

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206088Orig1s000

REMS

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: June 16, 2014

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Division of Risk Management (DRISK)

Deputy Director: Reema Mehta, Pharm.D., M.P.H., Acting Deputy Director
DRISK

Subject: Review evaluates if a REMS is needed for Otezla

Drug Name: Otezla (apremilast) tablets

Therapeutic Class: PDE-4 inhibitor

Dosage form: Oral tablet

Application Type/Number: NDA 206088

Applicant/sponsor: Celgene Corporation

OSE RCM #: 2013-2240

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1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the NDA 206088 for Otezla (apremilast) to assess the need for a Risk Evaluation and Mitigation Strategy (REMS). An application for Otezla (apremilast) was received by the Division of Dermatological and Dental Products (DDDP) from Celgene Corporation on September 23, 2013. The Applicant did not propose a risk evaluation and mitigation strategy (REMS) for Otezla.

1.1 BACKGROUND

Otezla (apremilast), a phosphodiesterase-4 (PDE-4) inhibitor, is currently approved for treatment of adult patients with active psoriatic arthritis (PsA).¹ The Sponsor has proposed an indication for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Apremilast works by increasing cAMP levels which decreases inflammation by modulating expression of TNF α , IL-23, IL-17, and other inflammatory cytokines. Otezla is available as an oral tablet. The proposed dosing regimen for moderate to severe plaque psoriasis is 30 mg twice daily (BID).

Psoriasis is a chronic, systemic T-cell mediated inflammatory disease which affects approximately 1 – 3% of the population and manifests in the form of erythematous, scaly patches or plaques on the skin caused by the hyperproliferation on epidermal keratinocytes. Patients with psoriasis experience a reduced quality of life and functionality. Treatment goals include minimization of signs and symptoms such as plaques and scales, alleviation of pruritis, reduction of flare ups, and appropriate treatment of related conditions such as PsA and depression. Patients with mild to moderate disease may be treated with topical agents and patients with moderate to severe disease are treated with systemic agents (see Table 1).

Table 1. Treatments approved for use in adult patients with psoriasis

Therapy	Recommended dosage	Comments
Many topical products: corticosteroids, coal tar products, anthralin, vitamin D analogues, retinoids, immunomodulators	Ointments, gels, creams, oils, shampoos	Indication: mild to moderate psoriasis
Phototherapy: UVA or UVB	N/A	Indication: moderate to severe psoriasis
acitretin	25 mg/day starting dose	Indication: treatment of severe psoriasis; Boxed warning and Risk minimization action plan (RiskMAP) program to mitigate

¹ NDA 205437 for psoriatic arthritis (PsA) is designated as the primary NDA. The January 3, 2014 REMS memo by George Neyarappally explained reasons why a REMS was not warranted for the PsA indication. According to the Applicant, 39% of patients with psoriasis have PsA so there is significant overlap in these two patient populations. Others estimate that about 10 – 30% of psoriasis patients also have PsA. See Gladman DD, Antoni C, Mease P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005;64(Suppl 2):ii14–17.

Therapy	Recommended dosage	Comments
		the risk of teratogenicity
methotrexate (MTM)	2.5 to 5 mg once weekly	Select indication: symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy; Boxed warning for teratogenicity, hepatotoxicity, other serious safety issues
cyclosporine	2.0 2.5 mg/kg/day	Select indication: treatment of adult, non-immunocompromised patients with severe recalcitrant plaque psoriasis who have failed to respond to at least one systemic therapy or in patients for whom other systemic therapies are contraindicated or cannot be tolerated; Boxed warning for nephrotoxicity and other serious safety issues
alefacept	7.5 mg IV once weekly for 12 weeks has been used in clinical trials	Indication: Treatment of chronic moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy; Boxed warning for risk of lymphopenia, malignancies, and serious infections
etanercept	50 mg once weekly	Select indication: treatment of adults with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy; Boxed warning for serious infections and malignancies
adalimumab	40 mg given every other week	Select indication: treatment of adults with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy when other therapies are medically less appropriate; Boxed warning for serious infections and malignancies
infliximab	5 mg/kg every 8 weeks	Select indication: treatment of severe chronic plaque psoriasis in adults who are candidates for systemic therapy; Boxed warning for serious infections and malignancies
ustekinumab	45 mg every 12 weeks	Select indication: treatment of severe chronic plaque psoriasis in adults who are candidates for systemic therapy; Boxed

Therapy	Recommended dosage	Comments
		warning for serious infections and malignancies; REMS to inform healthcare providers about the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS)

1.2 REGULATORY HISTORY

May 15, 2013: A Pre-BLA meeting was held during which FDA agreed that the Applicant's plan not to submit a REMS was reasonable but stated that the final determination of the need for a REMS would be determined during review of the application.

September 23, 2013: Celgene Corporation submitted a NDA for Otezla. The submission did not include a proposed REMS.

March 21, 2014: Otezla was approved without a REMS for the treatment of adult patients with active psoriatic arthritis.

2 MATERIALS REVIEWED

The following is a list of materials that informed our review:

- Celgene Corporation. Proposed Prescribing Information for Otezla (apremilast), received May 15, 2013.
- Celgene Corporation. Clinical Overview for Otezla (apremilast), received May 15, 2013.
- Neyarapally G. REMS Review for Otezla (apremilast), dated January 3, 2014.
- Celgene Corporation. Apremilast 4-Month Safety Update, received January 22, 2014.
- Parks M, Deputy Director. CDER/OND/Office of Drug Evaluation II Approval Letter for NDA 205437, dated March 21, 2014.
- Lindstrom J. DDDP Information Request for apremilast, dated January 28, 2014.
- Celgene Corporation. Response to Request for Information for apremilast, received April 4, 2014.
- Dubitsky G. Division of Psychiatry Products: Consultative Review and Evaluation of Clinical Data, dated April 28, 2014.
- Trajkovic S. DDDP Clinical Review for Otezla (apremilast), dated May 23, 2014.

Below is a list of published materials that informed our review:

- Agency for Healthcare Research and Quality. Biologic and Nonbiologic Systemic Agents and Phototherapy for Treatment of Chronic Plaque Psoriasis. November 2012.
- Mease P and Armstrong A. Managing Patients with Psoriatic Disease: The Diagnosis and Pharmacologic Treatment of Psoriatic Arthritis in Patients with Psoriasis. Drugs 2014; DOI 10.1007/s40265-014-0191-y.
- Law R, Chapter 64, Psoriasis, Pharmacotherapy Principles and Practice, Second Edition, 2010.

3 REVIEW FINDINGS FOR OTEZLA

3.1 PDE-4 INHIBITOR CLASS ADVERSE EVENT PROFILE

The only other PDE-4 inhibitor which is currently approved is Daliresp[®] (roflumilast), a drug indicated to reduce the risk of COPD exacerbations in patients with severe COPD. Included in the Warnings and Precautions section of the Daliresp label are an increased frequency of psychiatric adverse reactions and significant loss of body weight. These safety issues are also included in the Warnings and Precautions section of the recently approved Otezla drug label under NDA 205437 corresponding to the psoriatic arthritis indication.

3.2 OVERVIEW OF CLINICAL PROGRAM

The clinical development program for Otezla included three Phase II studies and two Phase III studies for the treatment of plaque psoriasis. The three Phase II studies demonstrated a positive treatment effect of apremilast in patients with plaque-type psoriasis. Further, data from two Phase III studies in approximately 1250 psoriasis patients formed the primary basis of the submission for approval. The following is a summary of the Phase III studies:

- PSOR 008: Placebo-controlled, randomized (2:1 ratio) for 16 weeks (Weeks 0-16), followed by a 16 week maintenance phase (placebo subjects switched to apremilast 30 mg BID (Weeks 16-32), followed by 20 week randomized withdrawal (placebo, apremilast 30 mg BID) (Weeks 32-52), followed by long-term extension (208 weeks, Weeks 52-260). Total study duration of 5 years. The study included 562 patients receiving apremilast and 282 patients receiving placebo.
- PSOR 009: The study was identical in design to PSOR 008 and included 275 patients receiving apremilast and 138 patients receiving placebo at week 0.

3.2.1 Efficacy

The primary efficacy endpoint of the Phase III studies (PSOR 008 and 009) was the proportion of patients treated with apremilast 30 mg BID or placebo who achieved a 75% reduction in the Psoriasis Area and Severity Index (PASI-75) at Week 16 compared to baseline. The major secondary endpoint was the Static Physician Global Assessment (sPGA).

The drug was found to be efficacious based on studies PSOR 008 and 009, and with respect to the primary endpoint for studies, demonstrated a statistically significant greater proportion of apremilast-treated subjects and an ACR-20 response compared to placebo-treated subjects. After 16 weeks of treatment, in PSOR-008, 33.1% of apremilast treated subjects achieved PASI-75 score, compared to 5.3% of placebo treated subjects, a treatment effect of 27.8% ($p < 0.0001$). In PSOR-009, 28.8% of apremilast treated subjects achieved PASI-75 score, compared to 4.4% of placebo treated subjects, a treatment effect of 24.4% ($p < 0.0001$).

In PSOR-008, 21.7% of apremilast treated subjects and 3.9% of placebo-treated subjects achieved sPGA response, a treatment effect of 17.8%, ($p < 0.0001$). In PSOR-009, 20.4% of apremilast subjects and 4.4% placebo treated subjects achieved sPGA response, a treatment effect of 16% ($p < 0.0001$).

3.2.2 Safety

Common adverse events

The safety profile of apremilast was assessed in 30 studies including 16 clinical pharmacology studies and 14 Phase II/III studies. A total of 1739 psoriasis patients were exposed to apremilast; 1184 of these patients were treated with apremilast 30 mg BID in the Phase III studies. The assessment of safety for the apremilast 30mg BID was primarily based on analysis of data from two Phase 3 trials (PSOR-008 and PSOR-009) and one Phase 2 trial (PSOR-005).² There were 1308 patients exposed to repeated dosing of apremilast at the proposed dose of 30 mg BID.

The most common adverse drug reactions included diarrhea, nausea, upper respiratory tract infection.

Select serious adverse events (SAEs)

Deaths

Of the subjects exposed to apremilast, 22 (1.9%) experienced a serious treatment related adverse event versus 11 (2.6%) of placebo patients. Of these patients, 6 deaths occurred in the psoriasis studies. Of six deaths reported in psoriasis trials, two were reported in subjects treated with placebo and four in subjects treated with apremilast. Detailed analysis of the individual deaths, including temporal relationship to apremilast dosing, does not suggest causal relationship.

Other SAEs

Regarding other SAEs, the proportion of patients experiencing a SAE was lower in the treatment groups than in the placebo group.

Although more apremilast patients experienced neuropsychiatric events versus patients in the placebo group, including insomnia, depression, apathy, panic attack, the small number of events and patterns of occurrence stratified by apremilast dosing (10, 20, and 30 mg bid) cannot definitely confirm that they were related to apremilast treatment. No increased risk of suicide or suicidal ideation and behavior was identified (0.1% apremilast group and 0.2% placebo group).

The mean weight loss for Apremilast Subjects as Treated with APR 30 BID was 1.51 kg at Week 16, with approximately 2% of apremilast treated patients experiencing weight loss of $\geq 10\%$ of body weight during the first 16 weeks of treatment and by the end of Week 52, approximately 5% of apremilast subjects had weight loss of $\geq 10\%$ of body weight.

Regarding the PsA indication, based on animal data and the limited embryo-fetal exposure in the human clinical trials, the Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP) required the Applicant to conduct a post-marketing, prospective, observational, pregnancy exposure registry study to follow apremilast-exposed female subjects who become pregnant and assess whether embryo-fetal exposure in humans could negatively impact pregnancy outcomes.

² PSOR-005 was a randomized, double-blind, placebo-controlled (16 weeks) followed by randomized, double-blind, active-controlled, dose-ranging study up to 4 year total treatment duration.

During the apremilast clinical trials (includes trials for several indications), a total of 22 pregnancies were reported. Of the 22 pregnancies, 5 pregnancies were reported in female subjects receiving apremilast, 1 pregnancy was reported in a female partner of a male subject blinded to treatment, and 11 pregnancies were reported in female partners of male subjects receiving. There were no congenital anomalies reported in any of the live births (n=7) and 3 patients had ongoing pregnancies at the time of the report. The remaining reports resulted in elective termination (n=3), spontaneous abortion (n=2), and lost to follow-up (n=2).

Notably, in the 120 day safety update for apremilast, the Applicant did not report any meaningful changes in the type, incidence, or intensity of any adverse event and no new safety concerns were identified.

Commensurate with the above discussion of adverse events associated with apremilast, the current version of the labeling includes the following in the Warnings and Precautions: depression, weight decrease, and drug interactions related to efficacy.

4 DISCUSSION

Psoriasis causes significant morbidity and decreased quality of life in the U.S. population. Although other drugs and biologics are used to treat moderate to severe plaque psoriasis, many are associated with serious safety issues (see Section 1.1, Table 1).

In the clinical trials, apremilast was found to be efficacious versus placebo with an acceptable safety profile. Based on the clinical trials program and the drug's mechanism of action, apremilast is not expected to be associated with some of the serious safety issues (i.e., serious infections) that biologic therapies used to treat psoriasis, such as TNF-alpha inhibitors. In the clinical trials for the PsA indication, the frequency of serious adverse events was low and did not vary across treatment arms. There was no apparent difference in the rates of serious adverse events, including death, between the treatment and placebo groups.

Apremilast use was associated with a low incidence of serious safety issues and incidence of non-serious safety issues. The safety concerns of interest associated with the administration of apremilast in the preclinical and clinical trials for psoriasis were neuropsychiatric events, including depression, weight loss, and potential teratogenicity. Based on the available data, severity of the events, and outcomes for the aforementioned risks, DRISK believes these risks do not warrant a REMS at this time and can be sufficiently mitigated through professional labeling. The risks of neuropsychiatric events and weight loss will be included in the *Warnings and Precautions* section of the professional labeling and Pregnancy-related information will be included in the *Use in Specific Populations* section of the professional labeling. Furthermore, the postmarketing, prospective, observational, pregnancy exposure registry study to follow apremilast-exposed female subjects who become pregnant and assess whether embryo-fetal exposure in humans could negatively impact pregnancy outcomes will be used to further characterize the potential risk of teratogenicity.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Otezla (apremilast). Otezla has proven efficacy in the treatment of moderate to severe plaque psoriasis. SAEs were reported slightly more frequently by placebo patients compared to Otezla

patients and there were no serious safety issues associated with Otezla which warrant a boxed warning. Thus, the benefit-risk profile for Otezla is acceptable and the risks can be mitigated through professional labeling.

Should DDDP have any concerns or questions, or feel that a REMS may be warranted for this product, please send a consult to DRISK.

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/s/

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