NDA 209606/S-006

**SUPPLEMENT APPROVAL**
**FULFILLMENT OF POSTMARKETING REQUIREMENT**

Bristol-Myers Squibb Company
Attention: Isabella Birns
Associate Director, Global Regulatory Strategy
P.O. Box 5326
Princeton, NJ 08543-5326

Dear Isabella Birns:

Please refer to your supplemental new drug application (sNDA) dated June 29, 2023, received June 29, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for IDHIFA (enasidenib) tablets.

This Prior Approval sNDA provides for the following based upon the results of study CC-90007-CP-004 designed to fulfil PMR 3240-4:

- Revisions to Section 5 Warnings and Precautions, subsection 5.2 Embryo-Fetal Toxicity; Section 8 Use In Specific Populations, subsections 8.1 Pregnancy; 8.2 Lactation, 8.3 Females and Males of Reproductive Potential, and Section 17 Patient Counseling Information to align with current labeling practices;

- Revisions to Section 7 Drug Interactions; subsection 7.1 Effect of IDHIFA on Other Drugs and Section 12.3 Clinical Pharmacology to reflect effect of enasidenib on the single dose pharmacokinetics of sensitive substrates of CYP1A2, CYP3A4, CYP2D6, CYP2C19, CYP2C9, CYP2C8, P-gp, OATP1B1, OATP1B3 and BCRP to address the potential for excessive drug toxicity;

- Revisions to include removal of CYP enzyme substrates from in vitro studies that have clinical DDI study results in Section 12.3 Clinical Pharmacology;

- Minor edits in Section 16 How Supplied/Storage And Handling to align with container labeling, along with minor edits throughout the US Prescribing Information.

## 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), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, 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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## 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.

Because none of these criteria apply to your application, you are exempt from this requirement.

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[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.

## FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submissions dated June 29, 2020, March 6, 2023, and June 29, 2023, reporting on and containing the final report for the following postmarketing requirement listed in the August 1, 2017, approval letter.

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*."

We have reviewed your submissions and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements listed in the August 1, 2017, approval letter that are still open.

## 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.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7

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

days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

## PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

## REPORTING REQUIREMENTS

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

If you have any questions, call Saumya Nathan, Senior Regulatory Project Manager, at 301-348-1963.

Sincerely,

*{See appended electronic signature page}*

Kelly Norsworthy, MD
Deputy Division Director
Division of Hematologic Malignancies I
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert or Medication Guide

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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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