



NDA 209606

NDA APPROVAL

Celgene Corporation
Attention: Penny Ng, MSc, MBA, RAC
Director, Regulatory Affairs
9225 Indian Creek Parkway, Suite 900
Overland Park, KS 66210

Dear Ms. Ng:

Please refer to your New Drug Application (NDA) dated December 30, 2016, received December 30, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Idhifa[®] (enasidenib) tablets, 50 and 100 mg.

This new drug application provides for the use of Idhifa[®] (enasidenib) tablets, 50 and 100 mg, for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

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 text.

EXPIRATION DATING PERIOD

The drug product is stable for 18 months when stored at 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature].

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). 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*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on July 21, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 209606.**” Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Idhifa[®] was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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 known serious risk of differentiation syndrome.

Furthermore, the new pharmacovigilance system that FDA is required to establish 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 study:

PMR 3240-1 Conduct a meta-analysis to characterize enasidenib-related differentiation syndrome, specifically incidence, appropriate diagnostic criteria, and effective

treatment based on patient-level data and pooled analyses for on-going trials in patients with acute myeloid leukemia: AG221-C-001, AG-120-221-C-001, AG-221-AML-004, and AG-221-AML-005. Submit the study report and analysis data set.

The timetable you submitted on July 21, 2017, states that you will conduct this study according to the following schedule:

Preliminary Protocol Submission:	10/2017
Final Protocol Submission:	01/2018
Study Completion:	02/2020
Final Report Submission:	12/2020

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of toxicity from longer-term use, from interactions with other drugs, or due to impaired hepatic function.

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

PMR 3240-2 Characterize the long-term safety of enasidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and data set with 3 years of follow-up from ongoing Study AG221-C-001, *A phase 1/2, multi-center, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamics, and clinical activity study of orally administered AG-221 in subjects with advanced hematologic malignancies with an IDH2 mutation*. Include data from approximately 280 patients with relapsed or refractory AML.

The timetable you submitted on July 21, 2017, states that you will conduct this trial according to the following schedule:

Trial Completion:	05/2019
Final Report Submission:	03/2020

PMR 3240-3 Conduct a trial to provide evidence sufficient to characterize the long-term safety of enasidenib compared to conventional care regimens in patients with acute myeloid leukemia (AML). Submit the final study report and data set with 3 years of follow-up from ongoing Study AG-221-AML-004, *A phase 3, multicenter, open-label, randomized study comparing the efficacy and safety of AG-221 versus conventional care regimens in older subjects with late stage acute myeloid leukemia harboring an isocitrate dehydrogenase 2 mutation*. Include data from approximately 140 patients with relapsed or refractory AML.

Include in the final study report the exploratory subgroup analyses and corresponding subject-level data related to pre- and post-treatment cytogenetics, specific IDH2 mutations, and mutation analyses for other genes (e.g., IDH2,

FLT3, NPM1, CEBPA, DNMT3A, NRAS) as obtained under the trial protocol or from medical history prior to trial enrollment.

The timetable you submitted on July 21, 2017, states that you will conduct this trial according to the following schedule:

Trial Completion:	09/2022
Final Report Submission:	07/2023

PMR 3240-4 Conduct clinical pharmacokinetic trials to evaluate the effect of multiple doses of enasidenib on the single dose pharmacokinetics of sensitive substrates of CYP3A4, CYP2D6, CYP2C19, CYP2C9, UGTs, P-gp, and BCRP to address the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.*”

The timetable you submitted on July 21, 2017, states that you will conduct this trial according to the following schedule:

Preliminary Protocol Submission:	09/2017
Final Protocol Submission:	12/2017
Trial Completion:	09/2019
Final Report Submission:	03/2020

PMR 3240-5 Conduct a clinical pharmacokinetic trial to determine an appropriate dose of enasidenib in patients with hepatic impairment. This trial should be designed and conducted 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 July 21, 2017, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2017
Trial Completion:	11/2018
Final Report Submission:	05/2019

Submit clinical protocols to your IND 117631 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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 NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

PMC 3240-6 Develop and report a control strategy for the drug product to minimize the risk of



The timetable you submitted on July 21, 2017, states that you will conduct this study according to the following schedule:

CBE-30 submission of Control Strategy:	09/2017
Implementation of Control Strategy:	11/2017

Submit clinical protocols to your IND 117631 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 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. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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 Jennifer Lee, Regulatory Project Manager, at (240) 402-4622.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
08/01/2017