CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

218784Orig1s000

Trade Name:	**VORANIGO tablets, 10 mg and 40 mg**
Generic or Proper Name:	**(vorasidenib)**
Sponsor:	**Servier Pharmaceuticals, LLC**
Approval Date:	**August 6, 2024**
Indication:	**VORANIGO is indicated for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible isocitrate dehydrogenase-1 (IDH1) or isocitrate dehydrogenase-2 (IDH2) mutation following surgery including biopsy, sub-total resection, or gross total resection**

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 218784

NDA APPROVAL

Servier Pharmaceuticals, LLC
Attention: Maya Kostova, PhD
US Regulatory Lead
200 Pier Four Blvd.
Boston, MA 02210

Dear Dr. Kostova:

Please refer to your new drug application (NDA) dated and received December 20, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Voranigo (vorasidenib) tablets.

This NDA provides for the use of Voranigo (vorasidenib) tablets for the treatment of adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation, following surgery including biopsy, sub-total resection, or gross total resection.

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 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.

[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 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 218784**." 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 Voranigo (vorasidenib), 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 and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

ADVISORY COMMITTEE

Your application for Voranigo (vorasidenib) tablets was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected in the intended population and 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 requirement for patients less than 12 years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients in this age group is so small.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 carcinogenicity.

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 this serious risk.

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

4659-1 Conduct a carcinogenicity study in mice to evaluate the potential serious risk of carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on August 6, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 04/2025
Final Protocol Submission: 08/2025
Study Completion: 10/2026
Final Report Submission: 04/2027

4659-2 Conduct a carcinogenicity study in rats to evaluate the potential serious risk of carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on August 6, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 04/2025
Final Protocol Submission: 08/2025
Study Completion: 06/2028
Final Report Submission: 12/2028

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 known serious risk of hepatotoxicity; to assess a potential serious risk of effects on growth and development in pediatric

[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.

patients; and to identify an unexpected serious risk of drug toxicity in patients with severe hepatic impairment.

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

4659-3 Conduct a comprehensive safety analysis from clinical trials in a sufficient number of pediatric patients to adequately characterize baseline risk factors and safety outcomes, including hepatotoxicity and effects on growth and development, following exposure to vorasidenib. Include assessment of clinical responses.

The timetable you submitted on August 6, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	06/2025
Final Protocol Submission (Analysis Plan):	10/2025
Study Completion:	06/2033
Final Report Submission:	12/2033

4659-4 Conduct a comprehensive safety analysis from clinical trials in a sufficient number of adult patients to adequately characterize hepatotoxicity following exposure to vorasidenib. The integrated safety analysis should include all adverse events, major safety events, dose-reductions, dose interruptions, and withdrawals, when all patients have completed at least two years of treatment with vorasidenib or withdrew earlier.

The timetable you submitted on August 6, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	01/2025
Final Protocol Submission (Analysis Plan):	11/2025
Study Completion:	01/2026
Final Report Submission:	07/2026

4659-5 Conduct a clinical pharmacokinetic trial to determine an appropriate dosage of vorasidenib to minimize toxicity in patients with severe hepatic impairment. Design and conduct the trial in accordance with the FDA Draft Guidance for Industry titled: "*Pharmacokinetics in Patients with Impaired*

Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on August 6, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 08/2025
Final Protocol Submission: 12/2025
Trial Completion: 10/2026
Final Report Submission: 04/2027

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 140832 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.

[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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4659-6 Conduct a clinical study to assess the effect of vorasidenib on the pharmacokinetics of a CYP3A substrate to determine recommendations on appropriate dose adjustments when vorasidenib is administered concomitantly with CYP3A substrates. Design and conduct the assessment in accordance with the FDA Guidance for Industry titled "*Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*".

The timetable you submitted on August 6, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2025
Final Protocol Submission:	08/2025
Trial Completion:	07/2026
Final Report Submission:	12/2026

4659-7 Complete survival follow-up of patients in the INDIGO trial to further characterize the efficacy and clinical benefit of vorasidenib in patients with Grade 2 astrocytoma or oligodendroglioma with susceptible IDH1 or IDH2 mutations.

The timetable you submitted on August 6, 2024, states that you will conduct this study according to the following schedule:

Study Completion:	05/2028
Final Report Submission:	11/2028

4659-8 Conduct an appropriate analytical and clinical validation study to establish and support the availability of an in vitro diagnostic device using clinical trial data that demonstrates the device is essential to the safe and effective use of vorasidenib for the treatment of patients 12 years of age and older with grade 2 IDH-mutant astrocytoma or oligodendroglioma following surgery including biopsy, sub-total resection, or gross total resection.

The timetable you submitted on August 6, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission:	08/2025

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 140832 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]

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

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

[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

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[8].

If you have any questions, email Maritsa Stephenson, Regulatory Health Project Manager, at maritsa.stephenson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- 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
08/06/2024 01:37:40 PM