CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215814Orig1s000

Trade Name:	REZLIDHIA capsules
Generic or Proper Name:	olutasidenib
Sponsor:	Forma Therapeutics, Inc.
Approval Date:	December 3, 2020
Indication:	For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 215814

NDA APPROVAL

Forma Therapeutics, Inc.
Attention: Nikole Shpilfogel, PharmD
Senior Manager, Strategic Alliances and Regulatory Affairs
300 North Beacon Street
Suite 501
Watertown, MA 02472

Dear Dr. Shpilfogel:

Please refer to your new drug application (NDA) dated February 15, 2022, received February 15, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for REZLIDHIA (olutasidenib) capsules.

This NDA provides for the use of REZLIDHIA (olutasidenib) capsules for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

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]

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 carton and container labeling submitted on November 9, 2022, 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 215814**." 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 REZLIDHIA (olutasidenib) capsules shall be 36 months from the date of manufacture when stored at 20°C - 25°C; excursions permitted to 15°C - 30°C.

ADVISORY COMMITTEE

Your application for REZLIDHIA was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues.

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 ages <12 years because necessary studies are impossible or highly impracticable. This is because the IDH1 mutation is very rare in children below 12 years of age.

We are deferring submission of your pediatric study for ages ≥12 to <18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a 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 Federal Food, Drug, and Cosmetic Act/FDCA. This required study is listed below.

4371-1 Conduct a clinical trial to confirm the appropriate dose of olutasidenib, and to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of

olutasidenib, in pediatric patients ages ≥12 to <18 years with IDH1-mutated gliomas. Patients should be followed for at least 12 months (52 weeks). Include at least 6 patients ≥12 to <18 years old.

Draft Protocol Submission:	08/2023
Final Protocol Submission:	11/2023
Study Completion:	01/2028
Final Report Submission:	01/2029

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]

Submit the protocol(s) to your IND 127313, 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 co-administering olutasidenib with OATP1B1 substrates, and to assess known serious risks of differentiation syndrome, hepatotoxicity, and other serious toxicities.

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 the signal of a serious risk and to assess the known serious risks.

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

[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.

4371-2 Conduct a clinical drug interaction study to evaluate the effect of repeated doses of olutasidenib on the pharmacokinetics of substrates of OATP1B1. Assess the magnitude of increased drug exposure and determine appropriate dosage recommendations when olutasidenib is administered concomitantly with OATP1B1 substrates. Design and conduct the study 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 November 17, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2023
Final Protocol Submission:	06/2024
Study Completion:	06/2027
Final Report Submission:	12/2027

4371-3 Conduct a study to further characterize the incidence and severity of differentiation syndrome, hepatotoxicity, and other serious toxicities that may develop with longer term use of olutasidenib, in patients with relapsed or refractory acute myeloid leukemia (AML). This data may come from Study 2102-HEM-101. Include data from approximately 179 patients with relapsed or refractory AML that received olutasidenib as monotherapy. Patients should be followed for 3 years. Data should include exploratory subgroup analyses and corresponding subject level data that includes cytogenetics, specific IDH1 mutations, and mutation analyses for other genes as obtained under the study protocol.

The timetable you submitted on November 17, 2022, states that you will conduct this trial according to the following schedule:

Trial Completion:	06/2023
Final Report Submission:	12/2023

Submit the datasets with the final report submission.

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.

Submit clinical protocols to your IND 127313 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 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 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:

4371-4 Conduct a clinical drug interaction study to evaluate the effect of repeated doses of a moderate CYP3A inducer on the pharmacokinetics of olutasidenib to assess the magnitude of decreased drug exposure and determine appropriate dosage recommendations when olutasidenib is administered concomitantly with moderate CYP3A inducers. Design and conduct the study 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 November 17, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2023
Final Protocol Submission:	12/2023
Study Completion:	12/2024
Final Report Submission:	06/2025

4371-5 Conduct a clinical drug interaction study to evaluate the effect of repeated doses of olutasidenib on the pharmacokinetics of substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A. Assess the magnitude of decreased drug exposures to determine appropriate dosage recommendations when olutasidenib is administered concomitantly with CYP substrates. Design and conduct the study 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 November 17, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2023
Final Protocol Submission:	06/2024
Study Completion:	06/2027
Final Report Submission:	12/2027

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 127313 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]

[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

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.

If you have any questions, call Sheila Ryan, PharmD, MPH, RAC, Senior Regulatory Health Project Manager, at (301) 796-2002.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

MARC R THEORET
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