



NDA 21-880

Celgene Corporation  
86 Morris Avenue  
Summit, New Jersey 07901

Attention: Gretchen Toolan  
Director, Regulatory Affairs

Dear Ms. Toolan:

Please refer to your new drug application (NDA) dated April 7, 2005, received April 7, 2005, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Revlimid® (lenalidomide) capsules 5 and 10 mg.

We acknowledge receipt of your submissions dated December 22, 2004; May 17 and 31, 2005; June 1, 14, and 24, 2005; July 8, 12, 20, 27, and 28, 2005; August 3, 5, 9, 10, 12, 15, 22, 24, 25, 26, and 31, 2005; September 5, 7, 22, and 30, 2005; October 4 and 19, 2005; and November 16 and 30, 2005; December 2, 5, 9, 15 and 21, 2005.

This new drug application, considered for approval under 21 CFR 314.520 (Subpart H), at your request, provides for the use of Revlimid® 5 mg and 10 mg capsules for the treatment of patients with transfusion dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5 q cytogenetic abnormality with or without additional cytogenetic abnormalities.

We have completed our review of this application, as amended. It is approved under the provisions of 21 CFR 314.520 (Subpart H), effective on the date of this letter, for use as recommended in the agreed upon labeling text, required patient labeling, and the components of the RevAssist<sup>SM</sup> Risk Minimization Action Plan (RiskMAP).

Under 21 CFR 314.520 (Subpart H), distribution of the drug is limited as described below and in the attached detailed RevAssist<sup>SM</sup> program. The primary goal of the RevAssist<sup>SM</sup> program is to prevent fetal exposures, pending complete and adequate characterization of the teratogenic potential of lenalidomide.

Revlimid® RiskMAP:

We remind you that your Revlimid® RiskMAP (called RevAssist<sup>SM</sup>) is an important part of the postmarketing risk management for Revlimid®, and must include each of the following components:

1. Registration in the RevAssist<sup>SM</sup> program of prescribers, pharmacies, nurses, and patients who agree to specific responsibilities in order to distribute, prescribe, dispense, and use Revlimid®.

2. Implementation of a program and distribution of materials to educate prescribers, pharmacies, nurses, and patients about the risks and benefits of Revlimid®, including materials which describe the roles of the RevAssist<sup>SM</sup> program participants.
3. Implementation of a reporting and data collection system for safety surveillance.
4. Implementation of a plan to monitor, evaluate, and improve minimization of drug exposure during pregnancy and compliance with restrictions for safe use under the RevAssist<sup>SM</sup> program.

The Revlimid® Risk Minimization Action Plan, as described in the attached documents adequately addresses each of these requirements. Any change to the program must be discussed with FDA prior to its institution and is subject to FDA's determination that the required components continue to be met. We expect your continued cooperation to resolve any problems regarding the RevAssist<sup>SM</sup> program that may be identified following approval of this application.

We remind you of your December 15, 2005 submission and your commitment to establish a pregnancy registry to monitor for potential human teratogenicity even if animal teratogenicity testing indicates that the RevAssist<sup>SM</sup> program for monitoring fetal exposure is unnecessary.

We also remind you of your post marketing study commitments specified in your submission dated December 21, 2005. These commitments, along with any completion dates agreed upon, are listed below.

1. The embryo-fetal toxicity assessment of Revlimid has not been adequately addressed. You have agreed to provide adequate information for this assessment in appropriate models designed to fully assesses the possible toxicity of Revlimid. You indicated you plan to conduct these studies in two different species that are appropriate to assess the full range of thalidomide embryo-fetal effects. As discussed, the rat is not an acceptable model. If the study with lenalidomide in the first species shows clear evidence of teratogenesis, than a confirmatory study will not be necessary. Although not generally considered "definitive" test systems for pharmaceutical products, additional studies of an exploratory nature on the embryo-fetal effects of lenalidomide (e.g., (b)(4) assay; (b)(4) assay), may be useful.

Protocol Submission: 06/06  
Study Start: 09/06  
Final Report Submission: 12/07

2. You have agreed to submit the study report and data from the ongoing study, CC-5013-MDS-004, a randomized, double-blind, placebo-controlled, multicenter, 3-arm study of the efficacy and safety of 2 doses of lenalidomide (5 mg daily versus 10 mg day 21 days of a 28 day cycle) versus placebo in red blood cell (RBC) transfusion-dependent patients with low-or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality when completed.

Protocol Submission: 03/05  
Study Start: 08/05  
Final Report Submission: 12/08

3. Following Revlimid dosing, approximately 2/3 of lenalidomide is excreted as unchanged

AUC) was 56% higher than in similar patients with normal renal function who received the same dose. Based on these data, you have agreed to conduct a study to determine the pharmacokinetics of lenalidomide in subjects with renal impairment. To assist with the study design, please refer to the FDA Guidance, "Pharmacokinetics in Patients with Impaired Renal Function."

Protocol Submission: 11/04  
Study Start: 03/06  
Final Report Submission: 12/07

4. Regarding the Evaluation/Surveillance Plan:

- You have agreed to submit a Pregnancy Exposure follow-up plan which will document your plan to follow-up pregnancy exposures to their outcome. This plan may be submitted as a post-marketing commitment.

Plan submission 06/01/06

- You have agreed to submit an Evaluation Plan of RevAssist to FDA within 3 to 6 months of approval. Please include, at a minimum, plans to study the Pharmacy Audit Plan, Outcomes of Pregnancy Exposures, and the Knowledge Surveys of physicians, nurses, and patients.

Plan submission 06/01/06

5. You have agreed to submit all exposed pregnancies within 15 days of receipt as 15 day expedited reports.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you must include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

Pursuant to 21 CFR Part 208, FDA has determined that Revlimid poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Revlimid. FDA has determined that Revlimid is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Revlimid. In addition, patient labeling could help prevent serious adverse events related to use of the product. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Revlimid.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert, Medication Guide and immediate container and carton labels). Marketing the product with FPL that is not identical

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission “**FPL for approved NDA 21-880.**” Approval of this submission by FDA is not required before the labeling is used.

As part of the approval under Subpart H, we acknowledge that you submitted to the Agency your promotional materials (both promotional labeling and advertisements) that are to be used within the first 120 days after approval. In addition, as required by 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all subsequent promotional labeling as well as advertisements at least 30 days before the intended time of initial distribution of the labeling or initial publication of the advertisement. Send one copy to the Division of Drug Oncology Products and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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

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 [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm)

If you have any questions, call Carl Huntley, Regulatory Project Manager, at (301) 796-1372.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.  
Director, Office of Oncology Drug Products  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration

Enclosure