# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

## 218944Orig1s000

| | |
|---|---|
| ***Trade Name:*** | **REVUFORJ tablets, 25 mg, 110 mg and 160 mg** |
| ***Generic or Proper Name:*** | **(revumenib)** |
| ***Sponsor:*** | **Syndax Pharmaceuticals, Inc.** |
| ***Approval Date:*** | **November 15, 2024** |
| ***Indication:*** | **REVUFORJ is a menin inhibitor indicated for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older.** |

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# 218944Orig1s000

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 218944Orig1s000

# APPROVAL LETTER

NDA 218944

**NDA APPROVAL**

Syndax Pharmaceuticals, Inc.
Attention: Christopher Murphy
Executive Director, Regulatory Affairs
730 3rd Avenue, Floor 9
New York, NY 10017

Dear Christopher Murphy:

Please refer to your new drug application (NDA) dated January 26, 2024, received January 26, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for REVUFORJ (revumenib) tablets.

We acknowledge receipt of your major amendment dated July 24, 2024, which extended the goal date by three months.

This NDA provides for the use of REVUFORJ (revumenib) tablets for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older.

## 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 Medication Guide) as well as annual reportable 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]

[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.

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 carton and container labeling submitted on November 8, 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 218944**." 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 REVUFORJ (revumenib) tablets shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled Room Temperature].

## ADVISORY COMMITTEE

Your application for REVUFORJ was not referred to an FDA advisory committee because review of this application did not raise significant safety or efficacy issues that were unexpected for a drug of this class and for treatment of patients with acute leukemia.

## 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 requirement for patients less than 1 year of age because necessary studies are impossible or highly impracticable. This is because of the small number and geographical dispersion of pediatric patients in this age group.

## 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 the known serious risks of sudden death, QTc prolongation, differentiation syndrome, and elevated transaminases; and to assess signals of serious risks of elevated parathyroid hormone, increased drug toxicity in patients with severe hepatic and renal impairment, and increased drug toxicity with use of OATP1B1 inhibitors, MATE1 substrates, and sensitive CYP3A4 substrates with revumenib.

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 these serious risks.

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

4730-1 Conduct a clinical trial to assess and further characterize known serious risks related to the use of revumenib of sudden death, QTc prolongation, differentiation syndrome and elevated transaminases, and assess serious potential risks such as elevated parathyroid hormone. The trial will determine whether long-term use of revumenib is associated with increased risk of cardiac deaths, recurrent differentiation syndrome, serious hepatotoxicity, and serious potential risk of endocrine-related disorders due to chronic menin inhibition. All patients should have at least 3 years of treatment or discontinued earlier.

The timetable you submitted on November 8, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion: 12/2027
Final Report Submission: 05/2028

4730-2 Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of revumenib and its metabolite M1 and serious potential risk of increased drug toxicities to determine an appropriate dosage of revumenib in patients with severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

The timetable you submitted on November 8, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 05/2025

| | |
|---|---|
| Final Protocol Submission: | 02/2026 |
| Trial Completion: | 01/2032 |
| Final Report Submission: | 07/2032 |

4730-3 Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of revumenib and its metabolite M1 and serious potential risk of increased drug toxicities to determine an appropriate dosage of revumenib in patients with severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing."

The timetable you submitted on November 8, 2024, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 06/2025 |
| Final Protocol Submission: | 02/2026 |
| Trial Completion: | 02/2032 |
| Final Report Submission: | 08/2032 |

4730-4 Complete the clinical pharmacokinetic trial to characterize the absorption, distribution, metabolism, and excretion of revumenib and its metabolite M1 and assess the serious potential risk of increased drug toxicities to determine an appropriate dosage of revumenib in patients with both hepatic and renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies."

The timetable you submitted on November 8, 2024, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Trial Completion: | 01/2025 |
| Final Report Submission: | 07/2025 |

4730-5 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of OATP1B1 inhibitors on the pharmacokinetics of revumenib and M1 to assess the serious potential risk of excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on November 8, 2024, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 06/2025 |

| | |
|---|---|
| Final Protocol Submission: | 03/2026 |
| Trial Completion: | 02/2031 |
| Final Report Submission: | 08/2031 |

4730-6 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of revumenib on the single dose pharmacokinetics of a substrate of the multidrug and toxin extrusion protein 1 (MATE1) transporter to assess the serious potential risk of excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on November 8, 2024, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 07/2025 |
| Final Protocol Submission: | 03/2026 |
| Trial Completion: | 03/2031 |
| Final Report Submission: | 09/2031 |

4730-7 Conduct a physiologically-based pharmacokinetic (PBPK) modeling study and a clinical pharmacokinetic trial if the FDA determines that the PBPK modeling study results are insufficient, to evaluate the effect of repeat doses of revumenib on the single dose pharmacokinetics of a sensitive substrate of CYP3A4 to assess the serious potential risk of excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on November 8, 2024, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 07/2025 |
| Final Protocol Submission: | 04/2026 |
| Study/Trial Completion: | 05/2033 |
| Final Report Submission: | 11/2033 |

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]

[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.

Submit clinical protocol(s) to your IND 142693 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:

4730-8 Complete the clinical pharmacokinetic trial to evaluate the effect of a high-fat meal on revumenib exposure and to evaluate appropriate administration of revumenib with regard to food. Design and conduct the trial in accordance with the FDA Guidance for Industry: “Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations.”

The timetable you submitted on November 8, 2024, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 08/2025 |
| Final Protocol Submission: | 04/2026 |
| Trial Completion: | 04/2031 |
| Final Report Submission: | 10/2031 |

4730-9 Conduct an in vitro study to clarify the activity of revumenib in acute leukemias with various KMT2A translocations. Include fusion partners that are rare and those that are not involved in the process of transcriptional elongation.

The timetable you submitted on November 8, 2024, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 03/2025 |
| Final Protocol Submission: | 12/2025 |
| Study Completion: | 04/2026 |
| Final Report Submission: | 06/2026 |

4730-10 Conduct a clinical trial to support the availability of an in vitro diagnostic device for identifying KMT2A translocations in patients with acute leukemias for the safe and effective use of revumenib.

The timetable you submitted on November 8, 2024, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Report Submission: | 01/2025 |

4730-11 Develop an oral solution formulation and conduct a study to assess relative bioavailability between the oral solution and capsule formulations. Design and conduct the trial in accordance with the FDA Guidance for Industry: “Bioavailability Studies Submitted in NDAs or INDs — General Considerations.”

The timetable you submitted on November 8, 2024, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 05/2025 |
| Final Protocol Submission: | 01/2026 |
| Trial Completion: | 05/2027 |
| Final Report Submission: | 11/2027 |

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 142693 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.*[4]

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

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

official USP monographs. More information on the USP-NF is available on USP's website[7].

If you have any questions, contact Rachel McMullen, Senior Regulatory Project Manager, at 240-402-4574 or rachel.mcmullen@fda.hhs.gov

Sincerely,

*{See appended electronic signature page}*

Marc R. Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

[7] https://www.uspnf.com/

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**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.**

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/s/

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MARC R THEORET
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