Xocova – Use in Pregnancy and Lactation

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. SUMMARY

Key Prescribing Information

- Pregnancy: Based on animal reproduction studies, XOCOVA may cause fetal harm when administered to pregnant women. Embryofetal toxicity, including skeletal malformations, fetal growth retardation, and embryofetal lethality, was observed in rabbits and rats at systemic exposures approximately 7 to 9 times the human exposure at the recommended human dose (RHD). Pre- and postnatal studies in rats also demonstrated offspring lethality, reduced body weight, and delayed morphological development at similar exposure multiples. There are insufficient human data to determine drug-associated risks in pregnancy. Pregnancy status should be verified prior to initiation, and females of reproductive potential should be advised of potential fetal risk.[1]

- Lactation: There are no data on the presence of ensitrelvir in human milk, its effects on the breastfed infant, or its effects on milk production. Ensitrelvir was detected in the milk of lactating rats at concentrations approximately twice those in maternal plasma. Due to the potential for adverse reactions in a breastfed child, breastfeeding is not recommended during the use of XOCOVA and for at least 2 weeks after the final dose.[1]

- Reproductive potential and fertility: Females of reproductive potential should use effective contraception during treatment and for 2 weeks after the final dose. In animal studies, ensitrelvir had no effects on fertility, mating performance, or early embryonic development in rats at exposures approximately 9 times the human exposure at the RHD.[1]

Please review select information from the **XOCOVA Full Prescribing Information** in the "Key Prescribing Information" section of this letter and read the attached **XOCOVA Full Prescribing Information** enclosed.

Clinical Studies

- Across the ensitrelvir clinical development program, pregnant and lactating women were excluded from the clinical trials.[2-11]
- In the Phase 2b/3 study, 1 pregnancy was reported in a participant receiving ensitrelvir 125 mg after completion of study treatment; follow-up information indicated that the participant subsequently gave birth and that both the participant and infant were healthy, with no adverse events reported.[9]
- No other pregnancy- or lactation-specific data are available from clinical studies
- Detailed summaries of the ensitrelvir clinical trials are provided in **Table 1 in the Appendix**.

Post-Marketing Safety Communication

- In Japan, post-marketing reports recorded 54 cases in which pregnancy was detected after administration of XOCOVA Tablets by marketing authorization holders (MAHs) between November 22, 2022, and October 31, 2024; these reports do not include assessment of causality or clinical outcomes.[12]

2. KEY PRESCRIBING INFORMATION

Indication 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:[1]

- 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.

As stated in the XOCOVA Full Prescribing Information:

Section 2.1 – Dosage and Administration: Pregnancy Evaluation Prior to Initiating XOCOVA
Verify pregnancy status of females of reproductive potential prior to initiating XOCOVA.[1]

Section 5.1 – Warnings and Precautions: Embryofetal Toxicity
Based on animal reproduction studies, XOCOVA may cause fetal harm when administered to a pregnant woman. In rabbits, embryofetal toxicity (including skeletal malformations and embryofetal lethality) was observed in rabbit offspring following exposure of pregnant rabbits to ensitrelvir at 7 times the human exposures at the recommended human dose (RHD). Likewise in rats, fetal growth retardation, low fetal body weight, skeletal variations, offspring lethality, low body weight in offspring, and retardation of morphological development were observed following exposure during gestation and lactation at exposures 9 times the human exposures at the RHD.[1]

Advise pregnant women and females of reproductive potential that XOCOVA may cause fetal harm. Verify pregnancy status of females of reproductive potential prior to initiating XOCOVA. Advise females of reproductive potential to use effective contraception during XOCOVA use and for 2 weeks after the final dose.[1]

Section 8.1 – Use in Specific Populations: Pregnancy

Risk Summary
Based on animal reproduction studies, XOCOVA may cause fetal harm when administered to a pregnant woman. Embryofetal toxicity (including skeletal malformations and embryofetal lethality) was observed in rabbits during the period of organogenesis at ensitrelvir exposures 7 times the human exposures at the recommended human dose (RHD). In rats, fetal growth retardation, low fetal body weight, and skeletal variations were observed during the period of organogenesis at ensitrelvir

exposures 9 times the RHD. In addition, lethality, low body weight, and retardation of morphological development were observed in pre-weaning pups during gestation and lactation at ensitrelvir exposures 9 times the RHD. Advise pregnant women and females of reproductive potential that XOCOVA may cause fetal harm.[1]

The available clinical data on the use of XOCOVA during pregnancy are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.[1]

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a risk of birth defects, loss, and other adverse outcomes. In the general population in the United States, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.[1]

Data

Animal Data

In an embryofetal development study in pregnant rabbits, ensitrelvir was administered at oral doses of 30, 100, or 300 mg/kg/day on gestation days (GD) 6-19. Embryofetal lethality, skeletal malformations and variations, abortion, and post-implantation loss were observed with maternal toxicity (decreased food consumption and body weight and body weight gain) at doses ≥100 mg/kg/day. Malformations of the axial skeleton included fused sternebra, branched rib, fused cervical centrum, supernumerary thoracic vertebra, fused thoracic arch, and fused caudal centrum. Skeletal variations included splitting of the thoracic centrum and increased frequencies of full supernumerary rib and/or supernumerary lumbar vertebra. No effects were observed at 30 mg/kg/day, which is estimated to be 3 times the human exposure at the RHD based on the area under the curve (AUC). In a second embryofetal development study in pregnant rabbits, ensitrelvir was administered at 300 mg/kg/day on GD 6-9, 10-12, 13-15, and 16-19. Similar malformations of the axial skeleton were observed, with most of the abnormalities present in animals dosed on GD 6-9; maternal toxicity (presenting as low food consumption) was also present during each segmented dosing period.[1]

In an embryofetal development study in pregnant rats, ensitrelvir was administered at oral doses of 20, 60, or 1000 mg/kg/day on GD 6-17. A delay in fetal development (as measured by decreased bone ossification and fetal body weight), as well as an increased incidence of short supernumerary rib, were observed at 1000 mg/kg/day. Decreased food consumption and body weight were also observed at this dose. No effects were observed at 60 mg/kg/day, which is estimated to be 5 times the human exposure at the RHD based on AUC.[1]

In a pre-and postnatal development study, ensitrelvir was administered to pregnant rats at oral doses of 20, 60, or 1000 mg/kg/day from GD 6 to postnatal day (PND) 20. Lethality, low body weight, and retardation of morphological development (delayed eyelid opening and sexual maturation) were observed at the highest dose of 1000 mg/kg/day, accompanied by maternal toxicity (total litter loss, decreased body weight and body weight gain, and decreased food consumption). No effects were observed at 60 mg/kg/day, which is estimated to be 5 times the human exposure at the RHD based on AUC.[1]

Section 8.2 – Use in Specific Populations: Lactation

Risk Summary

There are no data on the presence of ensitrelvir in human milk, the effects on the breastfed infant, or the effects on milk production. Ensitrelvir was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Due to the potential for

adverse effects in a breastfed child from XOCOVA, advise lactating women not to breastfeed while taking XOCOVA and for at least 2 weeks after the final dose.[1]

Data
In rats, ensitrelvir was excreted into the milk of lactating rats following a single oral administration of 2 mg/kg. Milk concentrations of ensitrelvir were approximately 2 times that of maternal plasma concentrations, observed 4 hours post-dose. The concentration of ensitrelvir in animal milk does not necessarily predict the concentration of ensitrelvir in human milk.[1]

Section 8.3 – Use in Specific Populations: Females and Males of Reproductive Potential

Based on animal data, XOCOVA may cause fetal harm when administered to pregnant women.[1]

Pregnancy Testing
Verify pregnancy status of females of reproductive potential prior to initiating XOCOVA.[1]

Contraception
Females
Advise females of reproductive potential to use effective contraception during use of XOCOVA and for 2 weeks after the final dose.[1]

Section 13.1 – Carcinogenesis, Mutagenesis, Impairment of Fertility

Impairment of Fertility
There were no effects on fertility, mating performance or early embryonic development when ensitrelvir was administered to rats at systemic exposures (AUC) approximately 9 times the exposure in humans at the RHD.[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.

3. CLINICAL STUDIES

Multiple clinical trials have been conducted to evaluate the efficacy and safety of ensitrelvir; pregnant and lactating women were excluded from these trials.[2-11] Detailed summaries of the ensitrelvir clinical trials are provided in **Table 1 in the Appendix**. Across the clinical trials, pregnancy-related procedures primarily focused on the prevention, monitoring, and documentation of unintended pregnancies occurring during study participation.

In the phase 2b/3 study, pregnancy was reported in 1 participant in the ensitrelvir 125 mg group after completion of study treatment. Follow-up information indicated that the participant subsequently gave birth, and both the participant and the infant were healthy, with no adverse events reported.[9]

4. POST-MARKETING SAFETY COMMUNICATION (JAPAN)

According to a PMDA *Alert for Proper Use of Drugs* (December 2024) in Japan, administration of ensitrelvir fumaric acid (XOCOVA Tablets) to pregnant women or women who may be pregnant is contraindicated due to a risk of teratogenicity.[12]

Fifty-four cases of pregnancy were detected after administration of XOCOVA tablets by MAHs (receipt of information from November 22, 2022 to October 31, 2024). These reports reflect post-

administration detection of pregnancy and do not include an assessment of causality or clinical outcomes.[12]

5. LITERATURE SEARCH, ABBREVIATIONS, & REFERENCES

LITERATURE SEARCH

As of July 2026, a computerized search of the published medical literature using internal and external databases (eg, PubMed®) did not identify any references on the use of ensitrelvir in pregnant and lactating patients.

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

AUC	area under the curve
COVID-19	coronavirus disease 19
CYP3A	cytochrome P450 3A
DDI	drug-drug interaction
FDA	Food and Drug Administration
GD	gestation day
MAH	marketing authorization holder
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PND	postnatal day
RHD	recommended human dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WOCBP	women of childbearing potential

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ENCLOSURE

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

APPENDIX

Table 1. Descriptions of Ensitrelvir Clinical Trials and Pregnancy- and Lactation-Specific Data.

Study Name	Study Design	Description	Relevant Exclusion Criteria	Results/ Outcomes
Phase 1 Studies[a]				
A Phase 1 Study of S-217622 in Healthy Adult Participants[2,13] (jRCT2031210202)	Phase 1	A 7-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	Across study parts that permitted enrollment of female participants (Part 2 [cohorts N and O], 4, 5, 6, and 7), pregnant or breastfeeding women were not eligible for participation. Female participants were eligible if they were of non-childbearing potential or were women of childbearing potential using a highly effective contraceptive method during the study intervention period and for at least 10 days after the last dose.	No pregnancies in female participants or partners of male participants were reported in the study.
A Study to Assess S-217622 in Participants with Renal Impairment and Healthy Participants[3,14] (NCT05363215)	Phase 1, open-label, parallel-group	Assessing the PK, safety, and tolerability of ensitrelvir in participants with mild, moderate, and severe renal impairment, and control participants with normal renal function	Female participants were eligible if they were not pregnant, not breastfeeding, and not of childbearing potential, or, if of childbearing potential, were using a highly effective contraceptive method. Of the total 32 participants, 1 female participant of childbearing potential with severe renal impairment was included in the study.	No pregnancy-related events were reported during the study.
A Study to Assess S-217622 in Participants With Mild and Moderate Hepatic Impairment and Healthy Control Participants[4,15] (NCT05409911)	Open-label, parallel-group	Assessed the PK, safety, and tolerability in participants with mild and moderate hepatic impairment and healthy control participants	Female participants were eligible if they were not pregnant, not breastfeeding, and not of childbearing potential, or, if of childbearing potential, were using a highly effective contraceptive method.	No pregnancies were reported in the study.
A Drug-Drug Interaction Study of S-217622 With Combined Oral Contraceptives in Healthy Adult Female Participants[5,16] (NCT06775730)	Phase 1, open-label, single-group	Clinical pharmacology study designed to evaluate the effect of ensitrelvir on the PK of combined oral contraceptives in healthy adult female participants	Pregnant or breastfeeding women were not eligible for participation.	No pregnancies were reported during the study.
Phase 2/3 Study[b]				
Phase 2/3 Study[6-9,17-19] (jRCT2031210350)	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	Female participants were eligible if they were not pregnant, not breastfeeding, and not of childbearing potential, or, if of childbearing potential, were using a highly effective contraceptive method.	**Phase 2a:**[6] No pregnancies were reported in the study. **Phase 2b:**[7] No pregnancies were reported in the study. **Phase 3 (SCORPIO-SR):**[8] No pregnancies were reported in the study. **Phase 2b/3:**[9] Pregnancy was reported in 1 participant in the ensitrelvir 125 mg group, confirmed on Day 28 (corresponding with the 6th week of gestation), occurring 23 days after the last dose of study intervention. On Day 35, the participant was hospitalized for hyperemesis gravidarum, with symptom improvement and discharge by Day 45. Follow-up information reported that the participant subsequently gave birth, and both the participant and the infant were healthy without any adverse events

Study Name	Study Design	Description	Relevant Exclusion Criteria	Results/ Outcomes
Phase 3 Studies[b]				
SCORPIO-PEP[10,20,21] (NCT05897541)	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	Female participants were eligible if they were not pregnant, not breastfeeding, and not of childbearing potential, or, if of childbearing potential, were using a highly effective contraceptive method.	No pregnancies were reported in the study.
SCORPIO-HR[11,22] (NCT05305547)	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	Pregnancy and lactation; currently pregnant or breastfeeding.	No pregnancies were reported in the study.

Pregnancy Testing, Management, and Follow-up:[2-11]

[a]**Phase 1 Studies:** Across the Phase 1 studies (PK, Renal Impairment, Hepatic Impairment, and DDI Studies), pregnant or breastfeeding women were not eligible to participate. Female participants were required to have a negative pregnancy test prior to study intervention, with additional pregnancy testing conducted according to protocol-defined schedules and, where specified, at the discretion of the investigator or sub-investigator. If pregnancy occurred during study participation, study intervention was discontinued and/or the participant was withdrawn. Pregnancy information was collected for female participants and female partners of male participants, with follow-up conducted per protocol. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) were classified as SAEs, and pregnancy outcomes were generally followed for approximately 6-8 weeks after the estimated delivery date. Any termination of pregnancy was reported regardless of fetal status or indication.

- **Phase 1 PK Study:** Women of childbearing potential (WOCBP) were required to have a negative highly sensitive pregnancy test (urine or serum, per local regulations) within 24 hours prior to the first dose. If a urine test result could not be confirmed as negative, a serum pregnancy test was required, and participants with a positive serum pregnancy test were excluded. Pregnancy testing (WOCBP only) was conducted prior to dosing and at protocol-defined follow-up visits across multiple study parts. In Part 4, pregnancy testing was conducted at screening and prior to dosing, with an additional pregnancy test at a later follow-up visit, as specified in the schedule of activities. Pregnancy follow-up continued until 3 months after the last dose in Parts 1-3 and until at least 10 days after the last dose in Parts 4-7.
- **Phase 1 DDI Study:** Women of childbearing potential were required not to have received oral contraceptives for at least 28 days prior to the first dose, to use a highly effective contraceptive method during treatment and for at least 14 days after the last dose, and to have a negative highly sensitive pregnancy test within 24 hours prior to the first dose.

[b]**Phase 2/3 and Phase 3 Studies:** Across these studies, pregnant and lactating women were excluded from participation. Women of childbearing potential were required to have a negative serum or urine pregnancy test prior to initiation of study intervention, typically performed on Day 1 before dosing, with repeat testing conducted on Day 28 (for SCORPIO-PEP and Phase 2b/3 Studies) or Day 29 (for SCORPIO-HR Study), or at study discontinuation. Additional pregnancy testing was permitted at the investigator's discretion or if pregnancy was suspected. Participants of reproductive potential were required to use effective contraception during treatment and for 14 days after the last dose of study intervention, and male participants with partners of reproductive potential were required to use condoms, as specified in study protocols. If pregnancy occurred during study participation, study intervention was discontinued immediately. Pregnancies in female participants and female partners of male participants were documented and reported to the sponsor within 24 hours of awareness (SCORPIO-HR, SCORPIO-SR, SCORPIO-PEP), along with pregnancy outcomes (birth, miscarriage, or abortion). Abnormal pregnancy outcomes, including spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, were considered SAEs.

Abbreviations: DDI, drug-drug interaction; PK, pharmacokinetics; SAEs, serious adverse events; WOCBP, women of childbearing potential.