CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204026Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	204026
Applicant Name	Celgene, Inc.
Date of Submission	04/10/12
PDUFA Goal Date	02/10/13
Proprietary Name / Established (USAN) Name	Pomalyst/pomalidomide
Dosage Forms / Strength	1, 2, 3, and 4 mg capsules
Proposed Indication(s)	For 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.
Action/Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Saleh Ayache, M.D./Angelo De Claro, M.D./Albert Deisseroth, M.D., Ph.D.
Statistical Review	Y. Wang, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Brenda Gehrke, PhD./Haleh Saber, Ph.D.
CMC Review/OBP Review	W. Michael Adams, M.S. /Nallaperum Chidambaram, Ph.D.
Microbiology Review	Steven P. Donald, M.S./Bryan Riley, Ph.D.
Clinical Pharmacology Review	Rachelle Lubin, Pharm.D./Bahru Habtemariam, Pharm.D.
DDMAC	James Dvorsky
DSI	Anthony Orencia, M.D./Susan D. Thompson, M.D.
CDTL Reviews	Albert Deisseroth, M.D., Ph.D.
OSE	Sarah K. Vee, PharmD./Kevin Wright, Pharm.D./ Yelena Maslov, Pharm.D./Kellie A. Taylor, Pharm.D., M.P.H./Carol Holquist, RPh
OSE/Epidemiology	
OSE/DRISK	Joyce Weaver, Pharm.D., Kate Oswell, M.A./Cynthia LaCivita, Pharm.D./Claudia Manzo, Pharm.D.
Other -	
Other –	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

Signatory Authority Review Template

1. Introduction

On April 10, 2012, Celgene submitted a NDA for pomalidomide, a thalidomide analogue for the treatment of patients with multiple myeloma that has relapsed after prior therapy. Pomalidomide is the third in the class of immunomodulatory agents (after thalidomide and lenalidomide). Both thalidomide and lenalidomide were approved in 2006 to treat multiple myeloma.

Pomalidomide is not approved in any country or region.

2. Background

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

Numerous chemotherapy treatment regimens exist in the literature. Most commonly the treatment regimens include a combination of a proteosome inhibitor, thalidomide analogue, steroid or alklyating agents (such as cyclophosphamide, melphalan). Recent data suggests that combination of triplet therapy (a proteosome inhibitor, thalidomide analogue, and steroid) may be better than the current US standard of doublet therapy (a proteosome inhibitor and steroid or a thalidomide analogue and steroid).

3. CMC/Device

Dr. Chidambaram and Mr. William Adams reviewed this application. In their reviews they state the following:

Commercial drug product is an immediate release hard gelatin capsules in 1mg, 2mg, 3mg and 4mg strengths. Capsules are color coded, and imprinted with drug name and strength. The market packages are 21-count and 100-count HDPE bottles with a (b) (4) *child resistant closure and a tamper evident seal…*

An initial expiry period of 18 months is recommended 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.

4. Nonclinical Pharmacology/Toxicology

Drs. Gehrke and Saber performed reviews and did not identify any issues that would preclude approval. Their findings included:

Pomalidomide is an immune-modulator and analogue of thalidomide, developed to treat patients with relapsed/refractory multiple myeloma. Thalidomide and lenalidomide (also a thalidomide analogue) have been approved for treatment of multiple myeloma. Thalidomide, lenalidomide, and pomalidomide are structurally related. Previously the mechanism of action of thalidomide and lenalidomide were not fully characterized, as also mentioned in the label for these drugs. The Applicant conducted studies to characterize the pharmacology of pomalidomide, while using thalidomide and lenalidomide as comparators in several pharmacology studies. Pomalidomide targets the protein cereblon, which is involved in poly-ubiquitination of proteins. The activity of pomalidomide was dependent on the presence of cereblon. …

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.

5. Clinical Pharmacology/Biopharmaceutics

Drs. Lubin and Habtemariam did not identify issues that would preclude approval; however, they noted issues that would need to be addressed with post-marketing requirements. Their findings included:

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.

6. Clinical Microbiology

The product microbiology review team did not identify any issues that would preclude approval.

7. Clinical/Statistical-Efficacy

The clinical application is based on primarily one clinical trial with support from other submitted trials.

Study CC-4047-MM-002 is a Phase 1/2 randomized open label trial designed to determine the MTD, safety and efficacy of CC-4047 (pomalidomide) alone or in combination with a low-dose dexamethasone regimen in 221 patients with relapsed multiple myeloma who have received at least 2 prior therapies that included a bortezomib, a proteasome inhibitor, and either lenalidomide or thalidomide. Median age of patients enrolled was greater than 60 years of age, slightly more males than females were enrolled, about 75% had a prior transplant, about 78% had received prior lenalidomide and were “refractory”, about 67% had received prior thalidomide and more than 60% had received prior bortezomib and were “refractory". The results below are reflected in the labeling.

	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)

The statistical reviewer concurred with the analyses presented above.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstration of efficacy for the indication.

8. Safety

The review team identified the following major risks for use with pomalidomide: embryo-fetal risk, thromboembolism, hematological toxicities (neutropenia, Thrombocytopenia, anemia) and non-hematologic toxicities (infection, dyspnea, neuropathy, dizziness, gastrointestinal (GI) toxicity, and fatigue).

I concur with the conclusions of the clinical and statistical review teams.

9. 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.

10. Pediatrics

Orphan designation

11. Other Relevant Regulatory Issues

Maternal Health was consulted and provided labeling recommendations which were incorporated into labeling.

Office of Surveillance and Epidemiology was consulted including DMEPA who provided labeling input.

Office of Scientific Investigation (OSI)
From their review of the inspectional findings:

Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication.

There are no other unresolved relevant regulatory issues.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Accelerated Approval for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and lenalidomide

- Risk Benefit Assessment

The risk benefit assessment suggests that this thalidomide analogue is likely 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.

- Recommendation for Post marketing Risk Management Activities

Routine post-marketing surveillance

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

We have asked the applicant:

Under Accelerated Approval (21CFR 314.500)

to conduct and submit for review (clinical report and raw data) the proposed trial, MM-007, a randomized, controlled trial which isolates the effect of pomalidomide

to determine the effect of CYP3A induction on the pharmacokinetics of pomalidomide

Under 505 o

to study the DVT/VTE risk based on anticoagulant prophylaxis use

to evaluate the effect of hepatic impairment on pomalidomide

to conduct and submit for review (clinical report and raw data) the proposed trial, MM-003, a randomized, controlled trial

to evaluate the effect of renal impairment on pomalidomide
to evaluate the effect of pomalidomide on the QT interval
to evaluate whether food should be considered when recommending pomalidomide dosing
to determine the effect of CYP3A inhibition on the pharmacokinetics of pomalidomide

PMC

to determine the effect of CYP1A2 inducer on the pharmacokinetics of pomalidomide

For final versions of the PMRs and PMC see the approval letter.

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/s/

AMY C BAIRD
02/07/2013

ANN T FARRELL
02/07/2013