phase 1, open-label, parallel-group study conducted in the US (NCT05409911) assessed the PK, safety, and tolerability of ensitrelvir in healthy participants and in participants with mild to moderate hepatic impairment compared with participants with normal hepatic function[2]
- Ensitrelvir was administered as a single oral 375 mg dose to 25 participants: nine with mild (Child-Pugh class A) hepatic impairment, eight with moderate (Child-Pugh class B) hepatic impairment, and eight with normal hepatic function[2]

Results

- Plasma concentrations of ensitrelvir were similar for participants with mild or moderate hepatic impairment and normal hepatic function (**Figure 1**)[2]
- Statistical analysis of PK values determined that:
  - Geometric mean ratios of maximum serum concentration (C_{max}) (90% confidence interval [CI]) were 0.886 (0.772-1.015) and 0.743 (0.604-0.913) for participants with mild and moderate hepatic impairment, respectively, compared to healthy controls (**Table 1**)[2]
  - $AUC_{0\text{-inf}}$ (90% CI) was 1.026 (0.815-1.293) and 0.872 (0.705-1.079) for participants with mild and moderate hepatic impairment, respectively, compared to healthy controls (**Table 1**)[2]

- Elimination half-life ($t_{1/2,z}$) was slightly higher in participants with mild and moderate hepatic impairment compared to healthy controls (Table 1 and Table 2)[2]
- Plasma unbound fraction was similar between the study groups (regardless of hepatic function), ranging from 1.1% to 1.6%[2]
- Ensitrelvir was well tolerated by participants with mild to moderate hepatic impairment and healthy control participants. Treatment-related treatment-emergent adverse events (TEAEs) were reported for 12.5% (1/8) of participants with normal hepatic function (mild diarrhea) and 11.1% (1/9) of participants with mild hepatic impairment (moderate decreased glomerular filtration rate). No TEAEs resulted in withdrawal of study treatment, and no serious adverse events were reported[2]
- No dose adjustment for ensitrelvir use was deemed required due to hepatic function[2]

Figure 1. Mean Plasma Concentrations of Ensitrelvir Following a Single 375 mg Dose[2]



Abbreviation: hr, hours
Figure adapted from Katsube et al. ECCMID. 2024.

Table 1. Summary of Ensitrelvir PK Parameters[2]

	Normal (N=8)	Mild (N=9)	Moderate (N=8)
T_{max} (h)[a]	2.0 (1.0-8.0)	2.0 (1.5-6.0)	3.0 (2.0-6.0)
C_{max} (µg/mL)	20.5 (15.1)	18.2 (17.0)	15.3 (30.4)
$AUC_{0\text{-inf}}$ (µg·h/mL)	1150 (24.4)	1180 (30.1)	1003 (24.6)
$t_{1/2,z}$ (h)	43.9 (16.9)	47.6 (19.6)	47.5 (23.0)
V_z/F (L)	20.7 (12.8)	21.8 (32.7)	25.6 (29.6)
MRT (h)	67.4 (20.9)	75.1 (32.7)	74.3 (22.2)
CL/F (L/h)	0.326 (24.4)	0.318 (30.1	0.374 (24.6)
CL_R (L/h)	0.0525 (24.0)	0.0518 (30.1)	0.0623 (49.6)
Feu (%)	15.8 (38.4)	16.2 (35.9)	16.3 (50.8)

Geometric Mean (CV% Geometric Mean).
Abbreviations: $AUC_{0\text{-inf}}$, area under concentration-time curve extrapolated from time zero to infinity; CL/F, apparent total clearance; CL_R, renal clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; Feu, fraction of dose excreted in urine; MRT, mean residence time; PK, pharmacokinetics; $t_{1/2,z}$, terminal elimination half-life; T_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution in the terminal elimination phase.
[a]Median (range).
Table adapted from Katsube et al. ECCMID. 2024.

Table 2. Statistical Analysis of Ensitrelvir PK Parameters[2]

	Mild vs Control	Moderate vs Control
C_{max}	0.886 (0.772-1.015)	0.743 (0.604-0.913)
$AUC_{0\text{-inf}}$	1.026 (0.815-1.293)	0.872 (0.705-1.079)
$t_{1/2,z}$	1.083 (0.927-1.266)	1.081 (0.907-1.289)

Geometric least squares mean ratio (90% confidence interval).
Abbreviations: $AUC_{0\text{-inf}}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration; PK, pharmacokinetics; $t_{1/2,z}$, terminal elimination half-life.
Table adapted from Katsube et al. ECCMID. 2024.

3. RETROSPECTIVE CHART REVIEW

Study Design

- A single-center, retrospective chart review assessed the outcomes of patients treated with ensitrelvir for SARS-CoV-2 in the Rinku General Medical Center (Izumisano, Japan) between November 2022 and April 2023 (Omicron variant-dominant period). Patients received daily oral treatment with ensitrelvir over 5 days with a 375 mg loading dose on Day 1 and 125 mg maintenance dose on Days 2 to 5. Antiviral activity as indicated by polymerase chain reaction or antigen testing and investigator assessments of clinical improvement were used to assess effectiveness[3]

Results

- A total of 32 hospitalized patients were included in the analysis, of which three patients had hepatic impairment, including one patient with liver metastasis from cancer of the sigmoid colon, one patient with liver failure, and one patient with chronic hepatitis B[3,4]
- All patients received 5 days of ensitrelvir treatment at the standard approved dosing of 375 mg loading dose on Day 1 and 125 mg on Days 2 to 5, with no dose adjustment. By Day 6, Patient 22 (liver failure) had viral clearance (defined as an antigen level of <89.73 pg/mL)[3,4]
    - At final measurement, all three patients with hepatic impairment had achieved viral clearance
- All patients, including those who had hepatic impairment, experienced clinical improvement as assessed by the investigator at the end of ensitrelvir treatment (Day 5)[3]
- Patient 27 (chronic hepatitis B) had a transient increase in body temperature to ≥37.5 °C after ensitrelvir treatment ended[3]
- No patients, including those who had hepatic impairment, discontinued treatment, there were no treatment-related adverse events, no patients progressed to severe disease, none were admitted to the intensive care unit, and none of the patients died up to Day 14[3]
- Virology outcome data for patients with hepatic impairment are presented in **Table 3**

Table 3. Virology Outcomes for Patients with Hepatic Impairment in a Single-Center Chart Review[3,4]

Patient	Underlying Diseases	Prior SARS-CoV-2 Treatment	Day -1 and Day 0	Day 1	Day 2	Day 3	Day 4	Day 5 (EOT)	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Treatment Outcome by Day 6[a]	Treatment Outcome at Final Measurement[a]	Viral Rebound
7	Liver metastasis from cancer of the sigmoid colon, breast cancer	Remdesivir[b] Casirivimab/ imdevimab		5000		1676.19					27.73								Viral Clearance	
22	Asthma, bronchitis, liver failure, cerebral infarction, renal failure	Remdesivir[b]	5000		5000			7.42	8.09	1.97	4.39	0.71	2.78	0.67	1.72	0.08	0.24	Viral Clearance	Viral Clearance	
27	Atrial fibrillation, chronic hepatitis B, CHF, chronic renal failure, pyelonephritis, HTN	Remdesivir[b] Casirivimab/ imdevimab	5000			1767.49	274.52	245.85	147.76	111.48			3.44	6.81	1.92	1.15	0.56		Viral Clearance	

This table is adapted under a Creative Commons CC BY 4.0 International License specific to the article published by Elsevier Ltd: Yamato M et al. J Infect Chemother. 2024:S1341-321X(24)00050-3

Shading indicates days patients were hospitalized.

Abbreviations: CHF, chronic heart failure; EOT, end of treatment; HTN, hypertension.

[a]Viral clearance defined as an antigen level of <89.73 pg/mL; viral rebound defined as an increase of antigen level of >89.73 pg/mL after viral clearance. bPatient received ≥3 days of remdesivir.

4. 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.[1]

Contraindications

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[1]

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.[1]

As stated in the XOCOVA Full Prescribing Information (FPI):

Section 7.3 Table 1 from the XOCOVA FPI provides example(s) of drugs that are contraindicated with XOCOVA.[1]

- *The table is provided as a guide and 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.*

Excerpted below is information from Table 1 listing examples of medicines contraindicated with Xocova due to potential hepatic complications. **See Table 1** in the XOCOVA FPI for the complete examples of drugs contraindicated with XOCOVA.

Excerpted Section of Table 1, XOCOVA FPI:

Relevant Examples of Drugs Contraindicated with XOCOVA Due to Risk of Potentially Serious or Fatal Interaction[1]

Drug Class	Examples of Drug within Class	Effect on Drug Concentration	Clinical Comment
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.
Microsomal triglyceride transfer protein (MTTP) inhibitors	lomitapide	↑ lomitapide	Co-administration is contraindicated due to potential for hepatotoxicity and gastrointestinal adverse reactions.

Section 8.7 – Hepatic Impairment

No dosage adjustment for XOCOVA is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The impact of severe hepatic impairment on the pharmacokinetics of ensitrelvir is unknown.[1]

Section 12.3 - Pharmacokinetics

No clinically significant differences in the pharmacokinetics of ensitrelvir was observed in mild (estimated glomerular filtration rate [eGFR] 60 to <90 mL/min as determined by MDRD equation), moderate (eGFR 30-<60 mL/min), or severe (eGFR 15-<30 mL/min) renal impairment, or mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The pharmacokinetics and safety of ensitrelvir have not been studied in patients with severe hepatic impairment (Child-Pugh Class C) or patients with kidney failure receiving dialysis.[1]

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.

5. LITERATURE SEARCH, ABBREVIATIONS, & REFERENCES

LITERATURE SEARCH

As of March 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has identified an additional relevant reference regarding use of ensitrelvir in patients with hepatic impairment. For your review, this reference is listed in the bibliography that follows:

> Ikeuchi K, Saito M, Okushin K, et al. Comparative effectiveness of antiviral treatment on household transmission of SARS-CoV-2: a retrospective cohort study using administrative data. *BMC Infect Dis*. 2025;25(1):1213. Published 2025 Sep 29. doi:10.1186/s12879-025-11651-6.

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 it should not be considered all-inclusive.

ABBREVIATIONS

3CL	3-chymotrypsin-like	FPI	Full Prescribing Information
$AUC_{0\text{-inf}}$	area under the plasma concentration-time curve from time 0 to infinity	hr	hours
CHF	chronic heart failure	HTN	hypertension
CI	confidence interval	MDRD	Modification of diet in renal disease
CL/F	apparent total clearance	MRT	mean residence time
CL_R	renal clearance	MTTP	Microsomal triglyceride transfer protein
C_{max}	maximum plasma concentration	PK	pharmacokinetics
COVID-19	coronavirus disease 19	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
CV	coefficient of variation	SCORPIO-HR	Stopping COVID-19 pRogression with early Protease InhibitOr-High Risk
CYP3A	cytochrome P450 3A	SCORPIO-PEP	Stopping COVID-19 pRogression with early Protease InhibitOr-Post-Exposure Prevention
DDI	drug-drug interaction	$t_{1/2,z}$	terminal elimination half-life
eGFR	estimated glomerular filtration	TEAE	treatment-emergent adverse event
EOT	end of treatment	T_{max}	time to maximum plasma concentration
FDA	Food and Drug Administration	US	United States
Feu	fraction of dose excreted in urine	V_z/F	apparent volume of distribution in the terminal elimination phase

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ENCLOSURE

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

APPENDIX

HEPATIC IMPAIRMENT REPRESENTATION IN ENSITRELVIR CLINICAL TRIALS

Multiple clinical trials have been conducted to evaluate the efficacy and safety of ensitrelvir in patients with COVID-19; some of these trials excluded patients with hepatic impairment. **Table 4** lists ensitrelvir clinical trials and hepatic impairment considerations

Table 4. Descriptions of Ensitrelvir Clinical Trials and Hepatic Impairment Considerations

Study Name	Trial Status	Study Design	Description	Hepatic Impairment Allowances
A Study to Assess S-217622 in Participants With Mild and Moderate Hepatic Impairment and Healthy Control Participants[5] (NCT05409911)	Completed	Phase 1, open-label, parallel-group	Assessed the PK, safety, and tolerability of ensitrelvir in participants with mild and moderate hepatic impairment compared with control participants with normal hepatic function	Enrolled patients with a diagnosis of clinically stable hepatic disease, mild (Child-Pugh class A, score 5 to 6) or moderate (Child-Pugh class B, score 7 to 9) hepatic impairment, and matched healthy controls. Study Details
A Phase 1 Study of S-217622 in Healthy Adult Participants[6-9] (jRCT2031210202)	Completed	Phase 1	A seven-part study to assess the safety, tolerability, and PK of single and multiple doses of ensitrelvir in healthy participants, as well as the effect of food, the comparison of PK of ensitrelvir in healthy Japanese and White participants, and DDI potential of ensitrelvir with CYP3A substrates	Excluded patients with history of hepatic conditions

Study Name	Trial Status	Study Design	Description	Hepatic Impairment Allowances
Phase 2/3 Study[10-14] (jRCT2031210350)	Completed	Phase 2/3, multicenter, randomized, double-blind, placebo-controlled	Evaluated the efficacy and safety of oral, once daily 125 mg or 250 mg ensitrelvir vs placebo given for 5 days in patients with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection regardless of risk factors for progressing to severe disease	Excluded patients with current or chronic history of moderate or severe liver disease of known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) Abnormal hepatic function was reported as a current medical condition in the safety analysis populations below; however, analysis based on hepatic function was not conducted • Phase 2a part: 2 patients (10.0%) and 1 patient (5.0%) given ensitrelvir 250 mg and placebo, respectively[15] • Phase 2b part: 1 patient (0.7%), 1 patient (0.7%), and 2 patients (1.4%) given ensitrelvir 125 mg, ensitrelvir 250 mg, and placebo, respectively[16] • Phase 3 part: 13 patients (2.2%), 5 patients (0.8%), and 13 patients (2.1%) given ensitrelvir 125 mg, ensitrelvir 250 mg, and placebo, respectively. Additionally, 1 patient treated with ensitrelvir 125 mg had a liver disorder[17]
SCORPIO-HR[18,19] (NCT05305547)	Completed	Phase 3, randomized, double-blind, placebo-controlled, multicenter	A 24-week clinical study assessed the safety, clinical and antiviral effects of ensitrelvir (oral once daily for 5 days) vs placebo in nonhospitalized patients with confirmed symptomatic COVID-19 with or without high risk factors for severe COVID-19	Excluded patients with known history of cirrhosis or liver decompensation (including ascites, variceal bleeding, or hepatic encephalopathy)

Study Name	Trial Status	Study Design	Description	Hepatic Impairment Allowances
SCORPIO-PEP[20-22] (NCT05897541)	Completed	Phase 3, randomized, double-blind, placebo-controlled, multicenter	Evaluated the safety and efficacy of ensitrelvir (oral once daily for 5 days) in the prevention of symptomatic COVID-19 from household contacts of people who tested positive for COVID-19, when compared to placebo	Excluded patients with severe liver dysfunction, such as known history of cirrhosis or liver decompensation (including ascites, variceal bleeding, or hepatic encephalopathy)
Pediatric trial[23,24] (jRCT2031230140)	Completed	Phase 3, randomized, double-blind, placebo-controlled	Evaluated the safety and efficacy of ensitrelvir (oral once daily for 5 days) in children with at least one moderate or severe COVID-19 symptom at screening	Excluded patients with severe hepatic impairment

Abbreviations: COVID-19, coronavirus disease 19; CYP3A, cytochrome P450 3A; DDI, drug-drug interaction; PK, pharmacokinetics; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoC, standard of care.