CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205437Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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) Memo

Date:	January 2, 2014
Reviewer(s):	George Neyarapally, Pharm.D., M.P.H., Risk Management Analyst (RMA), Division of Risk Management (DRISK) Kendra Worthy, Pharm.D., Team Leader, DRISK
Division Director:	Claudia Manzo, Pharm.D., Director, DRISK
Drug Name(s):	Otezla (apremilast) tablets
Subject:	REMS Memo
Indication:	Psoriatic arthritis (PsA)
Dosage form:	Oral tablet
OND Review Division:	Division of Pulmonary and Rheumatology Products (DPARP)
Application Type/Number:	NDA 205437
Supplement # and Date Received:	March 21, 2013
Applicant/sponsor:	Celgene Corporation
OSE RCM #:	2013-925

1. INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the New Drug Application (NDA) 205437 for Otezla (apremilast) tablets, to assess the need for a Risk Evaluation and Mitigation Strategy (REMS). The application for Otezla (apremilast), a new molecular entity (NME), was submitted to the Division of Pulmonary and Rheumatology Products (DPARP) by Celgene Corporation on March 21, 2013. The Applicant did not propose a risk evaluation and mitigation strategy (REMS).

Apremilast is an oral phosphodiesterase-4 (PDE-4) inhibitor. The indication proposed by the Applicant is the treatment of adult patients with psoriatic arthritis (PsA). The proposed dosing regimen is as follows: 30 mg orally BID.

1.1 MATERIALS REVIEWED

- Applicant's NDA submissions
- Clinical review

1.2 OVERVIEW OF CLINICAL PROGRAM

Mechanism of action

Apremilast is a PDE-4 inhibitor that works by increasing cAMP levels which decreases inflammation by modulating expression of TNF alpha, IL-23, IL-17, and other inflammatory cytokines.[1] Thus, apremilast is in clinical development as a novel treatment for different autoimmune diseases.[2]

Regarding the treatment of PsA, the proposed indication and a chronic immune-mediated skin condition, relevant modulation of cytokines specifically entails modulation of TNF-alpha and IL-23, along with the increased expression of anti-inflammatory cytokines such as IL-10.[3]

Safety and Efficacy Trials

Efficacy

The primary efficacy endpoint of the Phase 3 studies was the American College of Rheumatology (ACR) 20 at Day 85 and Week 16.[4] The major secondary endpoint was the Health Assessment Questionnaire-Disability Index (HAQ-DI) score.

The drug was found to be efficacious in three large phase III randomized controlled trials, and with respect to the primary endpoint for studies PSA-002, -003, and -004, demonstrated a statistically significant greater proportion of APR30-treated subjects (38%, 32%, and 41%, respectively) and an

[1] Celgene Corporation, New Drug Application Submission No. 205437 for (apremilast), March 21, 2013.

[2] Gavalda, Amadeu, et al. Phosphodiesterase-4 inhibitors: a review of current developments (2010 -- 2012). Expert Opin. Ther. Patents 2013; online.

[3] Harrison, Charlotte. PDE-4 inhibitor leads wave of target-specific oral psoriasis drugs. Nature Reviews Drug Discovery 2013;12:335.

[4] Celgene, *supra* note 1.

ACR20 response compared to placebo-treated subjects (19%, 19%, and 18%, respectively).[5] Additionally, APR30-treated subjects demonstrated a greater change in HAQ-DI from baseline vs. placebo-treated subjects for studies PSA- 002, -003, and -004 (-0.24 vs. -0.09; -0.19 vs. -0.05; and -0.19 vs. -0.07, respectively).[6]

Safety

The most common adverse reactions were diarrhea, nausea, URI, and headache.[7] One patient experienced a non-serious hypersensitivity reaction and experienced two positive re-challenges while on apremilast. A commensurate contraindication was added to the draft drug labeling.

Weight decrease between 5 – 10% of body weight was reported in 10% of patients treated with apremilast 30 mg BID compared to 3.3% treated with placebo. Thus, weight decrease is included in the Warnings and Precautions section of the label. Further, co-administration of CYP450 enzyme inducers may result in reduced efficacy of apremilast; this is thus is not recommended and is included in the Warnings and Precautions section of the label.

Based on the clinical trials program and mechanism of action, apremilast is not expected to be associated with some of the serious safety issues that biologic therapies such as TNF-alpha inhibitors.[8] In the clinical trials, 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. Based on animal data and the limited embryo-fetal exposure in the human clinical trials, DPARP is requesting one postmarketing requirement regarding 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 embryo-fetal exposure in humans could negatively impact pregnancy outcomes in comparison to an internal control group.[9]

The only PDE-4 inhibitor which is currently approved is Daliresp (roflumilast) which is indicated to reduce the risk of COPD exacerbations in patients with severe COPD. Included in the WARNINGS AND PRECAUTIONS section of the Daliresp label is an increased frequency of psychiatric adverse reactions and significant loss of body weight.

2. DISCUSSION

PsA is a prevalent disorder, affecting 2 - 3% of the population, causes significant morbidity, and negatively impacts patients' quality of life.[10] The agents commonly prescribed for PsA include non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroid injections, and disease-modifying antirheumatic drugs (DMARDs), such as sulfasalazine, and TNF-alpha inhibitors.

Some of these drugs, including biologics (i.e., monoclonal antibodies), TNF-alpha inhibitors, are associated with serious safety issues such as infection. Currently, six monoclonal antibodies are approved

[5] Dr. Keith M. Hull, Clinical Review, DPARP, OND, November 20, 2013.

[6] *Id.*

[7] Celgene, *supra* note 1; Hull, *supra* note 5.

[8] Harrison, *supra* note 3.

[9] Hull, *supra* note 5.

[10] Melinkova, Irena. Psoriasis market. Nature Reviews Drug Discovery 2009;8:767-8.

for the treatment of adult patients with active psoriatic arthritis: etanercept (ENBREL), infliximab (REMICADE), adalimumab (HUMIRA), golimumab (SIMPONI), certolizumab (CIMZIA), and ustekinumab (STELARA). These drugs have been shown to be efficacious and to have an acceptable safety profile.[11]

Out of these monoclonal antibodies, only Stelara has a REMS program in place. However, the risk that the Stelara REMS program is approved to mitigate is not an identified risk of concern for apremilast and thus the need for a REMS for Stelara does not inform the evaluation of the need for a REMS for apremilast. Specifically, the goal of the Stelara REMS program is to evaluate and mitigate the potential risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome (RPLS) associated with Stelara.[12]

In the clinical trials, apremilast was found to be efficacious versus placebo with an acceptable safety profile. Apremilast was not found to be associated with serious safety issues.

3. CONCLUSION

DRISK identified no serious safety issues which warrant requiring a REMS to ensure that the benefits of apremilast outweigh the risks. Thus, DRISK and DPARP are in agreement that a REMS for (apremilast) is not necessary at this time. The Applicant's proposal for labeling and routine pharmacovigilance is reasonable. Should DPARP identify additional safety information that warrants risk mitigation measures, please send a consult to DRISK.

[11] Hull *supra* note 5.

[12] Stelara REMS, most recent approval 9/2013, available at: http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111350 htm.

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/s/

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