DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21880/S-044

SUPPLEMENT APPROVAL

Celgene Corporation
Attention: Marion Ceruzzi, Ph.D.
Senior Director, Regulatory Affairs
400 Conneli Drive, Suite 2000
Berkeley Heights, NJ 07922

Dear Dr. Ceruzzi:

Please refer to your Supplemental New Drug Applications (sNDA) dated June 23, 2015, received June 23, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Revlimid® (lenalidomide) Capsules, 2.5, 5, 10, 15, 20 and 25 mg.

This "Changes Being Effected" supplemental new drug application provides for modifications to the approved Revlimid® (lenalidomide) risk evaluation and mitigation strategy (REMS).

APPROVAL

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

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

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Revlimid ® (lenalidomide) Capsules was originally approved on August 3, 2010, and the most recent modification was approved on February 17, 2015. The REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of inclusion of mobile applications into the REMS materials to provide an additional platform to accomplish internet-capable REMS activities, and a revised timetable for submission of assessments.

Your proposed modified REMS, submitted on June 23, 2015, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to include submission of an assessment by August 3, 2016, and every 2 years thereafter.

The revised REMS assessment plan must include, but is not limited to, the following list. Additions are noted by underline and deletions are noted by ~~strikethrough~~.

1. Pregnancies:
    a. Number of pregnancies reported during the REMS assessment reporting period and annually for each REMS reporting period
    b. Outcome of each pregnancy
    c. Follow-up of outstanding pregnancy reports from previous assessment reporting period
    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

2. Reporting on the restricted distribution program:
    a. The number of pharmacies and physicians certified, and patients enrolled during the current REMS assessment reporting period and during each previous REMS assessment reporting period
    b. Patient demographics for the current REMS assessment reporting period and for previous REMS assessment reporting periods 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 during this REMS assessment reporting period and for previous REMS assessment reporting periods

3. Documentation of safe use conditions
   Based on information collected through patient enrollment and mandatory surveys that are used to document safe use conditions, provide information on:
    a. Flagged prescriptions/documentations of safe use of particular interest include those that have the potential of allowing pregnant patients access to the drug, and those that result in a delay or interruption of treatment. Provide the following, relative to flagged prescriptions/documentations of safe use:

i. A summary of identified flags, the reasons for the flags, and the actions taken to correct. Provide for the reporting period; and summarize findings from each previous assessment report.
ii. The number and proportion of flagged prescriptions intended for an FRP due to lack of documentation of a negative pregnancy test, positive pregnancy test, and/or a delay in obtaining a pregnancy test.
iii. The number and proportion of flags that caused a delay in treatment initiation or a gap in therapy for patients. The time to resolution of flags (mean, minimum, maximum) and include a graph of time to resolution versus numbers of prescriptions (or number of mandatory surveys conducted to document safe use conditions) for the reporting period and for each previous reporting period.

4. Results from the Pharmacist Risk Assessment Survey Protocol regarding the serious risks and safe-use conditions.

5. Using patient survey data, documentation of choice of contraception (information from patients of method/use), and of changes to methods used (numbers of FRP using method at entry and ongoing): numbers/proportions using highly effective form of birth control; number/proportion using other less effective forms of birth control.

6. Data on the use of the mobile device application to conduct REMS functions
    a. Date the mobile application went live
    b. Number of downloads of the mobile application
    c. Number, age, and gender of patients using the mobile application for REMS functions, the number of instances of using the mobile application, and the functions conducted via the mobile application.
    d. Number of prescribers using the mobile application for REMS functions, the number of instances of using the mobile application, and the functions conducted via the mobile application.
    e. Proportion of above functions being conducted via mobile application vs other means (mail, email, fax)
    f. Summary of any feedback obtained on the use of the mobile application by stakeholders during the assessment period

7. Data on the pharmacy business-to-business protocol to conduct pharmacy REMS functions
    a. The number of pharmacies using the business-to-business protocol, and the date the pharmacies began using pharmacy business-to-business protocol
    b. The number and percentage of REMS transactions using the business-to-business protocol for each pharmacy
    c. Any problems in implementing the business-to-business protocol for each pharmacy
    d. Summary of feedback from pharmacies on use of the business-to-business protocol

8. 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 of 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). 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 the 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 21880 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

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 21880 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 21880/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 21880/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 21880/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 21880/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 21880

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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 Ms. Diane Leaman, Safety Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Robert C. Kane, MD
Deputy Director for Safety
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE

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

/s/

ROBERT C KANE
09/13/2015