NDA 021880/S-054

SUPPLEMENT APPROVAL
REMS MODIFICATION

Celgene Corporation
Attention: Lisa Suttner, MS, RAC
Director, Regulatory Affairs
556 Morris Avenue
Summit, NJ 07901

Dear Ms. Suttner:

Please refer to your supplemental new drug application dated and received December 8, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Revlimid (lenalidomide) capsules.

We acknowledge receipt of your amendment dated February 15, 2019, which constituted a complete response to our June 6, 2018, action letter. We also refer to your REMS amendments received August 16, 2019, February 7, 2020, and April 1, 2020.

This Prior Approval supplemental new drug application provides for modifications to the approved Revlimid (lenalidomide) risk evaluation and mitigation strategy (REMS).

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 REMS for Revlimid (lenalidomide) was originally approved on August 3, 2010, and the most recent REMS modification was approved on May 28, 2019. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS establishes a shared system (SS) REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Revlimid (lenalidomide) and ANDAs referencing Revlimid (lenalidomide) called the lenalidomide REMS Program, which will become applicable on the date of full approval of the first ANDA joining a shared system with Revlimid. The modification being approved results in a two-part REMS consisting of: (1) the requirements of the previously approved Revlimid REMS, and (2) the new shared system REMS for lenalidomide products. The requirements of the previously approved Revlimid REMS will remain applicable until full approval of the first ANDA joining a

shared system with Revlimid, at which time, they will automatically be replaced by the requirements of the shared system.

Your proposed modified REMS, submitted on April 1, 2020, amended and appended to this letter, is approved.

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

The REMS assessment plan applicable to the previously approved Revlimid REMS 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. Data on the use of the mobile device application to conduct REMS functions (per current and previous two reporting periods and cumulatively)
   a. Number of downloads of the mobile application
   b. Uses of the mobile application, and the functions conducted via the mobile application
   c. 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

4. REMS Pharmacy Compliance (per current reporting period and previous two reporting periods and for 5c. and 5d. cumulatively beginning June 4, 2018)
    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
                i. Documentation of completion of training for relevant staff
                ii. 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 Revlimid prescriptions dispensed that were written by non-certified prescribers
            2. Number of Revlimid prescriptions dispensed by non-certified pharmacies
            3. Number of Revlimid prescriptions dispensed to de-enrolled or non-enrolled patients
            4. Number of times a Revlimid 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

5. 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

6. Inform prescribers, patients, and pharmacists on the serious risks and safe-use conditions for Revlimid/lenalidomide (per current reporting period and previous two reporting periods beginning June 4, 2018)
   a. Ensure that Revlimid will only be dispensed to patients enrolled in the Revlimid 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 Revlimid 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 Revlimid
      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

7. 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.

The REMS Assessment Plan applicable to the Lenalidomide shared system REMS must include, but is not limited to, the following items:

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Program Implementation and Operations

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      iii. Criteria for de-certification
   b. Provide a copy of the audit plan
   c. Report of audit findings
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