Xocova - Use in Pre-Exposure Prophylaxis

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

- Nobori et al. (2024) conducted a study to evaluate the prophylactic effect of ensitrelvir in female mice. Ensitrelvir was administered at 4 different doses in 4 different treatment groups subcutaneously 24 hours before a challenge infection with a mouse-adapted strain of SARS-CoV-2[1]
  - The 64 mg/kg, 96 mg/kg, and 128 mg/kg ensitrelvir groups each significantly prolonged survival when compared to the vehicle group (P<0.0001); all female mice treated with vehicle died by Day 8 post-infection[1]
  - The 64 mg/kg and 96 mg/kg doses reduced weight loss on Days 3–7 (P<0.05); 128 mg/kg reduced weight loss on Days 2–7 (P<0.001) vs. vehicle[1]
  - Treatment groups had significantly lower lung viral titers than vehicle (P<0.0001)[1]
- Nakashima et al. (2024) conducted a study to assess pre-exposure and post-infection use of 1 of 3 doses of ensitrelvir to prevent the spread of COVID-19 in an *in vivo* aerosol transmission hamster model[2]
  - The lung and NALF transmission ratios were decreased by pre-exposure ensitrelvir in the contact hamsters in a dose-dependent manner compared with vehicle-treated hamsters; this included preventing infections in some pairs[2]
  - Pre-exposure ensitrelvir (750 mg/kg) suppressed body weight loss and lung weight increase in contact hamsters compared with vehicle-treated hamsters[2]

2. CLINICAL TRIALS

To date, **none of the clinical trials for ensitrelvir have evaluated its use for pre-exposure prophylaxis (PrEP);** only post-exposure prophylaxis (PEP) has been studied in the SCORPIO-PEP study.[3,4]

- In the Phase 3 SCORPIO-PEP trial, a statistically significant risk reduction for symptomatic COVID-19 was observed in the ensitrelvir group vs the placebo group at Day 10 [primary endpoint in mITT population: 2.9% (30/1030) vs. 9.0% (91/1011); RR: 0.33 (95% CI: 0.22–0.49); P<0.0001]

- Adverse events occurred in 15.1% (180/1190) patients in the ensitrelvir group and 15.5% (184/1187) in the placebo group. Two serious treatment-emergent adverse events (TEAEs) occurred in each group; none were considered related to the study drug. There were no treatment-related hospitalizations or deaths.[3,4]

3. PRE-CLINICAL TRIALS

Nobori et al. (2024) conducted a study to evaluate the prophylactic effect of ensitrelvir in female mice. Ensitrelvir was administered subcutaneously at 4 different doses in 4 different treatment groups 24 hours before a challenge infection with a mouse-adapted strain of SARS-CoV-2. The inoculated female mice were monitored for 14 days post-infection to evaluate the effect of ensitrelvir on survival and body weight compared with the vehicle-treated group. Additionally, lung viral titers were evaluated through Day 9 post-infection.[1]

Results

- A dose-dependent response to prophylactic ensitrelvir was observed for mortality, with 6.7% survival at 32 mg/kg, 60% survival at 64 mg/kg, 80% survival at 96 kg/mg, and 100% survival at 128 mg/kg[1]
    - The 64 mg/kg, 96 mg/kg, and 128 mg/kg groups each significantly prolonged survival when compared to the vehicle group (P<0.0001); all mice treated with vehicle died by Day 8 post-infection[1]
- The 64 mg/kg and 96 mg/kg doses significantly protected against weight loss from Days 3-7 (P<0.05) and the 128 mg/kg dose significantly protected against weight loss from Days 2-7 (P<0.001), when compared to vehicle group[1]
- The female mice in treatment groups had overall significantly lower lung viral titers than the vehicle group (P<0.0001)[1]
- Survival analysis was conducted to evaluate the effect of prophylactic administration of ensitrelvir on mortality in female mice infected with SARS-CoV-2. Female mice (37–57 weeks old) were nasally challenged with a lethal dose of SARS-CoV-2 MA-P10 strain 24 hours after receiving a single subcutaneous dose of ensitrelvir (32, 64, 96, or 128 mg/kg; N=15 mice per group) or vehicle[7]
    - Survival was monitored daily for 14 days post-infection:[1]
        - Vehicle group: 0% survival; all mice died within 8 days
        - 32 mg/kg: 6.7% survival (not statistically significant vs. vehicle; P=0.5715)
        - 64 mg/kg: 60% survival (P<0.0001 vs. vehicle)
        - 96 mg/kg: 80% survival (P<0.0001 vs. vehicle)
        - 128 mg/kg: 100% survival (P<0.0001 vs. vehicle)

Nakashima et al. (2024) conducted a study to assess pre-exposure and post-infection use of enstrelvir to prevent the spread of COVID-19 in an *in vivo* aerosol transmission hamster model. An index hamster was infected with SARS-CoV-2 and then placed in a habitat that allowed for aerosol-only transmission with a naïve contact hamster. The index hamster was given 1 of 3 dosage strengths of ensitrelvir orally at 8-hours post infection and then on Day 1 at an 8-hour and 16-hour interval post infection, while the contact hamster was given 1 of 2 dosage strengths subcutaneously 12 hours prior to co-housing. Body weight, lung weight, and viral titers from nasal lavage fluid (NALF) and lung tissues were analyzed and compared between the active treatment group, a vehicle-treated group, and a non-infected control group.[2]

Results

- The lung and NALF transmission ratios were decreased by pre-exposure ensitrelvir in the contact hamsters in a dose-dependent manner compared with vehicle-treated hamsters; this included preventing infections in some pairs[2]
- Body weight loss and lung weight increase were suppressed by pre-exposure ensitrelvir 750 mg/kg in the contact hamsters, compared with vehicle-treated hamsters[2]

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.[5]

CONTRAINDICATIONS

XOCOVA is contraindicated in patients with a history of clinically significant hypersensitivity reactions to ensitrelvir or any other components of the product.[5]

XOCOVA is contraindicated in patients taking drugs that are[5]:

- 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.[5]

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 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 pre-exposure prophylaxis. 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	NALF	nasal lavage fluid
COVID-19	coronavirus disease 2019	PK	pharmacokinetic
CYP3A	cytochrome P450 3A	SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
MHLW	Ministry of Health, Labour, and Welfare	US	United States
M^{pro}	main protease		

REFERENCES

1. Nobori H, Baba K, Kuroda T, et al. Prophylactic effect of ensitrelvir in mice infected with SARS-CoV-2. *Antiviral research*. 2024;224:105852. doi:10.1016/j.antiviral.2024.105852.

2. Nakashima M, Nobori H, Kuroda T, et al. Oral 3CL protease inhibitor ensitrelvir suppressed SARS-CoV-2 shedding and infection in a hamster aerosol transmission model. *Antiviral research*. 2024;232:106026. doi:10.1016/j.antiviral.2024.106026.
3. Hayden FG, Shinkai M, Clark TW, et al. Ensitrelvir to Prevent COVID-19 in Households: SCORPIO-PEP Phase III Placebo-Controlled Trial Results. Oral presentation presented at: CROI; March 9 - 12, 2025; San Francisco, CA.
4. Hayden FG, Ohmagari N, Clark TW, et al. Ensitrelvir for the prevention of COVID-19 among household contacts: key subgroup analyses of SCORPIO-PEP phase 3 study. Oral presentation presented at: ESCMID 2025; April 11 - 15, 2025; Vienna, Austria.
5. XOCOVA® (ensitrelvir) tablets, for oral use [Prescribing Information]. Shionogi Inc.

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