CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-880

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics NDA Review

Brand name: REVLIMID®

Generic name: Lenalidomide

Type of dosage form and strength(s): 5 and 10 mg capsules

Indication(s): the Applicant's proposed indication is, "... for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities."

NDA number, type: NDA 21-880, 1P

Applicant name: Celgene Corporation

Submission date (letter date): 15-AUG-2005 N 000 BZ
12-AUG-2005 N 000 BM
10-AUG-2005 N 000 BS
5-AUG-2005 N 000 SU
24-JUN-2005 N 000 BM
1-JUN-2005 N 000 BM
17-MAY-2005 N 000 BC
7-APR-2005 N 000
22-DEC-2004 RRZ 001

OCPB Division name: Division of Pharmaceutical Evaluation I

OND: **Division name**: Division of Oncologic Drug Products

OCPB Reviewer name: Gene M. Williams, Ph.D.

OCPB Team Leader name: Brian P. Booth, Ph.D.

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1. *Executive Summary*

A single commitment for clinical pharmacology and biopharmaceutics is recommended.

1.1. Recommendations

This NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

Approximately 2/3 of lenalidomide is excreted as unchanged drug in urine following Revlimid dosing. In multiple myeloma patients with mild renal impairment, exposure (plasma AUC) was 56% higher than in multiple myeloma patients with normal renal function who received the same dose. Based on these data, we recommend that a study be conducted to determine the pharmacokinetics of lenalidomide in subjects with renal impairment. The study design should be consistent with the FDA Guidance, "Pharmacokinetics in Patients with Renal Impairment."

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings (1-3 pages)

Lenalidomide is structurally similar to the teratogenic drug thalidomide.

Following oral administration, maximum lenalidomide plasma concentrations occur from 0.5 - 4 hours post-dose. Co-administration with food does not alter the extent of absorption. Half-life of lenalidomide elimination is approximately 3 hours and the pharmacokinetic disposition of lenalidomide is, at doses up to 10X the recommended clinical dose of 10 mg, linear. Approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore entails an active component. In mutliple myeloma patients with mild renal impairment, AUCs were 56% higher than in similar patients with normal renal function.

A search for circulating lenalidomide metabolites in human biomaterials (plasma, urine or feces) was not performed.

Results from human *in vitro* metabolism studies show that lenalidomide is not metabolized through the cytochrome P450 pathway. Human *in vitro* metabolism studies also show that lenalidomide does not inhibit or induce cytochromes P450.

The pharmacokinetics of lenalidomide in patients with renal impairment or hepatic impairment have not been systematically studied. The effects of age on the pharmacokinetics of lenalidomide have not been studied. No pharmacokinetic data are available in patients below the age of 18 years. The effects of gender on the pharmacokinetics of lenalidomide have not been studied. Pharmacokinetic differences due to race have not been studied.

Lenalidomide is a BCS Class 3 (high solubility – low permeability) substance. Based on the compositional proportionality of the strengths, the dosing regimen used in clinical trials, pharamacokinetic linearity, and comparative dissolution profiles, the Applicant requests and will be granted a waiver for an in vivo bioequivalence study comparing the 5 mg capsule strength studied in efficacy and safety studies and the 10 mg strength which will be marketed, in addition to the 5 mg strength.

2. *Question-Based Review*

2.1. General attributes of the drug

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

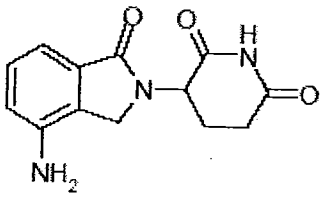
REVLIMID® for the treatment of transfusion dependent MDS (the current indication) has been granted Orphan Drug status.

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

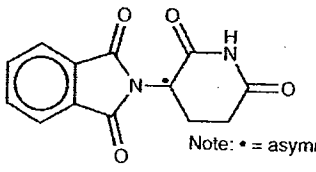
The active ingredient in the drug product is lenalidomide (CC-5013, CDC-501). Its International Union of Pure and Applied Chemistry (IUPAC) name is 3-(4'-amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione. a structural representation is shown below as **FDA Figure 1A.** To allow comparisons, a structural representation of thalidomide is included as **FDA Figure 1B.**

FDA Figure 1.

A. Lenalidomide -- Applicant's Section 1.2 from p. 1 of the Quality Overall Summary (Section 2.3.S)



B. Thalidomide – Package insert for THALOMID®



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