NDA 220442

NDA APPROVAL

Shionogi Inc.
Attention: Janet Ehlert, BSN, MBA, RAC-US
Executive Director, Regulatory Affairs, Global Development Projects
400 Campus Drive
Florham Park, NJ 07932

Dear Janet Ehlert:

Please refer to your new drug application (NDA) received June 16, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xocova (ensitrelvir) tablets.

This NDA provides for the use of Xocova (ensitrelvir) tablets 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 220442**". Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Xocova (ensitrelvir) tablets shall be 36 months from the date of manufacture when stored at 20°C to 25°C.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Saebyeol Jang
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6397
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for Xocova was not referred to an FDA advisory committee because this drug is not the first in its class, outside expertise was not necessary, and there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for birth to less than 12 years of age for this application because this product is ready for approval for use in adults and adolescents 12 years of age and older, and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4992-1 Submit the clinical study reports including the pharmacokinetic (PK) and pharmacodynamic modeling data and the supporting PK, safety, and virologic data from all the relevant studies in adult and pediatric patients to extrapolate efficacy of ensitrelvir to pediatric populations from 6 to less than 12 years of age weighing 30 kg or greater for post-exposure prophylaxis of COVID-19 in household contacts of an index case.

Final Report Submission: 11/2026

4992-2 Provide an assessment of the safety, pharmacokinetics, and antiviral activity of ensitrelvir in pediatric participants at least 3 years of age and weighing less than 30 kg. Data generated in relevant completed or ongoing clinical studies can be included as part of this assessment.

Study Completion: 12/2028
Final Report Submission: 08/2029

4992-3 Provide an assessment of the safety, pharmacokinetics, and antiviral activity of ensitrelvir in pediatric participants from birth to less than 3 years of age to support dosing recommendations for ensitrelvir use in children in this age group who have underlying risk factors for developing severe COVID-19.

Study Completion: 12/2029
Final Report Submission: 05/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. See guidance for industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.*

Submit the protocol(s) to your IND 157837, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We note that you have fulfilled the pediatric study requirement for ages 12 years and older for this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of emergence and transmission of ensitrelvir-resistant SARS-CoV-2 variants.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4992-4 Conduct a study to determine the impact of the following Mpro amino acid substitutions and insertions on ensitrelvir activity against SARS-CoV-2 in biochemical or cell culture assays: R4K, C44G, L50ins(HRSNF) (insertion of HRSNF after L50), P52L, S81F, R105S, A129V, S144L, H172N, R4K+A129V, T25A+E166A, C44G+L50ins(HRSNF), M49I+S144A, R105S+H172N, and A173V+L50ins(HRSNF).

The timetable you submitted on April 21, 2026, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2026
Study Completion:	12/2026
Final Report Submission:	02/2027

4992-5 Conduct a study to monitor genomic database(s) for the emergence of SARS-CoV-2 variants with amino acid polymorphisms in Mpro or Mpro cleavage sites. Conduct surveillance activities on at least a monthly basis. Conduct phenotypic analysis for any Mpro polymorphisms that are detected at a frequency ≥1% either globally or in the U.S. for any single month. Conduct phenotypic analysis for any Mpro cleavage site polymorphisms that are detected at a frequency ≥5% either globally or in the U.S. for any single month. These surveillance activities should continue for a period of 3 years post-approval, with re-assessment of the duration, frequency of reporting, and additional protocol methods to occur on an annual basis.

In the biannual interim reports, provide monthly counts of Mpro and Mpro cleavage site polymorphisms (minimum 0.1% frequency) globally, in the U.S., and in Japan. Provide ad-hoc reports (between biannual reports) whenever a novel Mpro or Mpro cleavage site polymorphism is detected at a monthly frequency ≥1% either globally, in the U.S., or in Japan. If evidence of ensitrelvir resistance emergence is detected in global sequences, additional analyses should be performed to determine the countries in which ensitrelvir-resistant variants are arising.

The timetable you submitted on May 20, 2026, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2026
Interim Report Submission:	12/2026
Interim Report Submission:	06/2027
Interim Report Submission:	12/2027
Interim Report Submission:	06/2028
Interim Report Submission:	12/2028
Study Completion:	06/2029
Final Report Submission:	06/2029

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of impaired growth in a breastfed infant exposed to ensitrelvir through breast milk.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

4992-6 Conduct a clinical lactation study in lactating women who have received ensitrelvir to measure concentrations of ensitrelvir in breast milk using a validated assay.

The timetable you submitted on May 20, 2026, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	11/2026
Final Protocol Submission:	05/2027
Trial Completion:	08/2028
Final Report Submission:	03/2029

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 157837 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o), REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[7] https://www.uspnf.com/

If you have any questions, contact Saebyeol Jang, Regulatory Project Manager, at (240) 402-9953 or saebyeol.jang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Wendy Carter, DO
Director (Acting)
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WENDY W CARTER
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