NDA 212327

NDA APPROVAL

Impact Biomedicines, Inc., a Wholly-owned Subsidiary of Celgene Corporation
Attention: Kimberly Burns, MS
Senior Manager, Global Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Ms. Burns:

Please refer to your new drug application (NDA) dated January 3, 2019, received January 3, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INREBIC (fedratinib) capsules.

This new drug application provides for the use of INREBIC (fedratinib) capsules for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).

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.

CONTAINER LABELING

Submit final printed container labeling that are identical to the container labeling submitted on July 12, 2019, 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Container Labeling for approved NDA 212327**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for INREBIC was not referred to an FDA advisory committee because this drug is not the first in its class.

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 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 evaluate long-term safety of fedratinib, to assess a signal of encephalopathy, including Wernicke's, evaluate utility of measures to manage this risk, or assess a signal of a serious risk of increased toxicity from increased drug exposure in patients with hepatic impairment or due to interactions with other drugs.

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 these serious risks.

Finally, we have determined that only clinical trials (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:

3664-1 Conduct a randomized, concurrently controlled clinical trial comparing fedratinib 400 mg once daily to best available therapy in patients with DIPSS-intermediate-2 or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib. The trial will enroll a sufficient number of patients to ensure that at least 150 subjects are treated with at least 6 cycles of fedratinib and are followed for at least 3 years from first dose, or until death. The protocol should include measures to assess and manage adverse events of nausea, diarrhea, vomiting, thiamine deficiency, and encephalopathy at baseline and during the trial. The final protocol must be agreed upon with the Agency.

The timetable you submitted on August 14, 2019, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	10/2019
Trial Completion:	12/2024
Final Report Submission:	06/2025

3664-2 Conduct a clinical pharmacokinetic trial to determine an appropriate dose of fedratinib to minimize toxicity in subjects 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*.[3]

The timetable you submitted on August 14, 2019, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2019
Trial Completion:	12/2021
Final Report Submission:	06/2022

3664-3 Conduct a clinical trial to evaluate the effect of coadministration of a dual CYP2C19 and CYP3A4 inhibitor on the pharmacokinetics and safety of a single dose of fedratinib. Design and conduct the trial in accordance with

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-hepatic-function-study-design-data-analysis-and-impact-dosing-and

the FDA guidance for industry entitled, *Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications.*[4] In addition, conduct physiologically based pharmacokinetic (PBPK) modeling using data from the clinical trial to determine an appropriate dose of fedratinib in patients dosed with fedratinib at steady state and coadministered with multiple doses of dual CYP2C19 and CYP3A4 inhibitor in accordance with FDA guidances for industry entitled, *In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies*[5] and *Physiologically Based Pharmacokinetic Analyses – Format and Content*.[6]

The timetable you submitted on August 14, 2019, states that you will conduct this trial according to the following schedule:

Preliminary Protocol Submission:	11/2019
Final Protocol Submission:	02/2020
Trial Completion:	08/2021
Final Report Submission:	02/2022

3664-4 Conduct a clinical trial to evaluate the effect of single dose of fedratinib on the single dose pharmacokinetics and safety of sensitive substrates of P-gp, BCRP, MATE-1/2K, and OCT2 transporters. Design and conduct the trial in accordance with the FDA guidance for industry entitled, *Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications.*[4]

The timetable you submitted on August 14, 2019, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2019
Trial Completion:	03/2021
Final Report Submission:	09/2021

Submit clinical protocols to your IND 078286 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

[4] https://www.fda.gov/media/82734/download
[5] https://www.fda.gov/media/108130/download
[6] https://www.fda.gov/media/101469/download

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:

3664-5 Conduct a clinical pharmacokinetic trial to determine an appropriate dose of fedratinib when fedratinib is coadministered with and without multiple doses of strong and moderate CYP3A4 inducers. Design and conduct the trial in accordance with the FDA guidance for industry entitled, *Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications.*[4]

The timetable you submitted on August 14, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2019
Trial Completion:	12/2020
Final Report Submission:	06/2021

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 078286 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 Prescribing Information, Medication Guide, and Patient Package Insert (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 *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[7]

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.[8] Information and Instructions for completing the form can be found at FDA.gov.[9] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[10]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). In addition, we request that for 5 years, you perform postmarketing surveillance for suspected encephalopathy, including Wernicke's encephalopathy, or thiamine deficiency occurring in patients receiving or who have received INREBIC, regardless of outcome (serious or non-serious) from any source as expedited (15-day) reports including initial and follow-up reports. Provide

[7] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[8] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[9] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[10] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

comprehensive summaries and analyses of these events as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)].

In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with duration of INREBIC therapy, the time from first INREBIC dose to adverse event onset, the time from last INREBIC dose prior to the event onset, concomitant therapies, treatment given for the event, and outcome.

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 FDA.gov.[11]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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, Senior Regulatory Health Project Manager, at (240) 402-4622.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[11] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

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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.

/s/

RICHARD PAZDUR
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