NDA 021880/S-63

SUPPLEMENT APPROVAL

Celgene Corporation
Attention: Lisa Suttner
Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Ms. Suttner:

Please refer to your supplemental new drug application (sNDA) dated and received May 14, 2021, 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 proposed modifications to the approved shared system risk evaluation and mitigation strategy (REMS) for lenalidomide products known as the Lenalidomide REMS Program..

We have completed our review of this 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. The 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 consist of removal of the mobile app for physicians, inclusion of the Patient REMS Application, clarifying language regarding the question for prescribers about days of therapy being prescribed, new language for reporting pregnancies, modification to the disclosure language on the Patient-Physician Agreement Forms (PPAFs), and a new election checkbox on the PPAFs for patients to request Lenalidomide REMS education materials.

Your proposed modified REMS, submitted on May 14, 2021, amended and appended to this letter, is approved.

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

The revised 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 Non-Compliance 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. Corrective actions taken
v. 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.

   Provide the following 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 lenadidomide (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

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

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).

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

If you have any questions you may contact Felicia Diggs, Safety Regulatory Project Manager, at (240) 402-4932 or via email at Felicia.Diggs@FDA.HHS.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
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
08/05/2021 02:02:34 PM