CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204026Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA#	NDA 204026
Applicant	Celgene
Date of Submission	April 10, 2012
PDUFA Goal Date	February 10, 2013
Trade Name (Non-proprietary name)	Pomalyst (pomalidomide)
Dosage forms / Strength	1, 2, 3, and 4 mg capsules
Applicant's Proposed Indication	For patients with multiple myeloma who have received at least two prior therapies including bortezomib (b) (4) and have demonstrated disease progression on or within 60 days of completion of the last therapy.
Recommended:	Accelerated Approval

Material Reviewed/Consulted	**Reviewer/Author**
Division Director	Ann Farrell, MD
Regulatory Project Manager	Amy Baird
Medical Officer Review	Saleh Ayache, MD, Angelo De Claro, MD, Albert Deisseroth, MD, PhD (CDTL)
Statistical Review	Yun Wang, PhD, Mark Rothmann, PhD
Pharmacology Toxicology Review	Pedro Del Valle, PhD, Brenda Gehrke, PhD and Haleh Saber, PhD
ONDQA-CMC Reviews	William Adams, PhD, Janice Brown, PhD, Nallaperum Chidambaram, PhD
ONDQA-Biopharm Review	Tien Mien Chen, PhD, and Angelica Dorantes, PhD
Microbiology	Steven Donald, PhD, and David Hussong, PhD
Clinical Pharmacology Review	Rachelle Lubin, PharmD, Bahru Habtemariam, PharmD, and Julie Bullock, PharmD
OSI/DGCPC Review	Anthony Orencia, MD, and Susan D. Thompson, MD
OPDP	James Dvorsky
OSE	Sarah K. Vee, PharmD/Kevin Wright, PharmD/ Yelena Maslov, PharmD/Kellie A. Taylor, PharmD, MPH/Carol Holquist, RPh
OSE-DRISK	Joyce Weaver, PharmD, Kate Oswell, MA/Cynthia LaCivita, PharmD/Claudia Manzo, PharmD

1. Introduction & Background

On April 10, 2012, Celgene submitted a New Drug Application (NDA) for pomalidomide in combination with dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received at least 2 prior regimens of established benefit, including both lenalidomide and bortezomib and have demonstrated disease progression on the last therapy. Pomalidomide is a thalidomide analogue for the treatment of patients with multiple myeloma that has relapsed after prior therapy. It is the third drug in the class of immunomodulatory agents (after thalidomide and lenalidomide). Both thalidomide and lenalidomide were approved in 2006 to treat multiple myeloma.

There are multiple drugs that are approved for the treatment of multiple myeloma, including melphalan, cyclophosphamide, liposomal doxorubicin, carmustine, thalidomide, lenalidomide, bortezomib and carfilzomib.

Multiple myeloma remains incurable with conventional therapy. Allogeneic stem cell transplant is curative.

Pomalidomide is not approved in any country or region.

2. CMC/Device

There are no issues that preclude approval from a CMC perspective. The CMC discipline has recommended an initial expiry period of 18 months for capsules in the commercial packaging systems with storage at USP controlled room temperature.

The Office of Compliance did not identify any issues that would preclude approval.

3. Nonclinical Pharmacology/Toxicology

There are no issues that preclude approval from a nonclinical perspective. Nonclinical discipline reviews conclude:

Animal toxicology studies were conducted in appropriate species, using the administration route and dosing regimens that adequately addressed safety concerns in humans. Pomalidomide-related toxicities were more evident in monkeys and included: reduction in platelet and WBC counts, lymphoid depletion, inflammation in the GI tract, and infection (likely related to lymphoid depletion). In the chronic toxicology study, one of the 12 monkeys in the high-dose arm developed acute myeloid leukemia (AML) when animals were treated for 9 months. An association between pomalidomide treatment and development of AML cannot be ruled out at this time. While pomalidomide was negative in the battery of genetic toxicology studies, secondary malignancies with immune-modulatory agents have been reported…

Pomalidomide was teratogenic in rats and rabbits. In the embryo-fetal developmental study conducted in rabbits, thalidomide was used as a comparator. Teratogenic and embryo-fetal toxic effects of pomalidomide were similar to those seen with thalidomide. A pregnancy Category X has been assigned to pomalidomide because of the teratogenic effects of this drug in animals and to be consistent with thalidomide and lenalidomide labels. Pomalidomide did not affect the fertility index in male or female rats, when tested in a fertility and early embryonic study. However, the number of viable embryos was reduced, which is likely secondary to the increase in post-implantation loss and the increase in resorption, as described in this study. This effect was seen when male and female rats treated with pomalidomide were mated. The reduction in the number of embryos was attributed to the exposure of females to pomalidomide, since treating male rats with pomalidomide and mating them with untreated females did not affect the viability of embryos.

4. Clinical Pharmacology

There are no issues that preclude approval from a Clinical Pharmacology perspective. Clinical Pharmacology findings are as follows:

The human ADME properties of pomalidomide were evaluated following a single 2 mg radiolabeled dose in healthy subjects. It was determined that the predominant (~70%) circulating radioactive entity was pomalidomide. Pomalidomide is eliminated

primarily through the kidneys (~ 73% of administered dose), with 2.2% of dose excreted as unchanged drug in urine. Approximately 15.5% of administered dose was excreted via the fecal route. Cytochrome P450 dependent metabolites accounted for 43% of the excreted radioactivity in humans. Circulating metabolites accounted for less than 10% of the total radioactivity. Pomalidomide is primarily metabolized by CYP3A4 and CYP1A2, with some contributions from CYP2C19 and CYP2D6.

The applicant conducted a food effect study to assess the influence of food on the PK of pomalidomide. However, the food effect study was conducted using a capsule formulation that failed to achieve bioequivalence with the to-be-marketed formulation. Therefore, the food effect study results were deemed unreliable to properly evaluate the effect of food on the PK of pomalidomide.

To date, population PK analysis, exposure-response analysis, organ impairment studies, and QT study results have not been submitted to the Agency for review.

There are several clinical pharmacology issues that will be addressed as PMRs. See action letter for these PMRs.

5. Clinical Microbiology

There are no microbiology issues that would preclude approval.

6. Clinical/Statistical-Efficacy

This application is based on the results of clinical trial CC-4047-MM-002; a multicenter, randomized, open-label study in 221 patients with relapsed and refractory multiple myeloma who had previously received lenalidomide and bortezomib and were refractory to the last myeloma therapy. The treatment arms were pomalidomide alone or pomalidomide plus low-dose dexamethasone.

The efficacy results demonstrated an overall response rate of 7% in patients treated with pomalidomide alone, and 29% in those treated with pomalidomide plus low-dose dexamethasone. The median response duration was not evaluable in the pomalidomide alone arm and was 7.4 months in the pomalidomide plus low-dose dexamethasone arm. See Table 1 below for results.

Table 1: Clinical trial CC-4047-MM-002 results:

	Study 1	
	pomalidomide (N=108)	pomalidomide plus low dose dexamethasone (N = 113)
Overall Response Rate (ORR)[1], n (%)	8 (7.4)	33 (29.2)
95% CI for ORR (%)	(3.3, 14.1)	(21.0, 38.5)
Complete Response (CR), n (%)	0 (0.0)	1 (0.9)
Partial Response (PR), n (%)	8 (7.4)	32 (28.3)

7. Safety

The most common side effects reported in the clinical trial include fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper respiratory tract infections, back pain, and pyrexia. Pomalidomide is approved with a Boxed Warning alerting patients and healthcare professionals that the drug can cause embryo-fetal toxicity and venous thromboembolism.

Because of this embryo-fetal risk, pomalidomide is available only through a restricted distribution program called the POMALYST Risk Evaluation and Mitigation Strategy (REMS) Program. Prescribers must be certified with the POMALYST REMS ™ Program by enrolling and complying with the REMS requirements. Patients must sign a Patient-Physician Agreement Form and comply with the REMS requirements. Female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements. Males must comply with contraception requirements. Pharmacies must be certified with the POMALYST REMS Program, must only dispense to patients who are authorized to receive pomalidomide and comply with REMS requirements.

8. Advisory Committee Meeting

Pomalidomide, a thalidomide analogue, was not discussed at an Oncologic Drugs Advisory Committee meeting due to the fact that the clinical trial design and findings were consistent with other products approved for the treatment of multiple myeloma. In addition, thalidomide and lenalidomide, another thalidomide analogue, are already approved for the treatment of multiple myeloma.

9. Pediatrics

Pomalidomide has orphan drug designation and is therefore exempt from PREA requirements.

10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

11. Labeling

The labeling was reviewed by all disciplines and consultant staff.

12. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action: Accelerated approval

- Risk Benefit Assessment

The risk benefit assessment suggests that pomalidomide is effective for the treatment of multiple myeloma and that the risks of treatment can be managed by a REMS program and labeling. The major risks are those seen with thalidomide and lenalidomide and include embryo-fetal risk, thromboembolism, myelosuppression, neuropathy, central nervous system effects (confusion, dizziness), and gastrointestinal disturbances. The risk benefit profile, which was also discussed by Drs. Farrell, Deisseroth, DeClaro and Ayache, is acceptable. In addition, the review team recommends approval of this NDA, and I concur.

- Recommendation for Post marketing Risk Management Activities

Routine postmarketing surveillance and REMS.

- Recommendation for other Post marketing Study Requirements (PMR)/Commitments (PMC)

See action letter for all PMRs/PMCs.

This application is being approved under accelerated approval. Therefore, the sponsor is required to submit the results of clinical trial CC-4047-MM-007 to verify clinical benefit. CC-4047-MM-007 is a randomized clinical trial of pomalidomide added to bortezomib and low-dose dexamethasone compared to bortezomib plus low-dose dexamethasone in patients with previously-treated multiple myeloma.

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/s/

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02/07/2013

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02/07/2013