CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-880

CHEMISTRY REVIEW(S)

NDA 21-880

Revlimid™

(Lenalidomide)

Celgene Corporation

Haripada Sarker, Ph.D.
HFD-150 Division of Oncology

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-880

2. REVIEW #1:

3. REVIEW DATE: 12-05-2005

4. REVIEWER: Haripada Sarker, Ph.D.

6. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 60,100	March 31, 2000

1. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (RRZ-001) -rolling	December 22, 2004
Amendment (N-000) - Labeling	April 7, 2005
Amendment (N-000-BC) – DP stability and spec. update	May 17, 2005
Amendment (N-000-BC) – DP dissolution update	August 25, 2005
Amendment (N-000-BC) – DS and DP Stability	September 30, 2005
Amendment (N-000)C – DP Labeling	October 27, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Celgene Corporation
Address:	86 Morris Avenue Summit, NJ 07901
Representative:	Gretchen Toolan

Telephone: 908-673-9551

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Revlimid™
b) Non-Proprietary Name: Lenalidomide
c) Code Name/#: CC-5013, CDC-501, Revlimid
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: P

e) Proposed Trade Name: Revlimid™

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Transfusion-Dependent Anemia Due to Low- or Intermediate-1-Risk Myelodysplastic Syndroms Associated with a Deletion 5q Cytogenetic Abnormality.

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

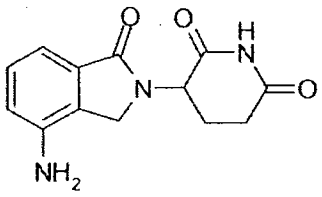
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structure:



Name (drug substance)	Lenalidomide (USAN Name)
Chemical Name (CAS)	3-(4'-amino-1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-2,6-piperidinedione
CAS number	191732-72-6
Molecular Weight	259.25
Molecular Formula	$C_{13}H_{13}N_3O_3$
Structural formula	As above

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COM-PLETED	COMMENTS
/	III	/	/	4	N/A	N/A	Not reviewed
/	III	/	/	4	N/A	N/A	Not reviewed
/	III	/		4	N/A	N/A	Not reviewed
/	IV	/	/	4	N/A	N/A	Not reviewed

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

ONDC: To be filled later

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	1-AUG-05	J. D. Ambrogio
Pharm/Tox	Acceptable with comment	5-Oct-05	Anwar Goheer
Biopharm	Acceptable	9-SEPT-05	Gene William
DMETS	Acceptable with comment	2-June-05	Kimberly Culley
Methods Validation	May be requested post-approval		Haripada Sarker
EA (Categorical Exclusion)	acceptable	3-Nov-05	Haripada Sarker
Microbiology	N/A		N/A

The Chemistry Review for NDA 21-649

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from a chemistry, manufacturing and controls standpoint because:

The applicant addressed all the deficiencies satisfactorily. The applicant has validated the analytical methods for specified impurities and degradants. The office of compliance has provided an overall acceptable recommendation (see attached). The following comments regarding retest for the drug substance and shelf-life for the drug product should be included in the action letter:

"A retest period of — for the drug substance and a shelf-life of twenty four months for the drug product will be granted based on stability data provided"

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Revlimid® (lenalidomide) is formulated as capsules and is supplied in 5 mg and 10 mg strengths. Lenalidomide is the active ingredient. Inactive ingredients include lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, yellow iron oxide, titanium oxide and black ink. The drug product is stored at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F). [See USP Controlled Room Temperature]. The applicant proposed 24 months of shelf-life for the drug product. Based on primary and supportive stability data, an expiration dating period of 24 months may be granted.

The chemical name for lenalidomide is 3-(4-amino-1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-2,6-piperidinedione. The molecular formula of lenalidomide is $C_{13}H_{13}N_3O_3$ with a molecular weight of 259.25. Lenalidomide possess piperidindione and indoline moieties. It has an asymmetric center and is manufactured as racemic mixtures. Lenalidomide bears an amino function on its aromatic ring system which contributes to its lower lipid solubility. — —

— . Two different HPLC methods are utilized for better

separation of the impurities and degradants in drug substance. Validations reports are provided for both the methods. Impurities in drug product are mostly carried over from the drug substance. Celgene provided real time stability test data on two drug substance batches over the period of — and photostability data on one batch over — Celgene has proposed a retest period of — for the drug substance. Based on provided real time stability data a retest period of — may be granted.

B. Description of How the Drug Product is Intended to be Used

REVLIMID® is supplied as white opaque capsules imprinted "REV" on one half and "5 mg" on the other half in black ink. For 10 mg capsules, blue/green and pale yellow opaque capsules imprinted "REV" on one half and "10 mg" on the other half in black ink. Both 5 mg and 10 mg capsules are packaged in bottles of 30 and 100 counts.

C. Basis for Approvability Recommendation

This application is recommended for APPROVAL from the stand point of chemistry, manufacturing and controls because all the deficiencies have been satisfactorily addressed and the office of compliance has provided an overall acceptable recommendation (see attached). The following comments regarding retest for the drug substance and shelf-life for the drug product should be included in the action letter:

"A retest period of — for the drug substance and a shelf-life of twenty four months for the drug product will be granted based on stability data provided".

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Haripada Sarker, Ph.D.
ChemistryTeamLeaderName/Date: Nallaperumal Chidambaram, Ph.D.
ProjectManagerName/Date: Carl Huntley

C. CC Block

77 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

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

/s/

Haripada Sarker
12/5/2005 03:30:12 PM
CHEMIST

Nallaperumal Chidambaram
12/5/2005 04:56:53 PM
CHEMIST