NDA 021880/S-067

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Lisa Suttner
Director, Regulatory Affairs
P.O. Box 5326
Princeton, NJ 08543

Dear Ms. Suttner:

Please refer to your supplemental new drug application (sNDA) dated and received October 28, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Revlimid (lenalidomide) capsules.

This Changes Being Effected sNDA provides for updating the Applicant name from Celgene to Bristol-Myers Squibb Company in the labeling and proposed modifications to the approved shared system risk evaluation and mitigation strategy (REMS) for Revlimid and lenalidomide products.

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Shared System (SS) REMS for lenalidomide products, of which Revlimid is a member, was originally approved on May 21, 2021, and the most recent REMS modification was approved on August 5, 2021. The SS REMS consists of elements to assure safe use, an implementation system and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consists of the transfer of the Drug Master File (DMF) holder from Celgene Corporation to Bristol-Myers Squibb Company (BMS), removing the Celgene logo and references to Celgene, and includes administrative updates (e.g., changes to contact department names). The proposed modification also consists of editorial changes to the REMS website, and changing the address of the REMS web portal.

Your proposed modified REMS, submitted to DMF 030795 on October 28, 2022, amended and appended to this letter, is approved.

This shared system REMS, known as the Lenalidomide REMS, currently includes products listed on the FDA REMS website[1].

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS remains the same as that approved on September 13, 2015.

The REMS assessment plan must include, but is not limited to, the following:

Health Outcomes and/or Surrogates of Health Outcomes

1. Pregnancies: (per reporting period and cumulatively)
    a. Number of pregnancies reported
    b. Outcome of each pregnancy
    c. Follow-up of outstanding pregnancy reports
    d. Root cause analysis of each reported pregnancy
    e. Link to most recent Periodic Safety Update Report (PSUR) or Periodic Benefit-Risk Evaluation Report (PBRER) that provides information on worldwide pregnancies. Discussion of any new information provided in the PSUR or PBRER regarding pregnancy

Program Implementation and Operations

2. Reporting on the restricted distribution program: (per current and previous two reporting periods and cumulatively; where applicable)
    a. The number of pharmacies and physicians certified, and patients enrolled
    b. Patient demographics for the current REMS assessment reporting period to include gender, age, diagnosis, females of reproductive potential (FRP)
    c. Number of female patients for whom pregnancy testing can be discontinued because menopause has been documented by follicle-stimulating hormone/luteinizing hormone (FSH/LH) levels
3. REMS Pharmacy Compliance (per current and previous two reporting periods and cumulatively; where applicable)
    a. Provide a copy of the Noncompliance plan to include the following:
        i. Criteria for non-compliance
        ii. Actions taken to address non-compliance for each event identified
        iii. Criteria for de-certification
    b. Provide a copy of the audit plan
    c. Report of audit findings
        i. The number of audits expected, and the number of audits conducted
        ii. The number and type of deficiencies noted
            1. Number that successfully completed a corrective and preventative (CAPA) plan within 30 days of receipt of CAPA
            2. Describe actions taken for any that did not complete the CAPA within 30 days of receipt of CAPA
            3. Include a unique ID for each pharmacy that had deviations to track deviations over time

iii. Documentation of completion of training for relevant staff
iv. The existence of documented processes and procedure for complying with the REMS

d. Non-compliance events: for each event provide the following
   i. Source of the report
   ii. Description of the event
   iii. Cause of the event
   iv. Patient risk category
   v. Corrective actions taken
   vi. Events:
      1. Number of lenalidomide prescriptions dispensed that were written by non-certified prescribers
      2. Number of lenalidomide prescriptions dispensed by non-certified pharmacies
      3. Number of lenalidomide prescriptions dispensed to de-enrolled or non-enrolled patients
      4. Number of times a lenalidomide prescription was dispensed because a certified pharmacy bypassed REMS authorization processes
      5. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences
      6. Number of pharmacies who were de-certified for non-compliance and reasons for de-certification

Safe Use Behaviors

4. Documentation of safe use conditions (per current and previous two reporting periods and cumulatively; where applicable)

   Based on information collected from the mandatory surveys (used to document safe use conditions) provide information that could represent potential fetal exposure or that might result in a delay or interruption in treatment.

   The following is provided in a tabular format:

   a. The total number of authorization numbers issued, and the number of authorization numbers flagged.
   b. The number and proportion of flagged authorization numbers intended for an FRP due to questions in the mandatory surveys related to pregnancy testing
   c. The number and proportion of flags that caused a delay in treatment initiation or a gap in therapy for patients due to REMS processes as the proportion of flagged authorization numbers compared to total authorization numbers. Include the time to resolution of flags in days (mean, minimum, maximum) for the reporting period and for each previous reporting period. Include the number of patients with a delay in treatment or a gap in therapy due to REMS processes.

Knowledge, Attitude, Behavior

5. Inform prescribers, patients, and pharmacists on the serious risks and safe-use conditions for lenalidomide (per current and previous two reporting periods and cumulatively, where applicable)
    a. Ensure that lenalidomide will only be dispensed to patients enrolled in the lenalidomide REMS Program with evidence or other documentation of safe-use conditions
        i. Number and proportion of total number of unflagged patient survey questions answered relating to knowledge compared to the total number of patient survey questions relating to knowledge reported per patient risk category
    b. Ensure healthcare providers counsel patients on the benefits and risks of lenalidomide therapy, including risks described in the boxed warnings
        i. Number and proportion of total number of unflagged prescriber surveys compared to the total number of prescriber surveys reported per risk category
    c. Educate pharmacies on the risks and safe-use conditions of lenalidomide
        i. Total number of pharmacy quizzes administered
        ii. Number of pharmacists with a passing rate/Total number of certified pharmacists on the last day of the reporting period

Overall Assessment of REMS Effectiveness

6. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021880 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,

ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021880 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 021880/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021880/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021880/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021880/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 021880

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on October 28, 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 *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 Carton and Container Labeling for approved NDA 020785/S-010**." Approval of this submission by FDA is not required before the labeling is used.

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.

[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.

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]

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).

[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

If you have any questions, contact Stacie Woods, Safety Regulatory Project Manager, at 301-796-4803, or via email at Stacie.woods@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Abhilasha Nair, M.D.
Supervisory Associate Director for Safety
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- REMS

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/

ABHILASHA NAIR
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