Xocova - Effect of Food on Pharmacokinetics

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.**

SUMMARY

- Ensitrelvir is taken as 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.[1]
- As stated in the **Xocova Full Prescribing Information** in section **12.3 Pharmacokinetics**: No clinically significant differences in ensitrelvir pharmacokinetics were observed following administration of a high-fat, high-calorie meal [total calories were 863 kcal (27.2% carbohydrates, 17.3% proteins, and 55.4% fat)].[1]
- The effect of food on ensitrelvir PK was assessed in a phase 1 study of single and multiple ascending oral doses[2-5]
  - Food intake reduced maximum concentration (C_{max}) and delayed time to maximum concentration (T_{max}) but did not impact area under the concentration-time curve (AUC). In addition, no clinically meaningful differences in C_{max} or AUC were observed between fasting and fed states. These results suggest ensitrelvir can be taken without food restrictions[2,3]

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Summary | Phase 1 Study Design | Phase 1 Study Results | Relevant Prescribing Information | Literature Search, Abbreviations, References

PHASE 1 STUDY DESIGN

A seven-part phase 1 study (2102T1211) conducted in Japan evaluated the safety, efficacy, and PK of single and multiple ascending doses of ensitrelvir, including the effect of food on ensitrelvir PK.[2-5] Please note that the three publications that report on the various parts of this phase 1 study use differing nomenclature. Therefore, we have used our own method of numbering the study parts for added clarity. The study design of the food effect analysis of the Phase 1 study is depicted in Figure 1.

Ensitrelvir Suspension

Part 1 was a single-center, randomized, double-blind, placebo-controlled study in Japanese healthy adult males that evaluated the safety, tolerability, and pharmacokinetics of single ascending oral doses of ensitrelvir (N=50). It consisted of six cohorts (A, B, C, D, E, and J) that examined the effect of a fasted state on the PK of ensitrelvir suspension; in Cohort C, the effect of food was also evaluated in a two-group, two-period crossover design.[2]

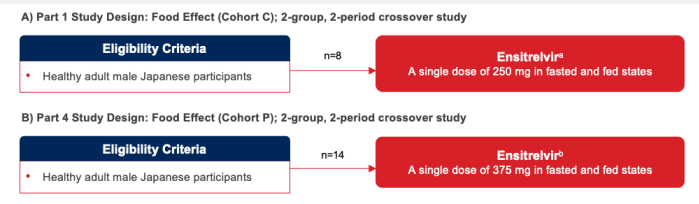
- Study subjects in a fasted state were administered placebo or ensitrelvir suspension doses of 20 mg (Cohort A), 70 mg (Cohort B), 250 mg (Cohort C), 500 mg (Cohort D), 1000 mg (Cohort E), and 2000 mg (Cohort J). Cohorts A, B, D, E, and J each included six participants[2,4]
- Blood samples for PK analysis were taken predose (hour [h] 0) and at several timepoints postdose (on Days 1 and 15 in Cohort A, and on Day 1 in Cohorts B, D, E, and J). Measures included C_{max}, T_{max}, area under the concentration-time curve from time 0 to last quantifiable time point ($AUC_{0\text{-last}}$), area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-inf}}$), terminal elimination half-life ($t_{1/2,z}$), terminal elimination rate constant (λ_z), mean residence time (MRT), apparent total clearance (CL/F), and apparent volume of distribution (V_z/F)[2,4]
- Cohort C (n=8) was conducted as a two-group, two-period crossover design, where study subjects were administered placebo or ensitrelvir 250 mg in a fasted or fed (high-fat/high calorie) state[2,4]
  - Blood samples for PK analysis of Cohort C were taken predose and at several timepoints postdose on Days 1 and 15 at 250 mg ensitrelvir. Measures included C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-T}}$, and $t_{1/2,z}$[2,4]

Ensitrelvir Tablets

Part 4 was a single-center, randomized, open-label, two-group two-period crossover study in Japanese healthy males examining the effect of food on the PK of ensitrelvir tablets.[3,4]

- In this one-cohort study (Cohort P), participants (n=14) were orally administered a single dose of ensitrelvir 375 mg (three 125 mg tablets) in the fasted and high-fat, high-calorie fed states[3,4]
- Blood samples for PK analysis were taken predose (h 0) and at several timepoints postdose (on Days 1 and 22). Measures included C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $t_{1/2,z}$, MRT, and V_z/F[3,4]

Figure 1. Food Effect Analysis of the Phase 1 Study[2-4]



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Summary | Phase 1 Study Design | Phase 1 Study Results | Relevant Prescribing Information | Literature Search, Abbreviations, References

PHASE 1 STUDY DESIGN

Figure 1. Food Effect Analysis of the Phase 1 Study[2-4]

A) Part 1 Study Design: Food Effect (Cohort C); 2-group, 2-period crossover study

Eligibility Criteria		
• Healthy adult male Japanese participants	n=8 →	**Ensitrelvir[a]** A single dose of 250 mg in fasted and fed states

B) Part 4 Study Design: Food Effect (Cohort P); 2-group, 2-period crossover study

Eligibility Criteria		
• Healthy adult male Japanese participants	n=14 →	**Ensitrelvir[b]** A single dose of 375 mg in fasted and fed states

The phase 1 study consisted of 7 parts that included multiple patient cohorts. Food effect analyses were performed in Part 1 (Cohort C out of the 6 Cohorts in Part 1) and in Part 4 (Cohort P, the only cohort in Part 4).[4]
[a]Ensitrelvir suspension was administered
[b]Ensitrelvir 125 mg tablets were administered

- Cohort C (n=8) was conducted as a two-group, two-period crossover design, where study subjects were administered placebo or ensitrelvir 250 mg in a fasted or fed (high-fat/high calorie) state[8-10]
  - Blood samples for PK analysis of Cohort C were taken predose and at several timepoints postdose on Days 1 and 15 at 250 mg ensitrelvir. Measures included C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-T}}$, and $t_{1/2,z}$[8-10]

Ensitrelvir Tablets

Part 4 was a single-center, randomized, open-label, two-group two-period crossover study in Japanese healthy males examining the effect of food on the PK of ensitrelvir tablets.[9,10]

- In this one-cohort study (Cohort P), participants (n=14) were orally administered a single dose of ensitrelvir 375 mg (three 125 mg tablets) in the fasted and high-fat, high-calorie fed states[9,10]
- Blood samples for PK analysis were taken predose (h 0) and at several timepoints postdose (on Days 1 and 22). Measures included C_{max}, T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $t_{1/2,z}$, MRT, and V_z/F[9,10]

Figure 1. Food Effect Analysis of the Phase 1 Study[8-10]

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PHASE 1 STUDY RESULTS

Ensitrelvir Suspension

Effect of Fasted State

Study Part 1 results of PK parameters of single-dose ensitrelvir suspension in the fasted state are presented in Table 1. In the fasted state, after single doses of ensitrelvir suspension of 20 to 2000 mg, median T_{max} ranged from 1.5 to 4 hours; C_{max} and $AUC_{0\text{-}inf}$ increased in an almost dose-proportional manner across the dose range. The geometric mean of $t_{1/2,z}$ ranged from 42.2 to 48.1 h. No clear relationship was found between the dose and $t_{1/2,\,z}$, MRT, or V_z/F across the dose range.[2,4]

Table 1. PK Parameters for Single-Dose Administration of Ensitrelvir (Part 1; Cohorts A-E, and J) in the Fasted State[2]

Parameters	Ensitrelvir (cohort/dose)					
	A/20 mg	B/70 mg	C/250 mg	D/500 mg	E/1000 mg	J/2000 mg
n	6	6	8	6	6	6
C_{max} (µg/mL)	1.70 (15.0)	5.20 (18.5)	15.2 (23.6)	32.6 (19.0)	63.8 (39.1)	96.9 (16.5)
T_{max} (h)	2.50 (1.00, 4.00)	1.50 (1.00, 4.00)	2.50 (1.00, 12.00)	2.00 (1.00, 4.00)	2.75 (1.00, 6.00)	4.00 (1.50, 8.00)
$AUC_{0\text{-}last}$ (µg•h/mL)	82.00 (19.5)	289.1 (15.4)	908.6 (15.8)	1975 (15.9)	3,341 (35.2)	6,311 (22.0)
$AUC_{0\text{-}inf}$ (µg•h/mL)	91.44 (24.3)	291.0 (15.7)	913.7 (16.2)	1987 (16.1)	3,370 (35.5)	6,346 (22.2)
$T_{1/2,z}$ (h)	42.6 (18.6)	45.7 (11.9)	43.1 (20.2)	42.2 (14.6)	48.1 (11.3)	43.1 (15.6)
MRT (h)	61.8 (18.7)	67.3 (13.4)	73.4 (12.7)	68.2 (9.0)	70.3 (9.3)	67.4 (8.4)
V_z/F (L)	13.5 (10.2)	15.9 (9.0)	17.0 (8.8)	15.3 (13.5)	20.6 (26.2)	19.6 (21.7)

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Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-}last}$, area under the concentration-time curve from time 0 to last quantifiable time point; C_{max}, maximum serum concentration; h, hours; MRT, mean residence time; PK, pharmacokinetics; $t_{1/2,z}$, terminal elimination half-life; T_{max}, time to maximum serum concentration; V_z/F, apparent volume of distribution.

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PHASE 1 STUDY RESULTS

Ensitrelvir Suspension (cont'd)

Effect of Food

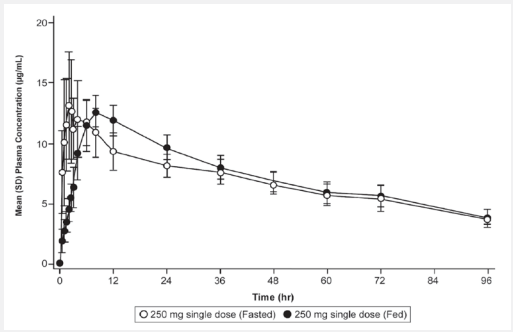
In study Part 1, the C_{max} and T_{max} of ensitrelvir 250 mg suspension in the fed state differed from those in the fasted state. Concomitant food intake reduced C_{max} by 15% and delayed T_{max} from 2.5 h in the fasted state to 8 h in the fed state. AUC values of ensitrelvir suspension (both $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) were comparable between the fasted and fed states (Table 2). These results suggest ensitrelvir can be taken without food restrictions.[2]

Concentration-time profiles of ensitrelvir following single-dose administration in the fasted and fed state are shown in Figure 2.

Table 2. Statistical Analysis of the Effect of Food on the PK of Ensitrelvir Following Single-Dose 250-mg Administration in the Fasted and Fed States (Part 1)[2]

Parameter	Cohort C/ 250 mg single dose				
	Fasted		Fed		GLS mean (90% CI) ratio (fed/fasted)
	n	GLS mean	n	GLS mean	GLS mean (90% CI) ratio
C_{max} (μg/mL)	8	15.2	8	13.0	0.8508 (0.7507/0.9644)
$AUC_{0\text{-last}}$ (μg · h/mL)	8	906.8	8	949.4	1.0470 (1.0061/1.0895)
$AUC_{0\text{-inf}}$ (μg · h/mL)	8	913.7	8	955.7	1.0460 (1.0047/1.0891)
$t_{1/2,z}$	8	43.1	8	40.5	0.9385 (0.8893/0.9905)

Figure 2. Effect of Food on the PK of Ensitrelvir Following a Single 250 mg Dose[2]



Safety

Ensitrelvir suspension was tolerated well with no major safety concerns. Among the treatment-emergent adverse events (TEAEs) observed in the ensitrelvir group were lower high-density lipoprotein cholesterol (HDL-C) (6/6 each in cohorts E and J; 7/8 each in cohorts F, G, and H), diarrhea (4/8 each in cohorts F, G, and H), headache (4/8 in cohort G and 2/8 in cohort H), and drowsiness (3/8 in cohort G); the last of which was observed after participants received midazolam. TEAEs were, for the most part, mild and resolved without treatment.[2]

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PHASE 1 STUDY RESULTS

Table 2. Statistical Analysis of the Effect of Food on the PK of Ensitrelvir Following Single-Dose 250-mg Administration in the Fasted and Fed States (Part 1)[2]

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Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the concentration-time curve from time 0 to last quantifiable time point; CI, confidence interval; C_{max}, maximum serum concentration; GLS, geometric least squares; PK, pharmacokinetics; $t_{1/2,z}$, terminal elimination half-life.

Safety

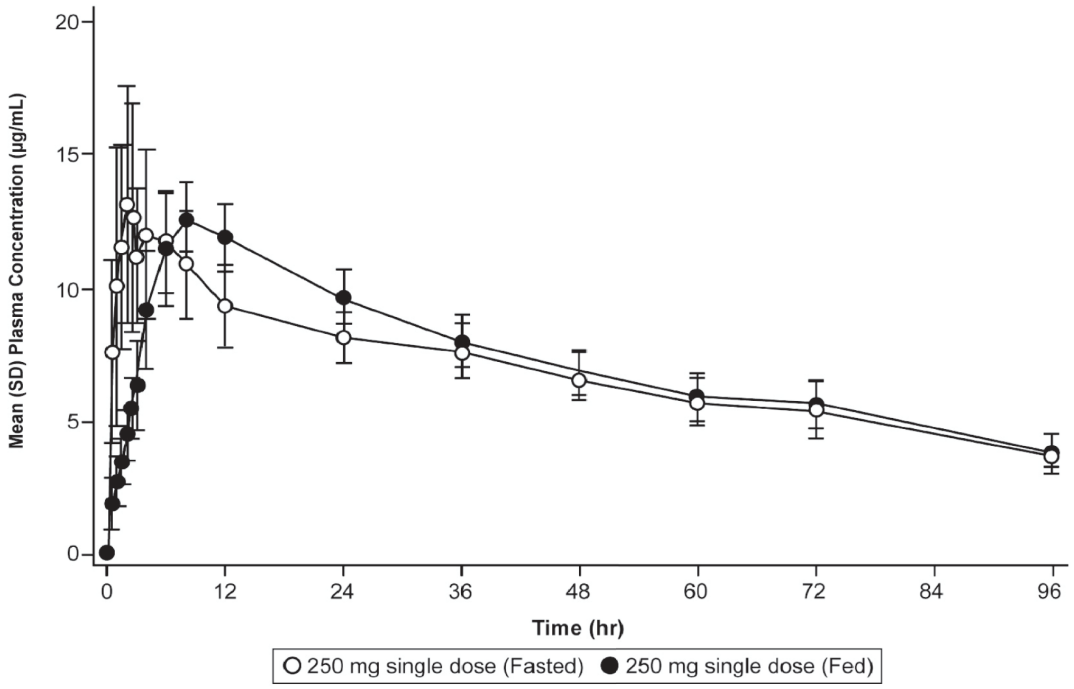
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PHASE 1 STUDY RESULTS

Figure 2. Effect of Food on the PK of Ensitrelvir Following a Single 250 mg Dose[2]



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Plasma concentration-time profiles of ensitrelvir following single-dose administration in the fasted and fed states.

Abbreviations: hr, hour; PK, pharmacokinetics; SD, standard deviation.

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PHASE 1 STUDY RESULTS

Ensitrelvir Tablets

Effect of Food

PK parameters determined for ensitrelvir tablets in Part 4 of the study are presented in **Table 3**. All participants were healthy Japanese adult males. Following a single ensitrelvir 375 mg dose, median T_{max} in the fed state was 6 h and in the fasted state was 2.5 h. The geometric least squares mean of fed/fasted ratios (90% confidence intervals [CIs]) of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were 0.9320 (0.8134-1.0679), 1.2435 (1.1400-1.3564), and 1.2447 (1.1396-1.3596), respectively. The 90% CIs for C_{max} were completely within the range of 0.80 to 1.25 indicating that there was no clinically meaningful difference in the exposure of ensitrelvir 375 mg between the fasted and fed states.[3]

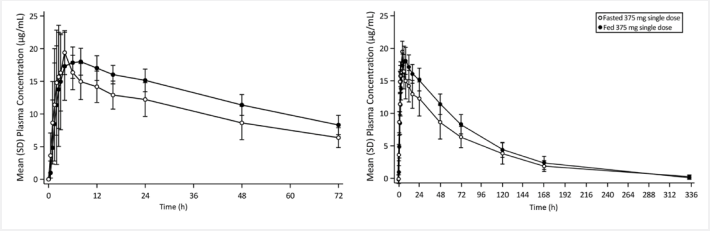
Food intake increased both $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ of ensitrelvir by ~25%; upper limits of Cis were slightly higher than 1.25.[3]

The plasma concentration profiles until a) 72 h and b) 336 h postdose following a single 375 mg dose of ensitrelvir tablets in fasted and fed states are presented in **Figure 3**.[3]

Table 3. Effect of Food on the PK of Ensitrelvir Following Single-Dose Administration of Ensitrelvir 375 mg for Healthy Japanese Adult Participants in Fasted and Fed States (Part 4)[3]

Parameter	GLS mean with 375 mg single-dose administration		Fed/fasted GLS mean ratio (90% CI)
	Fasted (n = 13)	Fed (n = 14)	
C_{max}, µg/mL	21.5	20.0	0.9320 (0.8134–1.0679)
$AUC_{0\text{-last}}$, µg · h/mL	1222	1519	1.2435 (1.1400–1.3564)
$AUC_{0\text{-inf}}$, µg · h/mL	1235	1538	1.2447 (1.1396–1.3596)

Figure 3. Mean (SD) Plasma Concentration Profiles of Ensitrelvir Until A) 72 h and B) 336 h Postdose Following Single-Dose Administration of Ensitrelvir 375 mg in the Fasted and Fed States for Healthy Japanese Participants[3]



Safety

Ensitrelvir was well tolerated with no new safety signals observed. Among the TEAEs that were more frequent in the ensitrelvir group vs the placebo group were decreased HDL (4/13 in the fasted 375 mg cohort, 7/14 in the fed 375 mg cohort), headache (1/13 in the fasted 375 mg cohort, 2/14 in the fed 375 mg cohort), and COVID-19 and nausea (1/14 in the fed 375 mg cohort). Except for the occurrence of COVID-19, all TEAEs were considered to be related to ensitrelvir.[3]

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Ensitrelvir Suspension | Ensitrelvir Tablets

PHASE 1 STUDY RESULTS

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	Fasted (n = 13)	Fed (n = 14)	
C_{max}, µg/mL	21.5	20.0	0.9320 (0.8134–1.0679)
$AUC_{0\text{-last}}$, µg · h/mL	1222	1519	1.2435 (1.1400–1.3564)
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Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the concentration-time curve from time 0 to last quantifiable time point; CI, confidence interval; C_{max}, maximum serum concentration; GLS, geometric least squares; PK, pharmacokinetics.

Fasted and Fed States (Part 4)[3]

Fasted and Fed States for Healthy Japanese Participants[9]

Safety

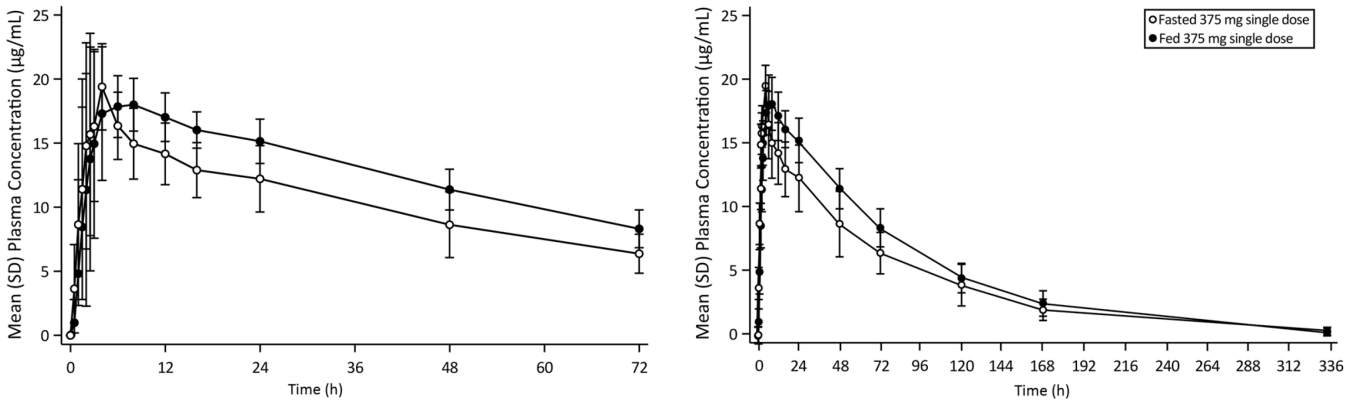
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PHASE 1 STUDY RESULTS

Figure 3. Mean (SD) Plasma Concentration Profiles of Ensitrelvir Until A) 72 h and B) 336 h Postdose Following Single-Dose Administration of Ensitrelvir 375 mg in the Fasted and Fed States for Healthy Japanese Participants[3]



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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]

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 Day1 and 125 mg (one 125-mg tablet) orally on Days 2 to 5 with or without food.[1]

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.[1]

As stated in the Xocova Full Prescribing Information:

Section 12.3 - Pharmcokinetics

No clinically significant differences in ensitrelvir pharmacokinetics were observed following administration of a high-fat, high-calorie meal [total calories were 863 kcal (27.2% carbohydrates, 17.3% proteins, and 55.4% fat)].[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.

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LITERATURE SEARCH

As of April 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has failed to identify any additional relevant references regarding information on ensitrelvir and food effect.

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.

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ABBREVIATIONS

3CL	3-chymotrypsin-like
λ_z	terminal elimination rate constant
AUC	area under the curve
$AUC_{0\text{-inf}}$	area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-last}}$	area under the concentration-time curve from time 0 to last quantifiable time point
CI	confidence interval
CL/F	apparent total clearance
C_{max}	maximum serum concentration
COVID-19	corona virus disease 19
FDA	Food and Drug Administration
GLS	geometric least squares
h, hr	hours
HDL-C	high-density lipoprotein cholesterol
MHLW	Ministry of Health, Labour and Welfare
MRT	mean residence time
PK	pharmacokinetics
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	SD, standard deviation
$t_{1/2,z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum serum concentration
US	United States
V_z/F	apparent volume of distribution

Xocova - Effect of Food on Pharmacokinetics

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.**

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ENCLOSURE

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