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APPLICATION NUMBER:

205437Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	March 21, 2014
From	Mary H. Parks, M.D. Deputy Director Office of Drug Evaluation II
NDA/BLA # Supplement #	NDA 205-437
Applicant Name	Celgene Corporation
Date of Submission	March 21, 2013
PDUFA Goal Date	April 21, 2014
Proprietary Name / Established (USAN) Name	(b) (4) (apremilast)
Dosage Forms / Strength	Film-coated tablets in 10-, 20-, and 30-mg strengths
Proposed Indication(s)	Treatment of psoriatic arthritis in adults
Action/Recommended Action for NME:	Approval

1. Introduction

This NDA is for Otezla (apremilast), a phosphodiesterase-4 (PDE-4) inhibitor specific for cyclic adenosine monophosphate (cAMP). This application proposes use of apremilast for the treatment of adults with psoriatic arthritis (PsA). PDE-4 inhibition results in increased intracellular cAMP levels but the specific mechanism by which apremilast exerts its therapeutic action in PsA is not well defined.

All review disciplines have recommended approval and this memo will only serve to highlight key findings supporting an overall approval recommendation and findings that merit additional investigation post-approval. Please also see Dr. Badrul Chowdhury's Division Director's memo for an excellent summary of this NDA.

2. Background

Psoriatic arthritis is an inflammatory arthritis occurring in a subset of patients with dermatologic manifestations of psoriasis. PsA can affect both peripheral joints and the axial skeleton. Current therapies for PsA include NSAIDs, corticosteroids, and small and large molecule disease-modifying anti-rheumatic drugs (DMARDs). Of the small molecule DMARDs employed, methotrexate is most commonly prescribed. Dr. Chowdhury has summarized the large molecule DMARDs approved for treatment of PsA in Table 1 of his memo. All of these are administered via injection (sc or iv) and were approved based on evidence of improvement of clinical signs and symptoms and physical function. Some also had evidence of radiologic improvement.

Similar durations of evaluation and efficacy endpoints were used in the apremilast program as those in the large molecule DMARDs.

3. CMC/Device

Please see review by Dr. Ciby Abraham. Overall recommendation is approval with PMC made by the biopharmaceutics reviewer (Section 5 of memo). Apremilast is an immediate-release tablet to be marketed in 10-, 20-, and 30-mg dosage strengths. All manufacturing and testing facilities associated with this application have acceptable inspection status. An expiry of (b) (4) was proposed and is supported by data reviewed. Storage condition is 30^0C or below.

The drug product will be available in bottles containing 60 tablets of the 30-mg strength for regular use. A blister pack containing the 10-, 20-, and 30-mg strengths will also be available as a starter pack.

4. Nonclinical Pharmacology/Toxicology

Please see review by Dr. L. Steven Leshin. Reproductive studies in mice and cynomolgus monkeys revealed dose-related increases in abortion/embryo-fetal death resulting in an agreement with the Pediatric and Maternal Health Staff (PMHS) recommendation for the applicant to establish a pregnancy registry as a postmarketing requirement.

5. Clinical Pharmacology/Biopharmaceutics

See reviews of Drs. Hughes and Dorantes (biopharmaceutics) and Drs. Agarwal, Brar, Zhang, and Bhattaram (clinical pharmacology/pharmacometrics).

There were multiple formulation changes throughout development and the to-be-marketed formulation (b) (4) was not studied in the pivotal Phase 3 trials, which employed (b) (4) The difference between the two is the (b) (4), described in more detail under Section 3.4 of the Biopharmaceutics review. Bridging of the formulations was deemed acceptable.

Phase 2 dose-finding studies identified bid dosing with an initial titration scheme as providing the best tolerability/safety profile while preserving efficacy. Consequently, all Phase 3 studies evaluated apremilast 20 and 30 mg bid dosing preceded by a one-week titration period. The recommended dosing schedule for all patients with exception for those with severe renal insufficiency is 30 mg twice daily preceded by a one-week titration schedule as follows:

Titration Schedule Upon Initiation of Apremilast

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 and on
10 mg in a.m.	10 mg in a.m. and p.m.	10 mg in a.m. 20 mg in p.m.	20 mg in a.m. and p.m.	20 mg in a.m. 30 mg in p.m.	30 mg in a.m. and p.m.

Evaluations in special populations identified a need for different dosing regimen in patients with severe renal insufficiency as a result of 2-fold increase in exposure. Dosing recommendation for these patients is 30 mg once-daily preceded by a titration schedule that skips the P.M. dosing. Labeling will reflect this difference in dosing recommendation.

Drug-drug interaction studies did not identify any potential for apremilast to interact with CYP3A4 substrates. A study evaluating co-administration with rifampin (CYP inducer) demonstrated a 3-fold decrease in apremilast exposure and labeling will be recommend for avoidance of co-administration with CYP inducers.

An adequate tQT study was conducted. The highest dose of apremilast studied was 50 mg bid. No signal for QTc prolongation was observed.

Both discipline reviews recommend approval. Biopharmeutics reviewers have requested a postmarketing commitment wherein the applicant is to complete additional dissolution method optimatization studies and submit final reports within 6 months of approval. An interim dissolution method and acceptance criterion was deemed acceptable.

6. Clinical Microbiology

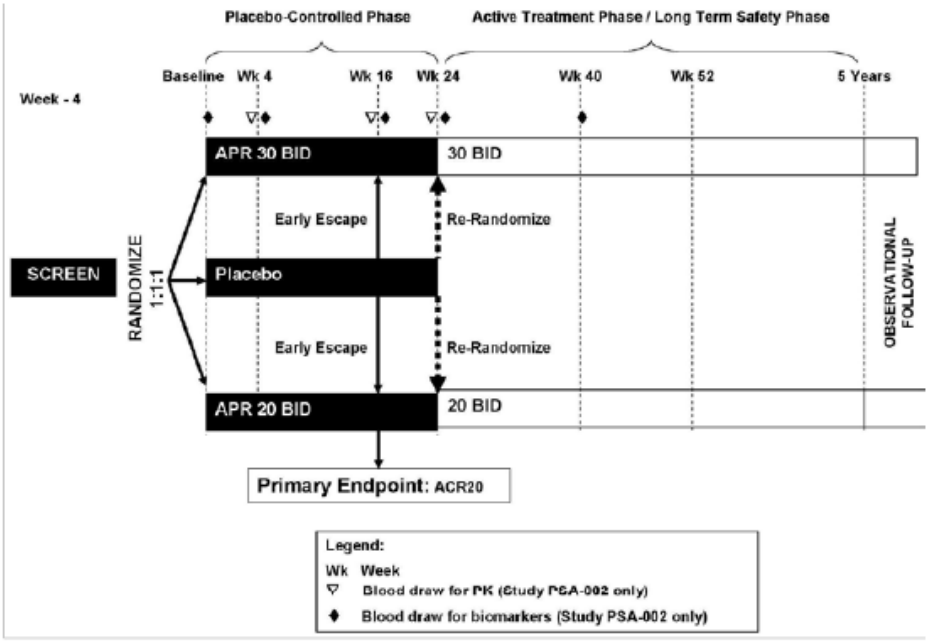
Not applicable.

7. Clinical/Statistical-Efficacy

Please see reviews from Dr. Keith Hull (clinical) and Dr. Robert Abugov (statistics).

Data supporting efficacy of apremilast for the treatment of psoriatic arthritis were derived from three similarly designed clinical trials, CC-10004-PSA-002, -003, and -004, hereafter referred to only by the last 3 digits in the trial number. All three trials were 24-week, double-blind, randomized, controlled trials enrolling adult patients with active psoriatic arthritis to either placebo, apremilast 20 mg bid, or apremilast 40 mg bid that was preceded by a 5-day titration period. The following figure obtained from Dr. Hull's review displays the trial design employed in all three trials.

Figure 1. Overview of Studies PSA-002, -003, and -004



*Adapted from sponsor's Apremilast Integrated Summary of Efficacy, page 20, Figure 1.

Week 24 was originally proposed to be the timepoint for primary efficacy analysis; however, the Agency later agreed to accept primary efficacy analyses performed at Week 16.

The primary endpoint was the proportion of patients achieving ≥ ACR20% improvement of the American College of Rheumatology (ACR) response criteria referred to as ACR20 and modified for PsA by the addition of the DIP joints of the toes and carpometacarpal joints to the total joint counts. The key secondary endpoint was the change from baseline in HAQ-DI score, a measure of physical function. Please see Dr. Hull's review under Section 6.1.4.1 which explains the relevance of these two efficacy endpoints and why they were deemed acceptable for PsA. There were other secondary endpoints evaluated based on a pre-specified hierarchy for testing. Dr. Nikolov discusses in his CDTL memo the rationale for (b) (4)

[redacted] (b) (4). This memo will only summarize the findings on the primary and key secondary endpoint.

The following table from Dr. Hull's review summarizes the primary efficacy results in this NDA.

Table 9. Primary Efficacy Analysis: Proportion of Subjects Achieving ACR20 at Week 16 in PsA Phase 3 Studies

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=168	APR20 BID N=168	APR30 BID N=168	PBO N=159	APR20 BID N=163	APR30 BID N=162	PBO N=169	APR20 BID N=169	APR30 BID N=167
Proportion of Subjects Achieving ACR20 at Week 16; n (%)	32 (19)	51 (30)	64 (38)	30 (19)	61 (37)	52 (32)	31 (18)	48 (28)	68 (41)
Treatment Effect Size[a], %	-	11	19	-	19	13	-	10	22
p-value APR dose vs. PBO	-	0.02	0.0001	-	0.0002	0.006	-	0.03	<0.0001
p-value APR30 vs. APR20	-	-	0.14	-	-	0.31	-	-	0.02

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from sponsor's NDA 205437 Integrated Summary of Efficacy, page 71, Table 18

The average treatment effect sizes across all three studies were 13% and 18% for apremilast 20 and 30 mg bid, respectively. There was a numerical advantage of apremilast 30 over 20 mg in 2 of the 3 studies with only PSA-004 showing this difference to be statistically significant.

For the major secondary endpoint, mean change from baseline in HAQ-DI, apremilast 30 mg bid demonstrated statistically significant effect over placebo in all three studies whereas apremilast 20 mg was significant in two of the three studies. Larger numeric treatment effects were observed with apremilast 30 mg over 20 mg. These data are summarized below in Table 10 from Dr. Hull's review.

Table 10. Mean Change of HAQ-DI from Baseline to Week 16 in PsA Phase 3 Studies

	Number of Subjects (%)								
	PSA-002			PSA-003			PSA-004		
	PBO N=165	APR20 BID N=163	APR30 BID N=159	PBO N=153	APR20 BID N=159	APR30 BID N=154	PBO N=163	APR20 BID N=163	APR30 BID N=160
Mean Change from Baseline	-0.09	-0.2	-0.24	-0.05	-0.16	-0.19	-0.07	-0.13	-0.19
Treatment Effect Size[a]	-	-0.11	-0.16	-	-0.10	-0.14	-	-0.07	-0.13
p-value APR dose vs. PBO	-	0.025	0.002	-	0.036	0.004	-	0.17	0.007
p-value APR30 vs. APR20	-	-	0.36	-	-	0.45	-	-	0.2

PBO: placebo; APR20: apremilast 20 mg; APR30: apremilast 30 mg. Table adapted from NDA 205437 Statistical Review, page 23, Table 11

8. Safety

Safety of apremilast was evaluated in several data pools, the primary source being PsA Phase 3 Data Pool which consisted of the three pivotal trials in the sought indication. Within this data pool, safety was presented from the 16-week, placebo-controlled portion which allows for direct comparisons of adverse events (AE) between treatment and placebo. The non-placebo-controlled portions of these trials were also evaluated for AEs that might arise after longer exposure to drug but with caveats on reliability due to inadequate comparator arms. Finally, a larger data pool consisting of Phase 2/3 trials investigating apremilast for psoriatic arthritis, psoriasis and rheumatoid arthritis and referred to as the unblinded data pool was also evaluated. In total, safety of apremilast in this NDA was evaluated in 2401 patients exposed to drug. Please see Dr. Hull's review under Section 7 for a detailed presentation of safety findings.

There were 6 deaths reported in this NDA, three in apremilast-treated patients (vitamin B12 deficiency, CV related (2)) and 3 in placebo-treated patients (suicide (2), intracranial hemorrhage).

Similar rates of serious adverse events (SAEs; 3-4%) were reported in the placebo-controlled portion of the PsA Phase 3 Data Pool with no particular concerning pattern identified. The most common SAE reported was psoriatic arthropathy (4 patients total; 2 on placebo, 1 each in apremilast dose groups). Evaluation of SAEs in the data pool with longer durations of exposure revealed a similar pattern in frequency and types of events. No discernible difference was noted between the two doses studied for SAEs.

More patients in the apremilast treatment groups discontinued due to an AE (6-7%) compared to placebo (4%) with the most common reasons for study discontinuation being nausea>diarrhea>headache. The AEs were dose- and duration-dependent with the majority of events being reported within 30 days of treatment initiation.

Based on previous experience with another PDE-4 inhibitor approved for COPD (roflumilast), Dr. Hull also presented findings for the following AEs of special interests: GI events, weight loss, psychiatric disorders (suicidal behavior/depression), infections, malignancies, vasculitis, and CV events. Of these, I will only highlight the results for weight loss and psychiatric disorders as they are being given special consideration for labeling.

Weight loss of unknown mechanism was observed in the apremilast trials. In the placebo-controlled period of the PsA trials, 58% and 57% of the apremilast 20 and 30 mg groups reported weight loss, respectively. Approximately 10% of patients between 5-10% of their body weight compared 3% in the placebo group. None of these resulted in study discontinuation. This adverse event will be described in labeling.

Higher rates of psychiatric adverse reactions, most commonly insomnia, anxiety and depression, were reported for roflumilast compared to placebo. Suicidal ideation and completed suicides have also been reported in that clinical development program and observed in post-marketing setting. This information is included under the Warnings and Precautions section of the roflumilast label. For this reason, the applicant for apremilast undertook a

planned assessment for psychiatric AEs and a consult review was also sought from the Division of Psychiatric Products (please see review from Dr. Phillip Kronstein).

As mentioned above, there were 2 completed suicides in this program but both occurred in the placebo group. Dr. Kronstein noted that the applicant failed to identify one of these suicides which may have been due to the particulars of this case wherein the study participant was found dead in his closed garage with a motorcycle running but autopsy established no cause of death versus the 2nd case which was a self-inflicted gunshot.

Within the PsA Phase 3 Data Pool, there was one case of attempted suicide and one case of suicidal ideation, both in the apremilast treatment group, and AEs of depression during the placebo-controlled period did not appear markedly different across the placebo, APR 20 and APR 30 treatment groups (see Table 34 from Dr. Hull's review).

The company sought to further evaluate for psychiatric AEs by performing a retrospective search for and classification of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). Dr. Kronstein raised some question about the correct application of C-CASA in this NDA (e.g., used Celgene physicians to rate cases instead of independent experts). He went through all available SAE narratives from the Unblinded Data Pool and while two additional cases of suicidal ideation and possible suicide attempts were identified in apremilast-treated patients there were also other cases identified for which treatment group is not known at this time. Dr. Kronstein has concluded "that there does not appear to be much of a signal for suicidal ideation or behavior". His consult does not make any recommendation on labeling but it should be noted that roflumilast's label discusses these safety concerns under the Warnings and Precautions and that the pre-market signal observed with that PDE-4 inhibitor was similar to apremilast. Unless there is evidence to support otherwise, apremilast should receive similar labeling as roflumilast for psychiatric AEs under the Warnings and Precautions section.

9. Advisory Committee Meeting

Early in the review process the Division did not identify any controversial issues related to efficacy and safety of apremilast for psoriatic arthritis and decided to not take this application to a public advisory committee meeting. The completed reviews for this NDA uphold that decision.

10. Pediatrics

A pediatric waiver was granted after discussion before the Pediatric Review Committee (PeRC).

11. Other Relevant Regulatory Issues

Please see reviews of Drs. Nikolov and Hull. There are no outstanding regulatory issues precluding approval.

The Pediatric and Maternal Health Staff Review has recommended a postmarketing commitment for the company to conduct a milk-only lactation study. Upon discussing this recommendation with the review team, a follow-up discussion with PMHS ensued and this PMC was not felt to be necessary for approval of this NDA. The rationale for not pursuing this recommendation is the feasibility of such a study. The efficacy of apremilast is modest relative to what has been observed with the biologic products approved for PsA and it is therefore unlikely to be prescribed to women with PsA who are nursing.

12. Labeling

Please see agreed-upon labeling with the action package. The review team did not agree with the applicant regarding (b) (4) I concur with the review team.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

Apremilast was shown to be effective based on agreed-upon endpoints in three similarly designed and conducted clinical trials. These trials were placebo-controlled and of sufficient duration to establish efficacy. Two doses of apremilast were studied and while a statistically significant difference in efficacy could not be demonstrated between the two doses, there was a numerically greater treatment effect on several endpoints across the three studies with the higher dose. The applicant has proposed marketing of apremilast 30 mg bid.

The safety database was adequate and no serious safety concerns precluding approval or necessitating a REMS were identified. The most common AEs were not considered serious; were self-limiting and could be managed through labeling. Similarly, potential serious safety signals (e.g., depression) were from only a few cases of suicidal ideation and suicide attempts and elevating this risk to Warnings and Precautions, similar to roflumilast, is appropriate to also ensure some vigilance on the part of prescribers. There was no notable dose-related safety finding and for this reason, the review team felt approval of apremilast 30 mg bid as the recommended dosing regimen was acceptable. I concur with their recommendation.

Several of the clinical reviews remarked on the more modest efficacy of apremilast than that observed with the approved biologics for the treatment of PsA. There is no regulatory

requirement that a new therapy be as effective or more effective than currently approved products but only that the product has been shown to be safe and effective for its intended use. As patients with PsA will have different responses in terms of both efficacy and safety to a variety of treatments, the availability of apremilast will allow for expanded treatment options and the oral route of administration should be considered a plus for this addition to the current armamentarium.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

A REMS was not deemed necessary based on the safety findings in this NDA review.

- Recommendation for other Postmarketing Requirements and Commitments

This application will be approved with one PMR and one PMC. Please see memos prepared by Dr. Sally Seymour, Deputy Director of Safety in DPARP. The PMR will be a pregnancy registry to monitor planned and unplanned pregnancies exposed to apremilast with the objective to evaluate whether there is an increased risk of birth defects. This safety concern arose from nonclinical studies but was not considered sufficient to preclude approval and could be appropriately managed with labeling. The PMC is for the development of a dissolution method and acceptance criterion.

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/s/

MARY H PARKS
03/21/2014