CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Memorandum

Date:	March 5, 2014
Reviewer:	Teresa McMillan, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, M.S., PharmD Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Otezla (Apremilast) Tablets 30 mg
Application Type/Number:	NDA 205437
Applicant/sponsor:	Celgene Corporation
OSE RCM #:	2013-790-2

*** This document contains proprietary and confidential information that should not be released to the public.***

1. INTRODUCTION

This review evaluates the [redacted] sample starter blister pack label and carton labeling for Otezla (Apremilast), NDA 205437, for areas of vulnerability that could lead to medication errors. These labels and labeling had not been previously submitted by the Applicant.

The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed labels and labeling in OSE Reviews #2013-790 and 2013-790-1 dated September 12, 2013 and December 18, 2013.

2. METHODS AND MATERIALS REVIEWED

The [redacted] sample starter blister pack label and carton labeling submitted to the FDA on March 3, 2014 (See Appendix A and B for images of the blister pack label and carton labeling) and OSE Reviews #2013-790 and #2013-790-1were evaluated.

3. MEDICATION ERROR RISK ASSESSMENT

Review of the proposed [redacted] sample blister pack label and carton labeling show that the applicant has added the "Sample-Not For Sale" statement and changed the titration statement to reflect 5 days instead of [redacted] We find the "Sample-Not For Sale" statement acceptable. However, for the change in titration days statement we defer to the Division. Also, upon further review we have identified vulnerabilities that were not previously identified and may lead to medication errors. The proposed [redacted] sample labels and labeling have the strength statement presented as [redacted] Since, the blister pack contains 10 mg, 20 mg, and 30 mg tablets, highlighting [redacted] strength presentation is misleading as it may lead the patients to believe that the blister pack only contains [redacted] strength. In addition, the net quantity of tablets contained within the starter blister pack and carton labeling has been omitted. We note similar deficiencies in the [redacted] starter blister pack label.

4. CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed [redacted] sample and [redacted] starter blister pack label and carton labeling can be improved to clarify the contents of the blister pack. Therefore, we have the following recommendations for the Applicant to be implemented prior to approval.

4.1 COMMENTS TO THE APPLICANT

A. [redacted] Sample Starter Blister Pack Label

1. The starter blister pack contains 10 mg, 20 mg, and 30 mg tablets. However, [redacted] strength presentation is highlighted on the principal display panel (PDP) and side panel. To clarify the contents of the starter pack, delete the [redacted] strength presentation from the PDP and side panel. Revise the statement [redacted] under the "STARTER PACK" and "SAMPLE-NOT FOR SALE" statements to the following:

This pack contains the following for titration over 5 days up to the prescribed dose of 30 mg:

Four-10 mg tablets

Four-20 mg tablets

Nineteen-30 mg tablets

27 TABLETS

B. [redacted] Sample Carton Labeling

1. The starter blister pack contains 10 mg, 20 mg, and 30 mg tablets. However, [redacted] strength presentation is highlighted on the principal display panel (PDP) and side panel. To clarify the contents of the starter pack, delete the [redacted] strength presentation from the PDP and side panel. Revise the statement [redacted] under the "STARTER PACK" statement to the following:

   Each pack contains the following for titration over 5 days up to the prescribed dose of 30 mg:

   Four-10 mg tablets

   Four-20 mg tablets

   Nineteen-30 mg tablets

   Five starter packs each containing 27 TABLETS

C. [redacted] Sample Starter Blister Pack Labels and Sample Carton Labeling

1. See Comments A1 and B1

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

REFERENCES

1. OSE Review #2013-790, Label, Labeling, and Packaging Review for Otezla (Apremilast), September 12, 2013, McMillan,T.
2. OSE Review #2013-790-1, Label, Labeling, and Packaging Review for Otezla (Apremilast), December 12, 2013, McMillan,T.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

TERESA S MCMILLAN
03/05/2014

LUBNA A MERCHANT
03/05/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 205437 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: proposed Otezla Established/Proper Name: apremilast Dosage Form: tablet Strengths: 10, 20, 30 mg		
Applicant: Celgene Corporation Agent for Applicant (if applicable):		
Date of Application: 3/20/13 Date of Receipt: 3/21/13 Date clock started after UN:		
PDUFA Goal Date: 3/21/14	Action Goal Date (if different):	
Filing Date: 5/20/13	Date of Filing Meeting: 4/24/13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) : Type 1		
Proposed indication(s)/Proposed change(s): Psoriatic Arthritis		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): IND 101761

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: **3** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53I?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	Electronic submission

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:		**X**		

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	**X**			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	**X**			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	**X**			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		**X**		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			Has been coded appropriately
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	**X**			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			Pt. Lblg: IFU 4/30/13
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 3/25/10 (tcon) ***If yes, distribute minutes before filing meeting***	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 12/19/12 ***If yes, distribute minutes before filing meeting***	X			PreNDA mtg.
Any Special Protocol Assessments (SPAs)? **Date(s):** 3/31/11 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			Quality SPA regarding registration stability for apremilast drug substance

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 20, 2013

BLA/NDA/Supp #: 205437

PROPRIETARY NAME: Otezla

ESTABLISHED/PROPER NAME: apremilast

DOSAGE FORM/STRENGTH: tablet/10mg, 20mg, 30mg

APPLICANT: Celgene Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of adult patients with active psoriatic arthritis

BACKGROUND: Celgene submitted an original NME NDA for 10, 20, and 30 mg tablets, for the treatment of psoriatic arthritis. The clinical development program is comprised of 4 clinical efficacy studies, including 1 randomized, double-blind Phase 2 study. The population for the 3 pivotal Phase 3 studies was subjects with active PsA despite current treatment with DMARDs. In each of these studies, apremilast was used alone or in combination with a stable dose of oral DMARDs.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Michelle Jordan Garner	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Susan Limb		Y
Clinical	Reviewer:	Keith Hull	Y
	TL:	Nikolay Nikolov	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:		

Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Sheetal Agarwal	Y
	TL:	Satjit Brar	Y
Biostatistics	Reviewer:	Bob Abugov	Y
	TL:	Joan Buenconsejo	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Steve Leshin	Y
	TL:	Marcie Wood	N
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Ciby Abraham	Y
	TL:	Alan Schroeder	Y
Quality Microbiology *(for sterile products)*	Reviewer:	N/A	
	TL:		
CMC Labeling Review	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:	N/A	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Teresa McMillan	Y
	TL:	Lubna Merchant	Y
OSE/DRISK (REMS)	Reviewer:	George Neyarapally	Y
	TL:	Kendra Worthy	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Anthony Orencia	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	ONDQA Biopharm – Minerva Hughes		Y
Other attendees	Steven Hertz/CSO/Compliance Nichelle Rashid/RPM/OSE Sarah Yim/Assoc. Direct/DPARP Bu Atul/OCP Suresh Doddapaneni/Dep Director/OCP Dinko Relic/CP reviewer/OCP Joann Lee/Sfty Eval/OSE-DPV Jie Li (Jenni)/Epidemiologist/OSE-DEPI Lydia Gilbert McClain/DD/DPARP Badrul Chowdhury/Direc/DPARP Jane Gilbert/MO/OSE-DPV Adrienne Rothstein/TL/OSE-DPV Sara Stradley/ADRA/ODEII		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues: (See filing letter 12/9/11)	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: None	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	☒ YES ☐ NO

If no, explain:	
• Advisory Committee Meeting needed? **Comments**: suggested date: 12/18/13 ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: ☐ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☒ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**: sent 4/10/13	☐ Not Applicable ☐ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☒ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Sandy Barnes, CPMS **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Regulatory Project Manager Date

Chief, Project Management Staff Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

MICHELLE Y JORDAN GARNER
02/28/2014

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the CMC and/or Biopharmaceutics Reviewer (ONDQA) or Biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA # 205437

Product Name: Apremilast Tablets

PMC #1 Description: Dissolution Method and Acceptance Criterion

PMC Schedule Milestones:		
	Final Protocol Submission:	NA
	Study/Trial Completion:	NA
	Final Report Submission:	09/30/2014
	Other:	NA

=

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS *FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL.*USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- ***DO NOT USE THIS FORM* IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

   ☐ Need for drug (unmet need/life-threatening condition)
   ☐ Long-term data needed (e.g., stability data)
   ☐ Only feasible to conduct post-approval
   ☒ Improvements to methods
   ☐ Theoretical concern
   ☐ Manufacturing process analysis
   ☐ Other

   Improvements to test methods are generally handled as PMCs and not PMRs.

2. Describe the particular review issue and the goal of the study.

   The dissolution method submitted to the NDA needed additional improvements to enhance the method's sensitivity to detect aberrant formulation changes. The objective of the PMC is to finalize and validate the improved method to maximize product quality assurance.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

   Select only one. Fill out a new sheet for each type of PMR/PMC study.

   ☒ Dissolution testing
   ☐ Assay
   ☐ Sterility
   ☐ Potency
   ☐ Product delivery
   ☐ Drug substance characterization
   ☐ Intermediates characterization
   ☐ Impurity characterization
   ☐ Reformulation
   ☐ Manufacturing process issues
   ☐ Other

   Describe the agreed-upon study:

   The Applicant agrees to improve the dissolution method and submit the final dissolution method and validation report, which includes the details of the methodology, method validation and bridging study results using the current and revised method for commercial and stability batches within 6 months of the action letter date. A new acceptance criterion will be proposed based on release data from a minimum of 50 commercial batches, 12 months long term and 6 months accelerated stability data from [redacted] (b) (4) validation batches, and 6 months long term and accelerated stability data from Celgene International validation batches.

5. To be completed by ONDQA/OBP Manager:

   ☒ Does the study meet criteria for PMCs? Yes
   ☒ Are the objectives clear from the description of the PMC? Yes

   ☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes

   ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs only)

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/s/

SALLY M SEYMOUR
02/27/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A prospective, observational, controlled, pregnancy exposure registry study [redacted (b) (4)] to monitor [redacted (b) (4)] pregnancies exposed to apremilast with the primary objective to evaluate whether there is any increase in the risk of birth defects [redacted (b) (4)]

PMR/PMC Schedule Milestones:

Final Protocol Submission:	September 2014
Study/Trial Completion:	September 2021
Final Report Submission:	June 2022

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☒ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

   The risk:benefit profile of apremilast in PsA appears to be favorable based on the data in this NDA. The primary risks of apremilast treatment in this patient population appear to be an increased risk of gastrointestinal adverse events and weight loss. However, the data from the non-clinical development suggests that apremilast increases the incidence of embryo-fetal deaths in mice and abortions in monkeys in a dose-dependent manner. Further, the pre-marketing embryo-fetal apremilast exposure data in humans has been limited to draw definitive conclusions on the potential risks of apremilast use on embryo-fetal development. Therefore, a post-marketing, prospective, observational, pregnancy exposure registry study to follow apremilast-exposed female subjects who become pregnant to accrue additional data to assess whether apremilast exposure in humans could negatively impact pregnancy outcomes in comparison to an internal control group.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

- The non-clinical development suggests that apremilast increases the incidence of embryo-fetal deaths in mice and abortions in monkeys in a dose-dependent manner
- The pre-marketing embryo-fetal apremilast exposure data in humans are limited.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A (b) (4), prospective, observational, controlled, pregnancy exposure registry study to monitor (b) (4) pregnancies exposed to apremilast with the primary objective to evaluate whether there is any increase in the risk of birth defects. The cohort study population will include pregnant patients with psoriasis and/or psoriatic arthritis (PsA) who have apremilast exposure during pregnancy and two comparison groups of patients who have not used apremilast (women with and without psoriasis/psoriatic arthritis who have not used apremilast).

Required

☐ Observational pharmacoepidemiologic study
☒ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
A prospective, observational, controlled, pregnancy exposure registry study.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

SALLY M SEYMOUR
02/27/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 22, 2014

TO: Michelle Jordan Garner, M.S., Regulatory Project Manager
Keith Hull, M.D., Medical Officer
Nikolay Nikolov, M.D., Cross Discipline Team Leader
Sarah O. Yim, M.D., Associate Director
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205437

APPLICANT: Celgene Corporation

DRUG: apremilast

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Standard review

INDICATION: psoriatic arthritis

CONSULTATION REQUEST DATE:	May 23, 2013 (signed)
INSPECTION SUMMARY GOAL DATE:	January 21, 2014 (original) (Extended: January 22, 2014)
DIVISION ACTION GOAL DATE:	March 21, 2014
PDUFA DATE:	March 21, 2014

I. BACKGROUND:
Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in up to two out of five psoriasis patients. The pathogenesis of psoriatic arthritis appears to reflect a complex interaction among resident dendritic, fibroblastic, and endothelial cells, and inflammatory cells attracted to the synovium by cytokines and chemokines. Apremilast (CC-10004) is a novel oral agent that modulates multiple inflammatory pathways through targeted enzymatic inhibition of phosphodiesterase type 4 (PDE4).

Two Phase 3 clinical studies were submitted in support of the sponsor's NDA. The CDER review division selected two domestic sites, one from each study, for inspection based principally on high treatment response.

Study Protocol CC-10004-PSA-002
CC-10004-PSA-002 was a Phase 3, double-blind, placebo-controlled, parallel-group study with two active-treatment groups. Subjects were randomized 1:1:1 to receive apremilast 20 mg twice a day (BID), apremilast 30 mg BID, or identically-appearing placebo for 24 weeks. The primary objective of the study was to evaluate the clinical efficacy of two doses of apremilast (20 mg or 30 mg orally BID), compared with placebo, on the signs and symptoms of psoriatic arthritis after 16 weeks of administration. The primary efficacy endpoint was the proportion of subjects in each treatment group who achieved the American College of Rheumatology criteria for a 20% improvement (ACR 20), compared with baseline, after 16 weeks of treatment.

Study Protocol CC-10004-PSA-004
CC-10004-PSA-004 was a Phase 3, double-blind, placebo-controlled, parallel-group study with two active-treatment groups. Subjects were randomized 1:1:1 to receive apremilast 20 mg BID, apremilast 30 mg BID, or identically appearing placebo for 24 weeks. The primary objective of the study was to evaluate the clinical efficacy of two doses of apremilast (20 mg or 30 mg orally BID), compared with placebo, on the signs and symptoms of psoriatic arthritis after 16 weeks of administration. The primary endpoint was the proportion of subjects in each treatment group who achieved the American College of Rheumatology criteria for a 20% improvement (ACR 20), compared with baseline, after 16 weeks of treatment.

These two study protocols were essentially identical having been conducted in a population of patients with moderate to severe psoriatic arthritis, except that CC-10004-PSA-004 required also at least one ≥ 2 cm psoriasis lesion.

II. RESULTS:

Name of CI City, State	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Final Classification*
Sanford M. Wolfe, D.O. Dayton, OH	CC-10004-PSA-004 N=14	June 26 - July 2, 2013	NAI
Anthony Hou, M.D. Upland, CA	CC-10004-PSA-002 N=9	June 28 - July 22, 2013	VAI
Celgene Corporation	Sponsor	July 29 - August 7, 2013	NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.
Preliminary= The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. Sanford Wolfe, D.O./Protocol CC-10004-PSA-004 Site #088
Dayton, OH

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from June 26 to July 2, 2013. Per ORA staff, a total of 16 subjects were screened and 14 subjects were enrolled and randomized. Twelve subjects were on-going participants at the completion of the study.

An audit of all screened subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to calculate the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Anthony Hou, M.D./Protocol CC-10004-PSA-002 Site #025
Upland, CA

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from June 28 to July 22, 2013. A total of nine subjects were enrolled and seven subjects were randomized. Three subjects were on-going participants at the completion of the study.

An audit of the nine enrolled subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to calculate the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for not updating informed consent documents at follow-up visits, and not reporting an adverse event promptly to the IRB.

Selected examples include the following:

(a) The clinical site did not update the IRB regarding Subject 0251008's adverse event. The subject was 30% compliant on Visit 3 Week #4. This patient stopped the study medication due to nausea and vomiting.

(b) Subject 025001 did not sign the latest version of the informed consent form dated 09/22/2010 on 10/26/2010 (Visit 2, Week 0), and form dated 11/18/2012 on 1/23/2013 (Visit 14, Week 130), respectively.

The List of Inspectional Observations (Form FDA 483) was communicated to the DPARP Medical Team who did not consider the above findings as significant. Dr. Hou responded adequately to these observations in a letter dated August 6, 2013.

c. Assessment of data integrity:
The regulatory deficiencies noted above are considered minor. Data submitted by this clinical site appear acceptable for this specific indication.

SPONSOR

3. Celgene Corporation
Warren, NJ

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.810, from July 29 to August 7 2013.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:
The Sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites, and monitoring of the investigator sites was considered adequate. No salient issues were identified. There was no evidence of under-reporting of adverse events.

No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued at the end of the Sponsor inspection.

c. Assessment of data integrity:
The study appears to have been conducted adequately. Data submitted by this Sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For this NDA, a single U.S. clinical investigator site for Study Protocol CC-10004-PSA-004 (Sanford Wolfe, D.O.) and a single clinical investigator site for Study Protocol CC-10004-PSA-002 (Anthony Hou, M.D.) were inspected in support of this application. The Sponsor (Celgene Corporation) was also audited.

No deficiencies were observed for Dr. Wolfe's clinical study site or the Sponsor. The final regulatory classification was NAI (No Action Indicated). Minor regulatory deficiencies were observed for Dr. Hou's clinical study site. The final regulatory classification was VAI (Voluntary Action Indicated).

The study data collected and submitted with the NDA appear generally reliable in support of the requested indication.

{See appended electronic signature page}

Anthony Orencia, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
01/22/2014

JANICE K POHLMAN
01/22/2014

KASSA AYALEW
01/22/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Memorandum

Date:	December 18, 2013
Reviewer:	Teresa McMillan, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, M.S., PharmD Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Otezla (Apremilast) Tablets 30 mg
Application Type/Number:	NDA 205437
Applicant/sponsor:	Celgene Corporation
OSE RCM #:	2013-790-1

*** This document contains proprietary and confidential information that should not be released to the public.***

1. INTRODUCTION

This review responds to a request from Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to evaluate the revised container labels, blister labels, and carton labeling for Otezla (Apremilast), NDA 205437, for areas of vulnerability that could lead to medication errors.

Celgene Corporation submitted an amendment to NDA 205437 proposing changes to the container labels, blister labels, and carton labeling that was previously submitted on March 21, 2013.

2. METHODS AND MATERIALS REVIEWED

The revised container labels, blister labels, and carton labeling submitted to the FDA on September 27, 2013 (See Appendix A and B for images of the container labels and carton labeling) and OSE Review #2013-790, dated September 12, 2013, were evaluated to assess whether the recommendations in that review were still relevant and if new recommendations should be proposed.

3. MEDICATION ERROR RISK ASSESSMENT

The applicant is proposing to delete the (b) (4) with no plans to replace. DMEPA has no concerns with this and finds the container size of 60 tablets appropriate. Additionally, the Applicant is proposing to delete the (b) (4) and replace it with 28 count- 30 mg (b) (4). We looked at the starter and (b) (4) (b) (4) to ensure that each is clearly labeled as such to minimize confusion between (b) (4).

4. CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container and blister labels, container labels, and carton labeling are acceptable and we do not have any additional recommendations.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

REFERENCES

1. OSE Review #2013-790, Label, Labeling, and Packaging Review for Otezla (Apremilast), September 12, 2013, McMillan,T.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TERESA S MCMILLAN
12/18/2013

LUBNA A MERCHANT
12/18/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Review

Date: December 3, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: The Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Drug: TRADENAME (apremilast), tablets for oral use

NDA: 205-437

Subject: Labeling revisions with regard to pregnancy and nursing mothers sections

Applicant: Celgene Corporation

Materials Reviewed: March 21, 2013, labeling submitted by sponsor

Consult Question: "Requesting a review of sections 8.1, 8.2, and 8.3 of the PI to access compliance regarding the new labeling standards for pregnancy and lactation that will be implemented in 2014."

INTRODUCTION

On March 21, 2013, Celgene Corporation submitted an original New Drug Application (NDA 205-437) for apremilast tablets for the treatment of adult patients with active psoriatic arthritis.

The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and update the Pregnancy and Nursing Mothers information in the apremilast labeling.

This review provides recommended revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Apremilast is an inhibitor of phosphodiesterase 4 (PDE4) which affects the activity of inflammatory cells that are present in psoriasis.[1] Apremilast causes an elevation of cyclic adenosine monophosphate (cAMP) through its inhibition of PDE4. Cyclic adenosine monophosphate functions as a suppressor of the immune functions of phagocytes through the generation of inflammatory mediators.[2] However, the mechanism by which apremilast exerts action of patients with psoriatic arthritis is not well defined.

No human pregnancy data are available with apremilast; however, dose-related increases in abortion/embryo-fetal death occurred in cynomolgus monkeys given apremilast at dose exposures 2.1-times the maximum recommended human therapeutic dose (MRHD). No human lactation data are available; however, apremilast was detected in rat milk.

Psoriatic arthritis is a form of arthritis that causes joint pain, stiffness and swelling and is usually coupled by a red, silvery scaled rash on the skin.[3] Treatment options are focused on controlling the symptoms and preventing further damage to joints.[3] During pregnancy, symptoms are unpredictable as some women experience an improvement in symptoms while some women report worsening of symptoms.[3] In 2012, the National Psoriasis Foundation released guidelines for treating psoriasis in women who are pregnant or breast feeding.[4] Those guidelines recommend the use of moisturizers and emollients as first line therapy, not including topical steroids which should be reserved for the second and third trimester only as needed.[4] Second-line therapy includes narrowband ultraviolet light B (UVB) phototherapy or light therapy.[4] TNF inhibitors and cyclosporine are recommended as last line therapy.[4] Lastly, the National Psoriasis Foundation does not recommend breastfeeding while taking any medications due to lack of

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[1] Schafer, P., Day, R. (2013). Novel systemic drugs for psoriasis: Mechanism of action for apremilast, a specific inhibitor of PDE4. *Journal American Academy of Dermatology*, 68(6), 1041-1042.
[2] Serezani, C., Ballinger, M., Aronoff, D., Peters-Golden, M. (2008). Cyclic AMP. *American Journal of Respiratory Cell and Molecular Biology,* 39, 127-132.
[3] Psoriatic Arthritis. Mayo Clinic. www.mayoclinic.com/health/psoriatic-arthritis/DS00476. Accessed 20 November 2013.
[4] National Psoriasis Foundation releases recommendations for psoriasis treatment in pregnant and breastfeeding women. National Psoriasis Foundation. www.psoriasis.org/news/stories/2011/11/28/NPF-release-treatment-pregnant-breastfeeding. Accessed 20 November 2013.

information;[4] however, this general recommendation is not supported by the American Academy of Pediatrics, Committee on Drugs.[5]

DISCUSSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The Drugs and Lactation Database (LactMed)[6] was searched for available lactation data on with the use of apremilast, and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breastmilk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Pregnancy Exposure Data

New drugs like apremilast generally have little or no human pregnancy experience prior to approval, unless the drug is specifically indicated for a pregnancy-related condition and obtaining human pregnancy data to adequately inform product labeling is important for all drug and biological products. Thus, collection of drug safety data on use during human pregnancy is often performed post-approval. The Food and Drugs Administration Amendments Act (FDAAA) of 2007 (see PL 110-85, Title IX, sec 905(a)(3)(C)(iv)) recommended complementary approaches to gather and analyze postmarketing data and information to assess the safety of use of a drug in domestic populations (such as in pregnant women) that were not included or underrepresented in the clinical trials used to approve a drug.

Options for collecting meaningful pregnancy exposure data include the establishment of a drug-based prospective cohort study (pregnancy exposure registry), collaboration with an established disease-based pregnancy exposure study, or enhanced pharmacovigilance with either an

[5] http://pediatrics.aappublications.org/content/early/2013/08/20/peds.2013-1985 full.pdf+html
[6] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT

established pregnancy surveillance program or reporting and follow-up on known pregnancy exposures.

In 2002, FDA published, "Guidance for Industry on Establishing Pregnancy Exposure Registries."[7] In this guidance, a pregnancy exposure registry is defined as a prospective observational study that actively collects information on a medical product exposure during pregnancy and associated pregnancy outcomes and is one method of collecting data on drug exposure during pregnancy before pregnancy outcomes are well established. Pregnancy exposure registries proceed from the point of drug exposure and pregnant women are enrolled before the outcome of pregnancy is known. Medical products that are considered good candidates for pregnancy exposure registries include those that have a high likelihood of use by women of childbearing potential. Pregnancy exposure registries are unlikely to be required when the product is not used or rarely used by women of childbearing potential. The decision to establish a pregnancy exposure registry should include consideration of both the need for pregnancy risk information and the feasibility of successfully completing the registry. In order to collect meaningful data, the size of a pregnancy exposure registry should be large enough to either detect a difference or show no difference between the exposed and control groups. An internal and/or external (in certain situations) control group is required for pregnancy exposure registries.

The Organization of Teratology Information Specialists (OTIS) has established the *Autoimmune Diseases in Pregnancy Study* which studies the possible effects of autoimmune diseases (such as multiple sclerosis, Crohn's Disease, rheumatoid arthritis, psoriatic arthritis, and psoriasis) and the drugs used to treat these conditions can have on pregnancy.[8] Numerous sponsors of FDA-approved drugs for autoimmune diseases collaborate with this OTIS study.

Enhanced pharmacovigilance can involve the establishment of a pregnancy surveillance program that is set up much like a pregnancy exposure registry; however, there are no control groups and data may be collected both prospectively and retrospectively. Alternatively, for the rare use of a product in pregnancy, enhanced pharmacovigilance may only involve the encouragement of sponsor reporting pregnancy exposures with follow-up on all reports. This last strategy is usually used for drugs with rare use in females of reproductive potential.

Annual interim pregnancy exposure reports for pregnancy registries or enhanced pharmcovigilance programs are generally submitted to FDA on an agreed upon schedule until FDA has acknowledged that sufficient data has been collected. Information on established drug-based or disease-based pregnancy exposure programs should be placed prominently in the pregnancy subsection of labeling to inform prescribers and patients that a pregnancy exposure registry is in existence.

[7] See Guidance for Industry: Establishing Pregnancy Exposure Registries, August 2002
[8] http://www.pregnancystudies.org/ongoing-pregnancy-studies/autoimmune-studies/

Drugs and Lactation

The American Academy of Pediatrics (AAP) recommends that all mothers who are able to breast-feed should do so until their infant reaches 1 year of age because the AAP considers breast-feeding to be the ideal method of feeding and nurturing infants.[9] Furthermore, breast-feeding is the most complete form of nutrition for infants and offers a range of health benefits for both mothers and breast-feeding infants.[9] Women make decisions about drug treatment and the continuation of lactation in the absence of data, and thus, women may choose to discontinue breast-feeding unnecessarily.

Many, but not all, drugs transfer to breast milk. The transport of a drug into breast milk is largely a function of the drug's physicochemical properties and its concentration in maternal plasma.[5] All of the following factors influence the amount of drug transfer into human milk: plasma and milk protein binding, molecular weight, mechanism of transport, degree of ionization, and clearance pathways. Factors that tend to produce higher human milk levels of drugs include: higher maternal plasma concentration, higher lipid solubility, higher pK_a, lower protein binding, and lower molecular weight. The mean pH of human milk is 7.2, about 0.2 units lower than that of plasma.[10] This difference influences the transfer of drugs into milk, more so for drugs that are weak bases with pK_a values in that range. Drugs with higher molecular weights, especially those with weights greater than 800 Daltons, must generally be actively transported or dissolved in the cells lipid membranes. Most drugs move between maternal serum and human milk based on equilibrium forces. However, a few drugs enter human milk by active transport. Not all drug transport systems in the breast have been identified. Drugs that are more lipid soluble may accumulate in the lipid fraction of the milk, leading to higher concentrations of drug in human milk than in maternal plasma.

Clinical lactation data should be available for drugs that are likely to be used in females of reproductive potential unless the drug has a known or potential serious safety concern that would preclude collection of such data. Nursing mothers labeling should adequately inform the use of a drug during lactation. Clinical lactation studies can be designed to assess the extent of drug into breast milk and the daily infant dose through breast milk; the severity and frequency of adverse events in breast-fed infants exposed o maternal drug through breast milk, and potential effects on milk production.

CONCLUSION

The pregnancy subsection of the apremilast labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of labeling was revised to comply with current labeling recommendations.

PMHS-MHT recommends a post-marketing requirement (PMR) for the collection of pregnancy exposure data in order to assess the safety of use of apremilast in pregnant women as this population was not represented in pre-marketing clinical trials and the drug will likely be used in females of reproductive potential. Furthermore, dose-related increases in abortion/embryo-fetal death occurred in cynomolgus monkeys with apremilast administration at dose exposures 2.1-

[9] The AAP Section on Breastfeeding, 2005

[10] Morriss, F., Brewer, E., Spedale, S., Riddle, L., Temple, D., Caprioli, R.., et al. (1986). Relationship of Human Milk pH During Course of Lactation to Concentrations of Citrate and Fatty Acids. *Pediatrics*, 78 (3); 458-464.

times the maximum recommended human therapeutic dose (MRHD). PMHS-MHT recommends that the sponsor consider fulfilling this PMR by establishing a drug-based pregnancy exposure program (pregnancy exposure registry or pregnancy surveillance program) or collaborating with an existing disease-based pregnancy exposure study such as the OTIS *Autoimmune Diseases in Pregnancy Study*. The method of data collection should be based on the ability and feasibility to collect meaningful data. The pregnancy subsection of apremilast labeling should include contact information for established drug- or disease-based pregnancy exposure programs.

PMHS-MHT also recommends a post-marketing commitment (PMC) for a milk-only clinical lactation study using a validated assay conducted in lactating women who are using apremilast therapeutically.

PMHS LABELING RECOMMENDATIONS

PMHS-MHT labeling excerpts are below with deleted text shown with a strikethrough and new text as underlined. The language below regarding the animal data were constructed by the Divisions pharmacology/toxicology team and may receive further edits. Please refer to final negotiated labeling for specific changes agreed upon with the sponsor.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm (8.1).

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRADENAME during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling [toll-free number].

Risk Summary

Adequate and well-controlled studies with TRADENAME have not been conducted in pregnant women. In animal embryofetal studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures 2.1-times the maximum recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. Although no teratogenic effects were observed in monkeys at doses corresponding to 2.1-times the MRHD, the study was insufficient to thoroughly evaluate the teratogenic risk due to abortion/embryofetal loss at higher doses. In mice, there were no apremilast-induced malformations up to exposures (b) (4) times the MRHD. The incidences of malformations and pregnancy loss in human pregnancies have not been established for TRADENAME. However, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. TRADE NAME should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Labor or delivery

The effects of TRADENAME on labor and delivery in pregnant women are unknown. In mice, premature delivery and dystocia were noted at doses corresponding to ≥ (b) (4) times the MRHD (on an AUC basis at doses ≥ 80 mg/kg/day) of apremilast.

Animal Data

Monkey embryofetal development: In an embryofetal developmental study, cynomolgus monkeys were administered apremilast at doses of 20, 50, 200, or 1000 mg/kg/day during the period of organogenesis (gestation days 20 through 50). There was a dose-related increase in spontaneous abortions, with most abortions occurring during weeks 3 to 4 of dosing during the first trimester, at doses approximately 2.1 times the MRHD and greater (on an AUC basis at doses ≥ 50 mg/kg/day). No abortifacent effects were observed at a dose approximately 1.4 times the MRHD (on an AUC basis at a dose of 20 mg/kg/day). Although there was no evidence for a teratogenic effect at 20 mg/kg/day, there were insufficient numbers of fetal monkeys to adequately address teratogenic risk at doses approximately 4.5 times the MRHD and greater (on an AUC basis at doses ≥50 mg/kg/day).

Mouse embryofetal development: In an embryofetal study, apremilast was administered at dosages of 250, 500, or 750 mg/kg/day to dams during organogenesis (gestation day 6 through 15). In a combined fertility and embryofetal development study, apremilast was administered at dosages of 10, 20, 40 or 80 mg/kg/day starting 15 days before cohabitation and continuing through gestation day 15. No teratogenic findings attributed to apremilast were observed in either study; however, there was an increase in postimplantation loss at doses corresponding to a systemic exposure of (b) (4) times the MRHD (≥20 mg/kg/day). At doses of ≥20 mg/kg/day skeletal variations included incomplete ossification sites of tarsals, skull, sternebra, and vertebrae. No effects were observed at a dose approximately (b) (4)-times the MRHD (10 mg/kg/day).

Mouse pre- and postnatal development: In a pre- and post-natal study in mice, apremilast was administered to pregnant female mice at doses of 10, 80, or 300 mg/kg/day from day 6 of gestation through day 20 of lactation, with weaning at day 21. Premature delivery, dystocia, reduced viability, and reduced birth weights occurred at doses corresponding to ≥ (b) (4) times the MRHD (on an AUC basis at doses ≥80 mg/kg/day). No adverse effects occurred at a dose (b) (4) times the MRHD (10 mg/kg/day). There was no evidence for functional impairment of physical development, behavior, learning ability, immune competence, or fertility in the offspring at doses up to approximately x times the MRHD (up to 300 mg/kg/day).

8.3 Nursing mothers

(b) (4)

It is not known whether TRADENAME or its metabolites are present in human milk; however, apremilast was detected in milk of lactating mice. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition. Caution should be exercised when TRADENAME is administered to a nursing woman.

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/s/

CARRIE M CERESA
12/03/2013

JEANINE A BEST
12/03/2013

LYNNE P YAO
12/06/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 25, 2013

To: Michelle Jordan Garner, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Adewale Adeleye, Pharm. D., MBA, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm. D., Team Leader, OPDP

Subject: NDA# 205437 - OTEZLA (apremilast) tablets for oral use (Otezla)

Reference is made to DPARP's consult request dated April 30, 2013, requesting review of the proposed Package Insert (PI) and Instructions for Use (IFU) for Otezla.

We refer to the e-mail from DPARP (Michelle Jordan) to OPDP (Adewale Adeleye) on November 19, 2013, indicating that there will be no IFU to review at this time.

OPDP has reviewed the proposed PI entitled, "Working Label IWord-Clinical and Clin Pharm-10.18.2013 (5).doc" that was downloaded from the eroom using the link sent via e-mail from DPARP to OPDP on November 12, 2013. OPDP's comments on the PI are provided directly on the attached marked-up copy of the labeling (see below).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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ADEWALE A ADELEYE
11/25/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	9/12/13
Reviewer:	Teresa McMillan, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, M.S., PharmD Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Otezla (Apremilast) Tablets 30 mg
Application Type/Number:	NDA 205437
Applicant/sponsor:	Celgene Corportation
OSE RCM #:	2013-789

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1. INTRODUCTION

This review evaluates the proposed container and blister labels, carton labeling, professional prescribing information, and packaging configuration for Otezla (Apremilast), NDA 205437 for areas of vulnerability that could lead to medication errors.
.

1.1 PRODUCT INFORMATION

The following product information is provided in the March 21, 2013 submission.

- Active Ingredient: Apremilast
- Indication of Use: Treatment of adult patients with active psoriatic arthritis.
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 30 mg
- Dose and Frequency:

  Initial titration schedule as shown below in Table 1.

  Table 1. Dose Titration Schedule

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

  Maintenance dose- 30 mg twice daily.

- How Supplied: Tablets are supplied in the following strengths and package configurations:

Package configuration	Tablet strength	NDC code
Bottles of 60	30 mg	59572-630-06
Two week starter pack	13-tablet blister titration pack containing: 10 mg, 20 mg, and 30 mg tablets with an additional (14) 30 mg tablets	59572-630-27

- Storage: Store at room temperature, [redacted] (b) (4)

2. METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,[1], the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following label and labeling submitted on March 21, 2013 (See Appendix B, C, and D for images of Container Labels, Blister Labels, and Carton Labeling. No image for prescribing information):

- Container Labels,
- Blister Labels,
- Carton Labeling,
- Professional Labeling

3. MEDICATION ERROR RISK ASSESSMENT

3.1 PACKAGE CONFIGURATION [STARTER PACK AND SAMPLE PACK]

The applicant proposes to market a 14 day package configuration for this product. This product requires a (b) (4) titration schedule requiring a dose of single tablet on day 1 and two tablets daily from day 2 to 7. The maintenance dose is one tablet twice daily. Additionally, a 60-count bottle packaging configuration is also proposed and is supported by the dosage and administration for this product.

The package is designed by this daily schedule. There was no Human Factors study included in the submission to support the approval of this packaging configuration. However, the proposed package design is appropriate for the dosage and administration instructions. The proposed product design requires the user to push the tablet through the blister for product retrieval. It is unclear if this packaging is (b) (4) We defer to chemistry manufacturing and control to determine if this packaging configuration is (b) (4) However, if ONDQA determines the product is not (b) (4) we do note that the blister label includes a statement to (b) (4)

(b) (4)

3.2 LABELS AND LABELING

There are inconsistencies between the container labels and carton labeling and the prescribing information. For example, (b) (4)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

(b) (4) (b) (4) However, this information has been omitted from the container and blister labels as well as the carton labeling and should be added to help mitigate medication errors involving manipulation of the tablets. We provide recommendations for the labels and labeling in Section 5.1 and 5.2.

4. CONCLUSIONS

DMEPA concludes that the proposed container and blister labels, carton labeling and professional labeling require revisions prior to approval. We also recommend the sample packaging configuration be the starter pack so that it includes the initial titration dose.

5. RECOMMENDATIONS

5.1 PRESCRIBING INFORMATION

DMEPA provides the following recommendations for consideration by the review division prior to the approval of this NDA

A. Highlights of Prescribing Information- Dosage and Administration

To maintain consistency in the presentation of the frequency of administration throughout the labels and labeling revise the statement (b) (4) to read as follows:

Titrate to the recommended dose of 30 mg twice daily, approximately 12 hours apart.

B. Full Prescribing Information- Dosage and Administration

To maintain consistency of the presentation of the frequency of administration throughout the labels and labeling revise the statement (b) (4) to read as follows:

The recommended dose of TRADE NAME is 30 mg twice daily, approximately 12 hours apart taken orally.

5.2 CONTAINER LABELS, BLISTER LABELS, AND CARTON LABELING

DMEPA recommends the following be implemented prior to the approval of this NDA

A. General Comments

1. Add the following statement after the strength and/or package type statements on the principal display panel to the following.

   Tablets should not be crushed, split, or chewed

2. Revise the storage statement to be consistent with the prescribing information. Revise to the following:

   Store at room temperature. (b) (4)

B. Blister Pack Label [Sample Pack]

The proposed sample pack (b) (4)

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

LUBNA A MERCHANT on behalf of TERESA S MCMILLAN
09/11/2013

LUBNA A MERCHANT
09/11/2013

CAROL A HOLQUIST
09/11/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 205437

Application Type: New NDA (NME)

Name of Drug: Otezla (proposed) (apremilast)

Applicant: Celgene Corporation

Submission Date: March 20, 2013

Receipt Date: March 21, 2013

1.0 Regulatory History and Applicant's Main Proposals

Celgene Corporation submitted a 505(b), NME application, for 30 mg apremilast tablets, for the treatment of psoriatic arthritis (PsA). This application includes data to support 4 clinical efficacy studies, including 1 randomized,double-blind Phase 2 study, and 3 pivotal Phase 3 studies. The population for the three pivotal Phase 3 studies was subjects with active PsA despite current treatment with disease modifying antirheumatic drugs (DMARDs). This application is an NME; therefore, it is being reviewed under "the Program."

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Need to remove brackets around 4-digit year.

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

NME

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

N/A 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- 7.1 Potent CYP3A4 Inducers, is not listed under 7 Drug Interactions

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery

8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- Section 17 is numbered as 17.1

NO 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- IFU is listed under Patient Counseling Information; however it only consists of 4 bullets.

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

- Should state "See FDA-approved patient labeling (Instructions for Use)" and remove what's listed.

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

/s/

MICHELLE Y JORDAN GARNER
08/02/2013