

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206088Orig1s000

CHEMISTRY REVIEW(S)



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

IV. Appendix:

Appendix 1: EES Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 206088/000	Sponsor:	CELGENE
Org. Code:	540		86 MORRIS AVE
Priority:	1		SUMMIT, NJ 07901
Stamp Date:	23-SEP-2013	Brand Name:	APREMILAST TABLETS
PDUFA Date:	23-SEP-2014	Estab. Name:	
Action Goal:		Generic Name:	APREMILAST TABLETS
District Goal:	23-APR-2014	Product Number; Dosage Form; Ingredient; Strengths	
			002; TABLET, FILM COATED; APREMILAST; 20MG
			001; TABLET, FILM COATED; APREMILAST; 10MG
			003; TABLET, FILM COATED; APREMILAST; 30MG
FDA Contacts:	C. STRASINGER	Prod Qual Reviewer	(HFD-800) 3017963776
	K. JENNINGS	Product Quality PM	3017962919
	D. WILLIAMS	Regulatory Project Mgr	(HFD-540) 3017965376
	S. DING	Team Leader	3017961349
Overall Recommendation:	ACCEPTABLE	on 09-JUN-2014	by S. IYER (HFD-310) 3017963319
	PENDING	on 25-OCT-2013	by EES_PROD
Establishment:	CFN: 3008305265	FES:	3008305265
	CELGENE CHEMICALS GMBH		
	UNTERE BRUHLSTRASSE 4		
	ZOFINGEN, SWITZERLAND	AADA:	
DMF No:			
Responsibilities:	DRUG SUBSTANCE MANUFACTURER	OAI Status:	NONE
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS		
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	27-DEC-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		



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Chemistry Assessment Section

Establishment: CFN: FEI: 3006323509
 CELGENE INTERNATIONAL SARL
 ROUTE DE PERREUX 1
 BOUDRY, SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-DEC-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-DEC-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

Establishment:	(b) (4)	
DMF No:		AADA:
Responsibilities:	DRUG SUBSTANCE OTHER TESTER	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	09-JUN-2014	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

Establishment:	(b) (4)	
DMF No:		AADA:
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER	
Profile:	TABLETS, PROMPT RELEASE	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	18-NOV-2013	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	

Establishment:	(b) (4)	
DMF No:		AADA:
Responsibilities:	FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	27-DEC-2013	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

Establishment: (b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-NOV-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-OCT-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: (b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-MAY-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No: (b) (4) **AADA:**

Responsibilities: INTERMEDIATE MANUFACTURER
INTERMEDIATE RELEASE TESTER

Profile: API NON-STERILE (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-JAN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

MARY GRACE LUBAO
09/29/2014

Executive Summary Section

NDA 206088

Otezla (apremilast) tablets
10 mg, 20 mg, 30 mg

Celgene Corporation

Caroline Strasinger, Ph.D.
Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

CMC Review of NDA 206088
For the Division of Dermatological and Dental Drug Products

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Chemistry Review Data Sheet

1. NDA 206088
2. REVIEW #: #1
3. REVIEW DATE: 6-JUN-2014
4. REVIEWER: Caroline Strasinger, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

23-SEP-2013

Amendment

21-NOV-2013

7. NAME & ADDRESS OF APPLICANT:

Name:

Celgene Corporation

Address:

86 Morris Avenue
Summit, NJ 07901

Representative:

Telephone:

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:

Otezla

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- b) Non-Proprietary Name (USAN): apremilast
c) Code Name/#: NA
d) Chem. Type/Submission Priority:
• Chem. Type: 6 (Re: NDA 205437)
• Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: phosphodiesterase 4 (PDE) inhibitor

11. DOSAGE FORM: film coated tablet

12. STRENGTH/POTENCY: 10 mg, 20 mg, 30mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

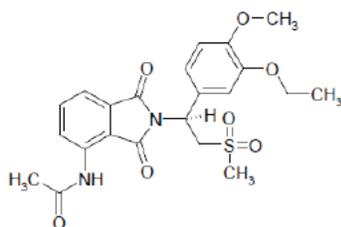
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Apremilast:

N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide

$C_{22}H_{24}N_2O_7S$

MW = 460.5



Executive Summary Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	N/A –MAPP 5015.5, Rev. 1	None
	III			4	Adequate	N/A –MAPP 5015.5, Rev. 1	None
	III			4	Adequate	N/A –MAPP 5015.5, Rev. 1	None
	III			4	Adequate	N/A –MAPP 5015.5, Rev. 1	None
	III			4	Adequate	N/A –MAPP 5015.5, Rev. 1	None
	III			4	Adequate	N/A –MAPP 5015.5, Rev. 1	None
	III			4	Adequate	N/A –MAPP 5015.5, Rev. 1	None
	III			4	Adequate	N/A –MAPP 5015.5, Rev. 1	None
	II			4	Adequate	7/12/2013	The DMF has been reviewed
	III			4	Adequate	N/A –MAPP 5015.5, Rev. 1	None

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")

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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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	205437	Apremilast Tablets

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	06/09/14	Office of Compliance
Pharm/Tox	N/A		
Biopharm	Adequate	05/2/14	Minerva Hughes
LNC	N/A		
Methods Validation	To be done per ONDQA's policy		
DMEPA	N/A		
EA	Claim for categorical exclusion is granted	03/22/13	Dr. Caroline Strasinger
Microbiology	Adequate	02/26/2014	N. Sweeny

The Chemistry Review for NDA 206088

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

An overall "Acceptable" recommendation has been made by the Office of Compliance.

All labels and labeling (Description and How Supplied sections) have been finalized.

Therefore, from the ONDQA perspective, this NDA is recommended for approval with a shelf life of 24 months.

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

None

II. Summary of Chemistry Assessments

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

All drug product and drug substance information for this NDA is referenced to NDA 205437.

Drug product:

The proposed commercial drug product, apremilast tablets, contains 10 mg, 20 mg, and 30 mg apremilast and standard compendial excipients. The drug product will be packaged as bottles containing 60 tablets of 30 mg strength for regular use, and as a blister pack containing 10 mg, 20, and 30 mg strengths as a 2-week starter pack. The drug product is manufactured with (b) (4). The drug product is manufactured and packaged at Celgene International Sarl facility in Boudry, Switzerland and (b) (4).

The drug product can also be packaged at (b) (4). All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate or do not require review due to adequate information provided in the referenced NDA 205437. An expiration dating period of 24 months stored at 30°C and below is proposed and supported by the submitted data in NDA 205437.

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Drug substance:

The drug substance Apremilast is a white to pale yellow powder. The Biopharmaceutics Classification System places this compound in class 4 which is low solubility/low permeability. The drug substance apremilast is (b)(4) by Celgene Chemicals in Zofingen, Switzerland. A retest period of (u)(4) months is proposed based on stability information provided in referenced NDA 205437.

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

Otezla (apremilast) tablets, 30 mg are for oral administration twice daily for the treatment of adult patients with moderate to severe plaque psoriasis. Titration is recommended to reduce the risk of gastrointestinal symptoms. A starter blister pack to assist in proper titration has been included as a packaging configuration. This packaging configuration also utilizes a 10 mg and 20 mg dose. The product should be stored below 30° C (86° F).

C. Basis for Approvability Recommendation:

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

An overall "Acceptable" recommendation has been made by the Office of Compliance.

All labels and labeling (Description and How Supplied sections) have been finalized.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Caroline Strasinger, PhD	13-MAY-2014
ChemistryTeamLeaderName/Date: Shulin Ding, PhD	13-MAY-2014
ProjectManagerName/Date: Catherine Tran-Zwanetz	13-MAY-2014

C. CC Block

19 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAROLINE STRASINGER
06/10/2014

MOO JHONG RHEE
06/10/2014
Chief, Branch IV