

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206088Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Tatiana Oussova, M.D., M.P.H.
Subject	Division Director Summary Review
NDA/BLA #	206088
Supplement #	
Applicant Name	Celgene Corporation
Date of Submission	Letter Date: 12/5/2013
PDUFA Goal Date	PDUFA Date: 9/23/2014
Proprietary Name / Established (USAN) Name	OTEZLA (apremilast)
Dosage Forms / Strength	Tablets, 10 mg, 20 mg, and 30 mg
Proposed Indication(s)	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic 1. therapy
Action/Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Snezana Trajkovic, M.D.
Statistical Review	Matthew Guerra, Ph.D.
Pharmacology Toxicology Review	Jianyong Yang, Ph.D.
CMC Review/OBP Review	Carolyn Strasinger, Ph.D.
Microbiology Review	
Clinical Pharmacology Review	Chinmay Shukla, Ph.D.
DDMAC	Puja Shah, PharmD
OSI	Roy Blay, Ph.D.
CDTL Review	Jill Lindstrom, M.D.
OSE/DMEPA	
OSE/DDRE	
OSE/DRISK	George Neyarapally, Pharm.D., M.P.H.
Other	

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OSI=Office of Scientific Investigations
 DDRE= Division of Drug Risk Evaluation
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

The applicant, Celgene, is seeking approval of OTEZLA® (apremilast) tablets, 30 mg twice daily for the following indication: treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

On March 21, 2014, OTEZLA® tablets, 30 mg were approved for the indication of treatment of adult patients with active psoriatic arthritis under NDA 205437 as New Molecular Entity (NME).

There are no outstanding clinical or regulatory concerns. The review team has completed the review of this application and recommended an approval. This review will briefly summarize the review team conclusions and findings that merit additional investigation post-approval and my concurrence with the approval recommendation.

2. Background

Psoriasis is chronic inflammatory disease characterized by circumscribed erythematous, scaly plaques on the skin. Sites of predilection include scalp, sacrum, umbilical area, and extensor surfaces of the limbs. Involvement is typically symmetrical. Nail involvement may occur, manifested as onycholysis, subungual hyperkeratosis, nail plate pitting, oil spots or salmon patches. Associated comorbidities include psoriatic arthritis, other autoimmune inflammatory diseases, coronary artery disease, metabolic syndrome, obesity and depression. For mild to moderate disease, therapeutic options include topical corticosteroids and topical tazarotene. For moderate to severe disease, therapeutic options include phototherapy, methotrexate, cyclosporine, acitretin, and various systemic biologic products.

Apremilast is a small molecule that acts as an inhibitor of phosphodiesterase 4 (PDE4). Phosphodiesterase 4 degrades cyclic AMP. Inhibition of PDE4 increases cAMP, which results in decreased expression of TNF- α , IL-23, and IL-17.

3. CMC/Device

No new information was submitted with this NDA other than providing 12-month stability data to support a 24 month expiry.

There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

Of note, significant findings in repeat dose toxicity studies in mice included arteritis. Two-year oral carcinogenicity studies in rats and mice did not find evidence of apremilast-induced tumors.

Apremilast is identified as Pregnancy Category C in labeling. Studies in monkeys revealed dose-dependent increases fetal loss. A pregnancy registry is in place to monitor pregnancy outcomes in patients exposed to apremilast during gestation.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The mean clearance of apremilast is 10L/hr, and the half-life is 6 to 9 hours.

Apremilast is extensively metabolized through hepatic cytochrome (CYP) oxidative metabolism. The primary path of metabolism is by CYP3A4. Co-administration of the strong CYP3A4 inducer rifampin with apremilast resulted in a 72% reduction of apremilast plasma exposure (AUC). Labeling language reflects avoiding concomitant use of strong CYP450 inducers with apremilast.

Apremilast exposure following a single dose was increased by 88% in subjects with severe renal impairment; therefore a dose reduction to 30mg once daily (following morning dose only during the initial titration) is recommended for these patients. Hepatic impairment did not affect apremilast exposure, and no dose adjustment is needed for this population.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The dose regimen, following an initial one-week titration intended to reduce the incidence of gastrointestinal adverse reactions, is 30mg twice a day.

The applicant submitted data from two randomized, placebo-controlled trials in support of the efficacy and safety of apremilast taken twice daily for the treatment of patients with psoriasis. The trials consisted of placebo-controlled period of Weeks 0-16 (randomization 2:1), followed by the maintenance period of Weeks 16-32 (all subjects are on apremilast 30 BID), followed by the randomized withdrawal period of Weeks 32-52 (only subjects who were randomized to apremilast at baseline and were responders at week 32, were re-randomized 1:1 to apremilast or placebo). Subjects were scheduled to be evaluated every 13 week in the long-term extension period through Week 260.

The trials enrolled adult subjects 18 years of age and older with a clinical diagnosis of moderate to severe plaque psoriasis, defined as at least 10% body surface area (BSA) involvement, a Psoriasis Area and Severity Index (PASI) score ≥ 12 and a static Physician Global Assessment (sPGA) score ≥ 3 (moderate), and be candidates for systemic or phototherapy.

Study 008 enrolled and randomized a total of 844 subjects (562 to OTEZLA and 282 to placebo) from 72 centers (34 in US, 17 in Canada, 15 in Europe, and 6 in Australia) and Study 009 enrolled and randomized a total of 413 subjects (275 to OTEZLA and 138 to placebo) from 45 centers (19 in US, 7 in Canada, and 19 in Europe).

The applicant attended an EOP2 meeting on 12 March 2010, at which it was conveyed that demonstrating success on the sPGA is a key component in establishing the efficacy of the proposed product; therefore, the Agency recommended this endpoint either be included into a composite endpoint (success on both the sPGA and PASI-75) or as a co-primary endpoint with PASI-75.

The protocol-specified primary efficacy endpoint was the proportion of subjects who achieved at least a 75% reduction in PASI (PASI-75) at Week 16 from baseline. The major protocol-specified secondary efficacy endpoint was the proportion of subjects in either arm who had an sPGA score of clear or almost clear at week 16 *and* a two-point reduction from baseline. Both endpoints were statistically significant and presented in the table below:

Endpoint	Study PSOR 008			Study PSOR 009		
	OTEZLA	Placebo	P-value	OTEZLA	Placebo	P-value
sPGA	122 (21.7%)	11 (3.9%)	>0.001	56 (20.4%)	6 (4.4%)	<0.001
PASI-75	186 (33.1%)	15 (5.3%)	<0.001	79 (28.8%)	8 (5.8%)	<0.001

Source: Statistical Review and Evaluation, Matthew Guerra, 5/9/2014.

8. Safety

The overall safety database in psoriasis, comprised of subjects with psoriasis who received apremilast 30mg BID, consisted of 1308 subjects, of which 1053 subjects were dosed for 6 months and 586 subjects for 1 year. The primary safety database for psoriasis, comprised of pooled data from the two Phase 3 studies (PSOR 008 and PSOR 009) and a Phase 2 study (PSOR 005), consisted of 1426 subjects, of which 920 received apremilast and 506 received placebo.

In the psoriasis development program, six deaths were reported, four in apremilast-treated subjects and two in placebo-treated subjects. Of the four deaths in apremilast-exposed subjects, none were deemed to be related to study drug administration.

The rates of serious and non-serious adverse events were similar across both apremilast-exposed and placebo-exposed groups. The most frequently reported adverse reactions were diarrhea, nausea, upper respiratory tract infection, and headache. Laboratory parameters were generally comparable across apremilast- and placebo-treated groups.

Seven solid malignancies (breast [two], prostate [two], rectal, renal, uterine) were reported in subjects from the apremilast group in the primary safety database for psoriasis, and one solid malignancy in subjects in the placebo group. There was not an increased rate of malignancies based on adjusted exposure.

In the Phase 3 trials, depression was reported at a higher rate in apremilast-exposed subjects than in placebo-exposed subjects in the controlled portion of the study, and by exposure adjusted rates over the study duration. Review team concluded that a causal association could not be excluded. Labeling contains information about the rates of depression from the psoriatic arthritis development program, and the information from the psoriasis development program will be added to the label as well.

In Phase 3 trials, diarrhea occurred with much higher frequency in apremilast-treated subjects compared to placebo (18.8% vs. 7.1% in one trial and 15.8% vs. 5.9% in the second trial). The highest incidence of diarrhea and nausea occurred during first 30 days of apremilast treatment; in 20% of subjects the duration of diarrhea exceeded 30 days.

In the Phase 3 studies, weight loss occurred more frequently and to a greater degree in the apremilast arms than in the placebo arms. Mean weight change during the first sixteen weeks was -1.45kg in the apremilast group and -0.02kg in the placebo group. During this same time period, 14.2% of apremilast-treated subjects lost >5% of the body weight versus 5.5% of placebo-treated subjects. Of note, a greater proportion of subjects who experienced weight loss of >5% of body weight also reported diarrhea compared to subjects who had weight loss of <5% of body weight. Multiple analyses did not suggest a causal association between weight loss and diarrhea.

Labeling contains information about weight decrease from the psoriatic arthritis development program, and the information from the psoriasis development program will be added to the label as well.

9. Advisory Committee Meeting

No Advisory Committee discussion was necessary for this application.

10. Pediatrics

This NDA is the subject to PREA requirements. The applicant requested a waiver for study of children 0 through 5 years of age for the reason that studies would be impossible or highly impracticable, and a deferral for study of children 6 to 17 years of age for the reason that the application is ready for approval for adults.

Both a waiver and a deferral requests were granted.

The applicant will be required to conduct two pediatric studies in pediatric subjects with psoriasis:

- a PK and safety study in (b) (4) ages 6 to 17 years old, and a clinical efficacy, safety and tolerability study in (b) (4) ages 6 to 17 years old.

These studies will be requested as post-marketing requirements under PREA.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

Labeling discussions with the applicant have concluded, with submission of agreed upon physician's labeling, patient labeling, and carton/container labeling.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action - This application will be approved.

- Risk Benefit Assessment

The overall risk benefit assessment supports approval of apremilast for the treatment of moderate to severe psoriasis in adult patients age 18 and above. The submitted efficacy data showed consistent efficacy in psoriasis. The major safety findings identified in the clinical program were gastrointestinal adverse events and weight loss. No major safety concerns were identified during development program.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

The following trials are recommended as postmarketing requirements under PREA:

1. PK and safety study in ^{(b)(4)} ages 6 to 17 years old
2. Clinical efficacy, safety and tolerability study in ^{(b)(4)} ages 6 to 17 years old

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

/s/

TATIANA OUSSOVA
09/23/2014