



NDA 218171

NDA APPROVAL

Xcovery Holdings, Inc.
c/o Veristat, LLC
Attention: John R Kirk, ScD
Principal Regulatory Strategist, US Agent
134 Turnpike Rd, Suite 200
Southborough, MA 01772

Dear Dr. Kirk:

Please refer to your new drug application (NDA) dated and received December 28, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ENSACOVE (ensartinib) capsules.

This NDA provides for the use of ENSACOVE (ensartinib) capsules for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have not previously received an ALK-inhibitor.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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](http://www.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

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on September 27, 2024, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the 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 218171.**" 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 ENSACOVE (ensartinib) capsules, shall be 30 months from the date of manufacture when stored at USP controlled room temperature storage conditions i.e., 20°C to 25°C (68°F to 77°F).

ADVISORY COMMITTEE

Your application for ENSACOVE (ensartinib) was not referred to an FDA advisory committee because outside expertise was not necessary; 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 waiving the pediatric study requirements for patients 0 to < 5 years of age because necessary studies are impossible or highly impracticable.

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>.

We are deferring submission of your pediatric study for patients ≥ 5 years of age because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of FDCA is required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. This required study is listed below.

- 4752-1 Conduct a molecularly targeted pediatric cancer investigation (Pediatric MATCH sub-study F) to assess the safety and preliminary efficacy of ensartinib in pediatric patients with advanced or metastatic solid tumors with ALK or ROS1 alterations.

Study Completion: 06/2025

Final Report Submission: 06/2026

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

Submit the protocol to your IND 111695, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study 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 this study. 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.

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 assess a signal of a serious risk of increased drug toxicity when ensartinib is used concomitantly with strong CYP3A and P-gp inhibitors and to identify an unexpected serious risk of increased drug toxicity in patients with moderate or severe hepatic impairment.

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>.

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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this signal of the serious risk and to identify the unexpected serious risk.

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

- 4752-2 Conduct a dedicated drug-drug interaction study to assess the effect of a strong CYP3A inhibitor and a P-gp inhibitor on the pharmacokinetics of ensartinib, to assess the serious potential risk of increased drug toxicity. For greater detail regarding the study design, data analysis and study report, refer to the FDA guidance for industry, "*M12 Drug Interaction Studies*".

The timetable you submitted on November 26, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 05/2025
Final Protocol Submission: 07/2025
Trial Completion: 12/2025
Final Report Submission: 06/2026

- 4752-3 Conduct a clinical study to assess the effect of moderate and severe hepatic impairment on the pharmacokinetics of ensartinib, to assess the serious potential risk of increased drug toxicity, to inform appropriate dose recommendations in patients with hepatic impairment. For details regarding the study design, data analysis and study report, refer to the FDA guidance for industry, "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*".

The timetable you submitted on November 26, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 05/2025
Final Protocol Submission: 07/2025
Trial Completion: 12/2025
Final Report Submission: 06/2026

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 111695 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 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 4752-4 Conduct a dedicated drug-drug interaction study to assess the effect of a strong CYP3A inducer on the pharmacokinetics of ensartinib. For greater details regarding the study design, data analysis and study report, refer to the FDA guidance for industry, “*M12 Drug Interaction Studies*”.

The timetable you submitted on November 26, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 05/2025

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>.

Final Protocol Submission: 07/2025

Trial Completion: 12/2025

Final Report Submission: 06/2026

- 4752-5 Conduct an integrated analysis of data from clinical trials and observational studies (e.g., real world evidence), post-marketing reports, and other sources to further characterize the safety and efficacy/effectiveness of ensartinib in older adults ages 65 years and older, and in patients of underrepresented racial and ethnic minority groups, with locally advanced or metastatic ALK positive non-small cell lung cancer. The analyses should support an evaluation of comparative efficacy/effectiveness and safety between the population primarily represented in the trial (eXALT3) and the aforementioned underrepresented racial and ethnic minority population as well as between younger patients represented in eXALT3 and the aforementioned older adult population.

The timetable you submitted on November 26, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan): 09/2025

Final Protocol Submission (Analysis Plan): 01/2026

Trial Completion: 12/2030

Final Report Submission: 06/2031

- 4752-6 Conduct an appropriate analytical and clinical validation study to support the development of an in vitro diagnostic device using clinical trial data that demonstrates that the device is essential to the safe and effective use of ensartinib for the treatment of patients with ALK-positive locally advanced or metastatic non-small cell lung cancer.

The timetable you submitted on November 26, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2025

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 111695 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical

studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁵

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.⁶ Information and Instructions for completing the form can be found at FDA.gov.⁷

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

⁵ For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/media/128163/download>.

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁷ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

official USP monographs. More information on the USP-NF is available on USP's website⁸.

If you have any questions, contact Tselaine Jones Smith, Regulatory Project Manager, at Tselaine.JonesSmith@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Paul G. Kluetz, MD
Supervisory Associate Director (acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

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

⁸ <https://www.uspnf.com/>

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/

PAUL G KLUETZ
12/18/2024 02:50:22 PM