CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204026Orig1s000

Trade Name: Pomalyst capsules.

Generic Name: pomalidomide

Sponsor: Celgene Corporation

Approval Date: February 8, 2013

Indications: treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

204026Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204026Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204026

ACCELERATED APPROVAL

Celgene Corporation
Attention: Paul McInulty
Director, Regulatory Affairs
400 Connell Drive, Suite 7000
Berkeley Heights, NJ 07922

Dear Mr. McInulty:

Please refer to your New Drug Application (NDA) dated April 10, 2012, received April 10, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pomalyst (pomalidomide) capsules.

We acknowledge receipt of your amendments dated April 12; May 11 and 31; July 3, 10, and 20; August 3, 7 (2), 13, 24, and 30; September 7 (2), 18, and 19; October 10, 22, and 29; November 5 and 26; December 4, 7, 14, 17 and 21, 2012; January 4, 7, 10, 14, 22, 24, 28, and 31; February 4, 6 (2), and 7, 2013.

This new drug application provides for the use of Pomalyst (pomalidomide) capsules in the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on January 31, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204026**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Pomalyst (pomalidomide) capsules was not referred to an FDA advisory committee because this drug is not the first in its class and the safety profile is similar to that of other drugs or biologics approved for this indication.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following an opportunity for a hearing in accordance with 21 CFR 314.530, withdraw this

approval. We remind you of your postmarketing requirements specified in your submission dated February 6, 2013. These requirements, along with required completion dates, are listed below.

PMR 2006-1 Conduct a randomized controlled trial (CC-4047-MM-007) that isolates and demonstrates the efficacy and safety of Pomalyst (pomalidomide) in patients with previously treated multiple myeloma.

Final Protocol Submission: 12/2012 (completed)
Trial Completion: 4/2018
Final Report Submission: 1/2019

PMR 2006-2 Conduct a clinical trial, per FDA guidance [Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations], to determine the effect of CYP3A induction, which may decrease drug exposure, on the PK of Pomalyst (pomalidomide).

Final Report Submission: 9/2013

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing requirements must be clearly designated "**Subpart H Postmarketing Requirement**."

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 indications 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 assess the known serious risk of venous thromboembolic events (VTE). 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 this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 2006-3 Conduct an observational multi-site inception cohort study of Pomalyst (pomalidomide) users to address the questions detailed below:

1. To determine the failure rate for each of the different types of initial VTE prophylaxis for multiple myeloma patients treated with a Pomalyst (pomalidomide)-containing regimen.

2. To determine the failure rate for each type of VTE treatment for those patients with multiple myeloma and a VTE who continue to receive ongoing treatment with a Pomalyst (pomalidomide)-containing regimen.

3. To determine the failure rate for each type of post-VTE prophylaxis for those patients with multiple myeloma and a VTE who continue to receive ongoing treatment with a Pomalyst (pomalidomide)-containing regimen.

This observational study will enroll relapsed and refractory multiple myeloma patients identified through data sources currently part of the current THAL/REV TEE-01 clinical trial; two managed care databases, and a large claims database.

The timetable you submitted on February 6, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	6/2013
Study Completion:	3/2016
Final Report Submission:	1/2017

Finally, we have determined that only clinical trials (rather than nonclinical or observational studies) will be sufficient to:

- Identify an unexpected serious risk of more frequent and/or more severe adverse effects of Pomalyst (pomalidomide) due to increased drug exposure resulting from the effects of hepatic impairment;
- Identify an unexpected serious risk of more frequent and/or more severe adverse effects of Pomalyst (pomalidomide) due to increased drug exposure resulting from the effects of renal impairment;
- Identify an unexpected serious risk of more frequent and/or more severe adverse effects of Pomalyst (pomalidomide) due to increased drug exposure resulting from the effect of CYP3A inhibition;
- Identify an unexpected serious risk of more frequent and/or more severe adverse effects of Pomalyst (pomalidomide) due to increased drug exposure resulting from the effect of food on drug absorption;

- Identify an unexpected serious risk of more frequent and/or more severe adverse effects of Pomalyst (pomalidomide) when it is used in combination with dexamethasone.
- Identify an unexpected serious risk of QT prolongation with Pomalyst (pomalidomide) treatment;

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 2006-4 Conduct a clinical trial, per FDA guidance [Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling], in patients with baseline hepatic impairment to determine the influence of hepatic impairment on the pharmacokinetics (PK) and safety of Pomalyst (pomalidomide).

The timetable you submitted on February 6, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	5/2013
Trial Completion:	5/2015
Final Report Submission:	2/2016

PMR 2006-5 Conduct a clinical trial, per FDA guidance [Pharmacokinetics in Patients with Impaired Renal Function--Study Design, Data Analysis, and Impact on Dosing and labeling, in patients with baseline renal impairment and those on chronic dialysis], to determine the influence of renal impairment on the PK and safety of Pomalyst (pomalidomide).

The timetable you submitted on February 6, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	5/2013
Trial Completion:	5/2015
Final Report Submission:	2/2016

PMR 2006-6 Conduct a clinical trial, per FDA guidance [Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations], in order to determine the effect of CYP3A inhibition, which may increase drug exposure and thereby drug toxicity, on Pomalyst (pomalidomide) pharmacokinetics.

The timetable you submitted on February 6, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	9/2012 (completed)
Trial Completion:	11/2012 (completed)

Final Report Submission: 9/2013

PMR 2006-7 Conduct a food effect clinical trial, per FDA guidance [Food-effect Bioavailability and Fed Bioequivalence Studies], in order to determine the effect of food on the pharmacokinetics of Pomalyst (pomalidomide). The trial should be conducted in patients age > 60 years old using the commercial formulation of pomalidomide.

The timetable you submitted on February 6, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 3/2014
Trial Completion: 12/2014
Final Report Submission: 9/2015

PMR 2006-8 Conduct a randomized controlled trial (MM-003) of the combination of pomalidomide and dexamethasone in patients with previously treated multiple myeloma, to determine the safety profile of pomalidomide and dexamethasone combination as compared to a treatment arm without pomalidomide.

The timetable you submitted on February 6, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 3/2011 (completed)
Trial Completion: 9/2012 (completed)
Final Report Submission: 6/2013

PMR 2006-9 Conduct a QT prolongation trial, per FDA guidance [E14 Clinical Evaluation of QT/QTc interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs], to assess the effect of Pomalyst (pomalidomide) on the QT interval.

The timetable you submitted on February 6, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 8/2013
Trial Completion: 5/2014
Final Report Submission: 2/2015

Submit the protocols to your IND 066188, with a cross-reference letter to this NDA. Submit 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 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 commitment:

PMC 2006-10 Conduct a clinical trial, per FDA guidance [Drug Interaction Studies—Study Design, data Analysis, Implications for Dosing, and Labeling Recommendations], in order to determine the effects of a CYP1A2 inducer (such as montelukast) on the PK of Pomalyst (pomalidomide). CYP1A2 induction may decrease Pomalyst (pomalidomide) exposure and result in diminished efficacy.

The timetable you submitted on February 6, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	3/2014
Trial Completion:	12/2014
Final Report Submission:	9/2015

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Pomalyst (pomalidomide) to ensure the benefits of the drug outweigh the risk of teratogenicity.

Pursuant to 505-1(f)(1), we have determined that Pomalyst (pomalidomide) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of teratogenicity that is listed in the labeling. The elements to assure safe use will require that healthcare professionals who prescribe Pomalyst (pomalidomide) are specially certified, that pharmacies who dispense Pomalyst (pomalidomide) are specially certified, that Pomalyst (pomalidomide) will only be dispensed to patients enrolled in the REMS program with evidence or documentation of safe-use conditions, and that female patients or female partners of male Pomalyst (pomalidomide) patients who report a pregnancy during treatment with Pomalyst (pomalidomide) will be enrolled in a registry. These elements are intended to avoid pregnancy occurrence and, should pregnancy occur, monitor and report pregnancy outcomes.

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.

Your proposed REMS, submitted on February 6, 2013, and appended to this letter, is approved. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Pomalyst (pomalidomide) into interstate commerce.

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

1. Pregnancies:

    a. Number of pregnancies reported during the current REMS assessment reporting period and during each previous REMS assessment 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. Discussion of any new information provided in the most recent Periodic Safety Update Report (PSUR) regarding pregnancy. In the electronic REMS assessment submission, include a hyperlink to the most recent PSUR that provides information on worldwide pregnancies.

2. Reporting on the restricted distribution program:

    a. 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/documentation of safe use:

        i. A list of identified flags, the reasons for the flags, and the actions taken to correct. Provide for the reporting period (by month); and summarize findings from each previous assessment report.

        ii. Provide 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. Provide the number and proportion of flags that caused a delay in treatment initiation or a gap in therapy for patients. Provide 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. 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 each REMS assessment report must be submitted with the title of the report stating that this is a REMS assessment report, and each report must address all items in the REMS assessment plan outlined in this approval letter.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

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 204026 REMS CORRESPONDENCE
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.

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

NDA 204026 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA204026
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 204026
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing aproval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action 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 Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling
REMS

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

/s/

ANN T FARRELL
02/08/2013
Farrell, M.D. for Pazdur, M.D.