CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206088Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	18 September 2014
From	Jill Lindstrom, MD FAAD
Subject	Cross-Discipline Team Leader Review
NDA #	206088
Applicant	Celgene Corporation
Date of Submission	23 September 2013
PDUFA Goal Date	23 September 2014
Proposed Proprietary Name	OTEZLA
Established (USAN) names	apremilast
Dosage forms / Strength	Tablet/10mg, 20mg, 30mg
Proposed Indication	Treatment of adult pations with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Recommended:	*Approval*

1. Introduction

OTEZLA (apremilast) tablet is an oral drug product for which the applicant seeks approval under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy. The applicant received marketing approval for OTEZLA for the indication of psoriatic arthritis on 21 March 2014. This memo summarizes the findings of the multi-disciplinary review team and provides the rationale for my recommended action.

2. Background

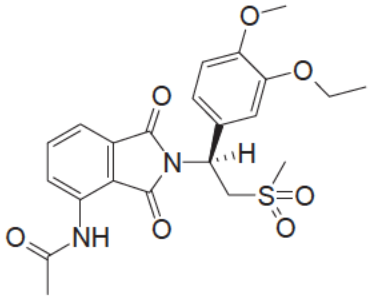
Psoriasis is chronic inflammatory disease characterized by circumscribed erythematous, scaly plaques on the skin. Sites of predilection include scalp, sacrum, umbilical area, and extensor surfaces of the limbs. Involvement is typically symmetrical. Nail involvement may occur, manifested as onycholysis, subungual hyperkeratosis, nail plate pitting, oil spots or salmon patches. As a result of the isomorphic response (Koebner's phenomenon), lesions may appear at sites of minor trauma, such as the elbows and knees. 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 systemic biologic products such as TNF antagonists and ustekinumab.

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

The applicant did not include information in Module 3 of their application but referenced NDA 205437, which was approved on 21 March 2014; the drug product is the same for both applications.

The drug substance, apremilast, is a PDE4 inhibitor which has the physical appearance of a yellow-to-white powder. The chemical name is N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide and the molecular formula $C_{22}H_{24}N_2O_7S$; the molecular weight is 460.5. The chemical structure of apremilast is



The drug product, OTEZLA tablets, are diamond-shaped film-coated tablets in 10 mg, 20 mg, and 30 mg strengths. None of the excipients are novel. The composition is described in the following table:

		Tablet Strength (mg/tablet)		
Component	**Function**	**10mg**	**20mg**	**30mg**
Apremilast	Active ingredient	(b) (4)	(b) (4)	(b) (4)
Microcrystalline cellulose	(b) (4)			
Lactose monohydrate				
Croscarmellose sodium				
Magnesium stearate				
(b) (4				(b) (4)

Source: derived from applicant's submission NDA 205437 Module 2.3 p.6.

In the original application for NDA 204537, the applicant provided 9-month stability data and was granted an 18 month expiry. The applicant has now provided 12-month stability data to support a 24 month expiry.

The applicant markets two container closure configurations: i) bottles composed of high-density polyethylene, and ii) starter packs composed of [redacted] blisters with push-through foil. The contents of these configurations are detailed in the following table:

Package configuration	Tablet strength
Bottles of 60	30 mg
Two week starter pack	13-tablet blister titration pack containing 10mg x 4, 20mg x 5, 30mg x 5, and 30mg x 14 tablets.

The CMC reviewer, Dr. Carolyn Strasinger, concluded that the applicant provided sufficient information to assure the identity, strength, purity and quality of the drug product, and did not recommend any postmarketing commitments.

4. Nonclinical Pharmacology/Toxicology

Oral repeat dose toxicity studies were conducted in mice and monkeys. Significant findings in mice included arteritis. No toxicities were identified in monkeys. Apremilast partially inhibited the HERG channel, but only at high concentrations; in an anesthetized dog study the QTc interval was not prolonged.

Apremilast was not genotoxic as assessed by the Ames assay, an in vitro chromosome aberration assay of human peripheral blood lymphocytes, and an in vivo mouse micronucleus assay. Two-year oral carcinogenicity studies were conducted in both rats and mice, but neither study found 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.

The Nonclinical Pharmacology/Toxicology reviewer, Dr. Jianyong Yang, found the application acceptable from a pharmacology/toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

OTEZLA (apremilast) tablets are marketed in 10mg, 20mg and 30mg strengths. The dose regimen, following an initial one-week titration intended to reduce the incidence of gastrointestinal adverse reactions, is 30mg twice a day,. In healthy subjects, apremilast is readily absorbed from the gastrointestinal tract with an average absolute bioavailability of 73%, and the mean time to reach peak plasma concentration is approximately 2.5 hours. Co-administration of food did not affect the bioavailability of apremilast. Apparent clearance of apremilast is 20% lower in subjects with psoriasis compared to healthy controls. Apremilast is metabolized by both CYP-mediated oxidative metabolism (primarily CYP 3A4 in vitro) and non-CYP-mediated hydrolysis. The mean clearance of apremilast is 10L/hr, and the half-life is 6 to 9 hours. Apremilast exposure following a single dose was increased by 88% in subjects with severe renal impairment; 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. Although apremilast exposure is somewhat higher in women and the elderly, no dose adjustment is necessary based on age (for adults), race or ethnicity.

In a thorough QT study, apremilast did not demonstrate a significant impact on repolarization.

The Clinical Pharmacology reviewer, Dr. Chinmay Shukla, and the Biopharmaceutics reviewer, Dr. Minerva Hughes, recommended *Approval* of the application (pending successful resolution of labeling negotiations).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted data from two pivotal trials, Study PSOR 008 and PSOR 009 to establish the effectiveness of their product taken twice daily (30mg BID following initial titration) in the treatment of psoriasis. These trials were multi-center, prospective, randomized, double-blind, parallel group studies with two arms, active and placebo. The population enrolled was adult subjects 18 years of age and older with plaque psoriasis, $\geq$10% body surface area (BSA) involvement, a score on the static Physicians Global Assessment (sPGA) of $\geq$3, and a score on the Psoriasis Area Severity Index (PASI) of $\geq$12. Per the protocol, subjects were allowed to use low-potency corticosteroids to the face, axillae and groin, and coal tar shampoo and salicylic acid preparations to the scalp, in addition to study drug.

The applicant attended an EOP2 meeting on 12 March 2010, at which it was conveyed that treatment success for any subject would be considered to have been demonstrated if the subject achieved success on both the PASI and sPGA (clear or almost clear with at least 2 point reduction from baseline).

The applicant did not request a special protocol assessment, and no agreement letter was issued.

The primary efficacy endpoint per the protocol was the proportion of subjects in either arm who achieved a PASI-75 response at week 16 compared to baseline. A key secondary efficacy endpoint was the proportion of subjects in either arm who had an sPGA score of clear or almost clear *and* a two-point reduction from baseline. The efficacy results from the pivotal trials are 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: derived from Statistical Review and Evaluation, Matthew Guerra, archived 5/9/2014.

The reader is referred to the reviews of Dr. Matthew Guerra and Dr. Snezana Trajkovic for further information and additional analyses, including post hoc explorations of the data and sensitivity analyses. Both Dr. Guerra and Dr. Trajkovic concluded that the data support a determination of efficacy.

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. The size of the safety database is adequate to characterize adverse events.

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 considered by the investigator as 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.

Cardiovascular events were uncommon, and rates were not increased compared to population databases. During the controlled period of the studies comprising the primary safety database, the rates for Major Adverse Cardiac Events (MACE), adjudicated, were he same in the active and placebo groups. During the active-only extension period of these studies, the rates when adjusted for exposure did not increase. A consult was obtained from Dr. Shari Targum, MD, of the Division of Cardiovascular and Renal Products; Dr. Targum concluded that the data did not reveal an increased risk for drug-related cardiac adverse reactions.

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 studies comprising the primary safety database, seven subjects treated with apremilast reported solid malignancies:

There were no cases of tuberculosis reactivation reported. Screening for latent tuberculosis was not required for enrollment in the pivotal trials; active or inadequately treated tuberculosis was an exclusion criterion. No opportunistic infections were reported in subjects in the primary safety database for psoriasis, and the rates of serious infections were similar across the active and placebo groups.

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. A consult was obtained from Dr. Gregory Dubitsky, MD from the Division of Psychiatry Products; Dr. Dubitsky concluded that while the data did not support an inference that apremilast caused depression, a causal link could not be excluded. Labeling contains information about the rates of depression from the psoriatic arthritis development program, and the applicant agreed to inclusion of information from the psoriasis development program as well.

In the Phase 3 studies, weight loss occurred more frequently and to a greater degree in the apremilast arms than 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. Labeling contains information about weight decrease from the psoriatic arthritis development program, and the applicant agreed to inclusion of information from the psoriasis development program as well.

The reader is referred to the clinical review by Dr. Snezana Trajkovic for a full discussion of the safety data.

9. Advisory Committee Meeting

Not applicable, as no Advisory Committee meeting was held for this application because it did not raise controversial issues that would benefit from outside discussion. The drug is currently marketed for treatment of psoriatic arthritis.

10. Pediatrics

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.

These requests were presented to the Pediatric Review Committee (PeRC) on June 4, 2014. PeRC agreed with the applicant's requests for waiver of studies in children less than six years of age and deferral of studies in children 6 years of age and older.

The applicant proposed to conduct two pediatric studies in 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

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted

12. Labeling

Professional labeling was reviewed in its entirety; labeling negotiations are ongoing at the time of close of this review. The proprietary name will be the same (OTEZLA) as the marketed product. New information is incorporated into the existing package insert in sections 1 Indications and Usage, 2 Dosage and Administration, 5 Warnings and Precautions, 6 Adverse Events, and 14 Clinical Studies.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: approval

- Risk Benefit Assessment: OTEZLA demonstrated modest efficacy in the treatment of subjects with moderate to severe psoriasis. Though the treatment effects were not large (for PGA, 16% and 17.8% in the pivotal trials, respectively), the endpoint represents a clinically meaningful improvement for the subject or patient in whom it is achieved. The dosage form (tablet) and route of administration (oral) may represent a useful addition to the therapeutic armamentarium. Risks include weight loss and depression.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies: No REMS is recommended at this time.

- 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

- Recommended Comments to Applicant

None.

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/s/

JILL A LINDSTROM
09/19/2014