

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206088Orig1s000

OTHER REVIEW(S)

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.

NDA/BLA # NDA 206088
Product Name: Otezla (apremilast) tablets, 10, 20 and 30 mg

PMR/PMC Description: A dose finding, pharmacokinetics and safety trial in subjects with moderate to severe plaque psoriasis between the ages of 6 to 17 years

PMR/PMC Schedule Milestones:

Final Protocol Submission: 3/2015
Study/Trial Completion: 7/2016
Final Report Submission: 1/2017
Other:

Other: _____

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

Phase 3 studies were conducted in population 18 years of age and older. Otezla is currently approved for the treatment of active psoriatic arthritis. In this application the applicant is proposing a new indication of treatment of moderate to severe psoriasis, and according to PREA, clinical studies in pediatric population are required. The literature reveals that prevalence of psoriasis in pediatric patients age 0 to 6 years of age is low, therefore the studies in this age group would be impossible or highly impracticable. Moderate to severe psoriasis exists in pediatric population age 6 to less than 17 years of age although with lower prevalence than in adults. Studies in adults are complete and ready for approval, thus it is feasible to conduct post-approval studies in pediatric patients with moderate to severe psoriasis.

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.”

Although the clinical presentation and course of psoriasis is similar in adults and pediatric patients, it is not known whether the exposure-response relationship is the same for this first-in-class drug for psoriasis.

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.

Conduct of dose finding, pharmacokinetic and safety trial in pediatric patients with moderate to severe plaque psoriasis age 6 to 16 years and 11 months.

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)
- 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

Continuation of Question 4

- 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
-

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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

X *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/

DAWN WILLIAMS
09/23/2014

TATIANA OUSSOVA
09/23/2014

PMR/PMC Development Template

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NDA/BLA # NDA 206088
Product Name: Otezla (apremilast) tablets, 10, 20 and 30 mg

PMR/PMC Description: A safety and efficacy trial in pediatric subjects with moderate to severe plaque psoriasis between the ages of 6 to 17 years

PMR/PMC Schedule Milestones:

Final Protocol Submission: 3/2017
Study/Trial Completion: 3/2019
Final Report Submission: 9/2019
Other: _____

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
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- Other

Phase 3 studies were conducted in population 18 years of age and older. Otezla is currently approved for the treatment of active psoriatic arthritis. In this application the applicant is proposing a new indication of treatment of moderate to severe psoriasis, and according to PREA, clinical studies in pediatric population are required. The literature reveals that prevalence of psoriasis in pediatric patients age 0 to 6 years of age is low, therefore the studies in this age group would be impossible or highly impracticable. Moderate to severe psoriasis exists in pediatric population age 6 to less than 17 years of age although with lower prevalence than in adults. Studies in adults are complete and ready for approval, thus it is feasible to conduct post-approval studies in pediatric patients with moderate to severe psoriasis.

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.”

Although the clinical presentation and course of psoriasis is similar in adults and pediatric patients, it is not known whether the exposure-response relationship is the same for this first-in-class drug for psoriasis. Therefore, in addition to a dose-finding, pharmacokinetics and safety trial, a safety and efficacy trial in pediatric subjects is needed as well.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

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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.

Conduct a trial in pediatric patients with moderate to severe plaque psoriasis age 6 to 16 and 11 months to evaluate efficacy and safety of apremilast tablet.

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)
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/s/

DAWN WILLIAMS
09/23/2014

TATIANA OUSSOVA
09/23/2014

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MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: July 15, 2014

TO: Dawn Williams, Regulatory Project Manager
Snezana Trajkovic, M.D., Medical Officer
Jill Lindstrom, M.D., Medical Team Leader
Division of Dermatologic and Dental Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 206088

APPLICANT: Celgene Corporation

DRUG: Apremilast

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

CONSULTATION REQUEST DATE: November 22, 2013
 CLINICAL INSPECTION SUMMARY DATE: July 18, 2014
 DIVISION ACTION GOAL DATE: September 9, 2014
 PDUFA DATE: September 23, 2014

I. BACKGROUND:

The Applicant submitted this NDA to support the use of apremilast for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

The pivotal studies CC-10004-PSOR-008 and CC-10004-PSOR-009, both entitled “A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Apremilast (CC-10004) in Subjects with Moderate to Severe Plaque Psoriasis” were inspected in support of the indication.

The clinical sites of Drs. Hamilton, Poulin, and Wasel were selected for inspection because of their relatively large enrollments, a relatively high percentage of treatment responders, and possible randomization irregularities.

II. RESULTS (by Site):

Name of CL, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Hamilton, Tiffani 11800 Atlantis Place Alpharetta, GA 30022	CC-10004- PSOR-008/ 8/ 13	14-22 Apr 2014	NAI. Pending final classification.
Poulin, Yves 2880 Chemin des Quatre- Bourgeois Quebec, QC G1V 4X7 CAN Canada	CC-10004- PSOR-009/ 120/ 18	10-14 Mar 2014	NAI
Wasel, Norman 10140 - 117 St NW, Suite 200 Edmonton, AB, CAN T5K 1X3	CC-10004- PSOR-009/ 122/ 20	7-11 Apr 2014	VAI. Pending final classification.

Key to Classifications

NAI= No deviation from regulations.

VAI= Deviation(s) from regulations.

OAI= Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Hamilton, Tiffani

11800 Atlantis Place
Alpharetta, GA 30022

- a. **What was inspected:** At this site for Protocol CC-10004- PSOR-008, 19 subjects were screened, and 13 subjects were enrolled in the study. All subjects signed informed consent forms prior to participation in the study. Source documents were compared to line listings. Records reviewed for randomized subjects included, but were not limited to, sponsor and monitor communications, monitoring logs, financial disclosure forms, investigator training, IRB approvals, blood chemistries, BSAs, PASI scores and sPGAs, concomitant medications, adverse events, medical histories, and drug accountability. The use of the “Sitepad” to record subject questionnaires and investigator assessments was reviewed.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Poulin, Yves

2880 Chemin des Quatre-Bourgeois
Quebec, QC G1V 4X7
CAN Canada

- a. **What was inspected:** At this site for Protocol #CC-10004-PSOR-009, 23 subjects were screened, 18 subjects were enrolled, and 11 subjects completed the first 52 weeks of the study. All subjects signed informed consent forms prior to study enrollment. The study records of all 23 screened subjects were audited. Records reviewed included, but were not limited to, investigator agreements, IRB, sponsor and monitor communications, delegation of authority, computerized data collection, adverse event reporting, concomitant therapies, financial disclosure, and test article accountability.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records and their comparison with data listings revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Wasel, Norman

10140 - 117 St NW, Suite 200
Edmonton, AB, CAN T5K 1X3

- a. What was inspected:** At this site for Protocol CC-10004-PSOR-009, 22 subjects were screened, and 20 subjects were enrolled in the study. All screened subjects signed informed consent forms prior to participation in the study. The records of all of the enrolled subjects were reviewed for PASI scores, BSA, and sPGA. Records reviewed included, but were not limited to, Form FDA 1572s, investigator training, delegation of authority logs, sponsor, monitor, and IRB correspondence, subject recruitment, subject binders, clinical assessment/efficacy source data consisting of hard copies, electronic source data and electronic case report forms (eCRFs), subject questionnaire data, PASI score calculations, SitePad[®] tablet usage and data capture in StudyWorks[®], adverse events, financial disclosure forms, drug accountability, and sponsor monitoring correspondence and logs.
- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Observations included a failure to maintain adequate records in that only the site study coordinator had electronic access to StudyWorks[®] and was solely responsible for transmission and retrieval of SitePad[®] source data to and from the StudyWorks[®] website. While having access to the study data during the collection and transmission process and the ability to retrieve that data for purposes of review is good clinical practice, there is no regulatory requirement that the investigator maintain such access. The investigator's responsibility as described in the regulations is to prepare and maintain adequate and accurate case histories. As there were no specific examples of inadequate records cited in the inspection report, Dr. Wasel appears to have complied with the requirement of maintaining adequate and accurate records, and this particular observation would not be applicable to his site. Another observation was that nine subjects were not re-consented at their next scheduled visit with the current revised informed consent form (ICF). Revisions to the ICF included changes to the Reproductive Risks section, options for birth control, and subjects' rights as a study participant. Dr. Wasel, in his written response of April 24, 2014, committed to maintaining personal access to study data and noted that his site has implemented new procedures to ensure that subjects are consented (or re-consented) in a timely manner.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Hamilton, Poulin, and Wasel were inspected in support of this NDA. Dr. Poulin's site was not issued a Form FDA 483, and the final classification of this inspection was No Action Indicated (NAI). Dr. Hamilton's site was also not issued a Form FDA 483. The classification of this inspection is NAI pending receipt and review of the Establishment Inspection Report (EIR). Dr. Wasel's site was issued a Form FDA 483. The classification of this inspection is Voluntary Action Indicated (VAI) pending receipt and review of the EIR. The data generated by these clinical sites appear adequate in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
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
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/s/

ROY A BLAY
07/16/2014

JANICE K POHLMAN
07/16/2014

KASSA AYALEW
07/16/2014

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

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

Memorandum

Date: June 2, 2014

To: Dawn Williams
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

Snezana Trajkovic
Clinical Reviewer, DDDP

Jill Lindstrom
Cross-Discipline Team Leader, DDDP

From: Puja Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 206088
OTEZLA[®] (apremilast) tablets, for oral use

Background

This consult review is in response to DDDP's May 6, 2014, request for OPDP's review of the draft package insert (PI) for OTEZLA[®] (apremilast) tablets, for oral use. OPDP reviewed the substantially complete version of the draft PI provided by the Division of Medical Policy Programs (DMPP) on May 21, 2014. Our comments on the PI are included directly on the attached copy of the labeling.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

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/s/

PUJA J SHAH
06/02/2014