CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209483Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	October 19, 2017
From	Snezana Trajkovic, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	209483
Applicant	Promius Pharma, LLC
Date of Submission	January 30, 2017
PDUFA Goal Date	November 30, 2017
Proprietary Name / Established (USAN) names	Impoyz/ clobetasol propionate
Dosage forms / Strength	Cream 0.025%
Proposed Indication(s)	Topical treatment of moderate to severe plaque psoriasis
Recommended:	*Approval*

1. Introduction

Clobetasol propionate cream, 0.025% is a drug product for which the applicant seeks approval under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act for the topical treatment of moderate to severe plaque psoriasis in patients 18 years of age and older. The proposed dose and dosing regimen for clobetasol propionate cream, 0.025% is to apply a thin layer of to the affected skin areas twice daily for up to 2 consecutive weeks. Clobetasol propionate cream, 0.025% is supplied as a 60g and 112g aluminum tube.

2. Background

The active ingredient, clobetasol propionate, is a synthetic, fluorinated corticosteroid, and at the concentration of 0.025% is considered as a potent corticosteroid. There are several approved clobetasol propionate products available in various dosage forms (cream; ointment; solution, gel, aerosol, foam, lotion, shampoo, spray and emulsion) for this moiety. Currently marketed clobetasol propionate products are available in concentration of 0.05% and, are ranked as super-high potent corticosteroids (Class I). The applicant's product provides for a lower concentration (0.025%).

Clobetasol propionate cream, 0.025% was developed under the IND 110,799 by Promius Pharma, LLC. During their development program, the applicant interacted with the Agency as follow:

SPA – Non agreement:
The applicant submitted SPA on 9/9/2015. The no agreement letter was communicated to the applicant on 10/16/2015 that included the following and agreements and non-agreements:

Non-agreements:

(b) (4)

The Agency agreed with the applicant's proposal to:

(b) (4)

Pre-NDA meeting:
A pre-NDA meeting was held on 10/12/2016. During the meeting, the content and format of the NDA application were discussed.

3. CMC/Device

Drug substance
The active pharmaceutical ingredient (API) used in the drug product, clobetasol propionate cream, 0.025%, is clobetasol propionate. The chemical name for clobetasol propionate is 21-chloro-9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate. The drug substance is manufactured by (b) (4)

Drug Product
The drug product, clobetasol propionate cream, 0.025% is as a white-to-cream colored crystalline powder practically insoluble in water. The drug product, clobetasol propionate cream, 0.025% has the following composition:

Table 1: Qualitative and Quantitative Composition of DFD-06 (Clobetasol Propionate Cream, 0.025%)

Ingredients	Reference / Standard	% w/w	Function
Clobetasol propionate	USP	0.025	Active
Cetostearyl alcohol	NF	(b) (4)	
Glyceryl stearate & PEG 100 stearate	IH*		
White wax	NF		
Diethylene glycol monoethyl ether	NF		
Butylated hydroxytoluene	NF		
Isopropyl myristate	NF		
Cyclomethicone	NF		
Methylparaben	NF		
Propylparaben	NF		
Purified water Q.S.	USP		

Source: Applicant's submission

Clobetasol propionate cream, 0.025% is packaged in 60g and 112g aluminum tube and a physician sample.

Stability and Shelf-life
Stability data from the stability samples packaged in the proposed commercial container closure systems support an expiration dating period of 24 months when stored at controlled room temperature, 20 to 25°C (68 to 77°F), excursions permitted between 15°C and 30°C (59 - 86°F).

The facility review team from the Office of Process and Facility has issued an "Approval" recommendation for the facilities involved in this application.

The product quality review team made the following conclusion: "The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product."

4. Nonclinical Pharmacology/Toxicology

The applicant obtained the right of reference from Fougera Pharmaceuticals Inc. for all the Temovate topical formulations. The applicant is relying on FDA's findings of safety and efficacy of the Temovate NDAs (NDA 19322; NDA19323; NDA19966; NDA 20337 and; NDA 20340) to support the nonclinical safety of their drug product. In addition, the applicant conducted the following non-clinical studies:

- Four-week dermal toxicity study in rats
- Thirteen-week repeat-dose dermal toxicity study in rats
- A 28-day dermal toxicity and toxicokinetic study in minipigs
- Acute dermal study in rabbits
- Dermal photoirritation study in mice
- Dermal sensitization study in guinea pigs.
- Ocular irritation study using the bovine corneal opacity and permeability (BCOP) assay

Due to extent of immunosuppression observed during the 13 week repeat-dose dermal toxicity stud in rats, the Agency has waived the requirement for a two-year dermal carcinogenicity study in rats.

A 4-week dermal toxicity study in rats
In this study, a prototype and final to-be-marketed formulations of DFD-06 were evaluated. At dose of 0.1 mg clobetasol propionate/kg/day, corticosteroid class related moderate systemic toxicity was observed. The systemic toxicity was characterized by decreased white blood cells, alterations in clinical chemistry parameters and histopathological changes such as decreased cellularity/atrophy in lymphoid organs and adrenals indicating significant immunosuppression. Dermal findings included slight erythema and minimal epidermal atrophy. The findings were similar between the two formulations.

A 13-week dermal dose range-finding stud in rats
Clobetasol propionate cream at concentrations of 0 (saline control), 0 (vehicle control), 0.001, 0.005, and 0.025% was applied twice daily to ~10% total body surface area to Sprague Dawley rats (n=10/sex/group) for 13 weeks (20085039) in a dose range-finding Study. Test article-related effects attributed to the immunosuppressive properties of corticosteroids were observed in all treated animals and included the following: reductions in total leukocytes; decrease in weight of adrenals, thymus, spleen, liver and lungs, thymic atrophy and decreased hematopoiesis in the bone marrow.

A 28-day derma toxicity and toxicokinetics study in minipigs
Daily dermal administration of clobetasol propionate cream at concentrations up to 0.05% (1.0 mg/kg/day clobetasol propionate) for 28 days resulted in test article-related changes in body weight, clinical pathology, histopathology and, organ weights. Based on lower adrenal weights in both males and females treated with the lowest dose tested (0.1 mg/kg

as 0.005% cream), a NOAEL could not be determined in this study. These findings are consistent with topical exposure to corticosteroids.

Acute dermal irritation/corrosion study in rabbits
Clobetasol propionate cream, 0.025% w/w produced reversible "very slight erythema" that was barely perceptible and cleared by Day 7. Clobetasol propionate cream, 0.025% w/w is not corrosive to the skin of rabbits under the conditions of this test.

Dermal sensitization study in guinea pigs
Clobetasol propionate cream, 0.025% was tested for delayed contact hypersensitivity in Hartley Albino guinea pigs. Cuinea pigs received three topical induction applications of clobetasol propionate cream, 0.025% once per week for 3 weeks, administered as a 6 hour occluded dermal application. Two weeks after the third induction, animals in Groups 1 and 2 were challenged with clobetasol propionate cream at naïve sites.

The results of the study showed that clobetasol propionate cream, 0.025% is not a dermal sensitizer under conditions of this assay.

Dermal photoirritation study in mice
Clobetasol propionate cream, 0.025% was screened for phototoxic potential when co-administered with ultraviolet light from a solar simulator to healthy mice. Neither clobetasol propionate cream, 0.025% nor the vehicle showed to be phototoxic under the conditions of this tests.

Bovine corneal opacity and permeability (BCOP) assay
Based on the CDER decision criteria, clobetasol propionate cream 0.025% is not a severe ocular irritant.

Pharmacology/Toxicology reviewer, Jill C Merrill, PhD., has recommended the following: "Clobetasol Propionate Cream, 0.025% is approvable from Pharmacology/Toxicology perspective."

I agree with the recommendation of Dr. Merrill.

5. Clinical Pharmacology/Biopharmaceutics

Clobetasol propionate is a synthetic, fluorinated corticosteroid. Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in the treatment of psoriasis is unknown. The contribution to efficacy by individual components of the vehicle has not been established.

In support of this NDA, the applicant conducted the following trials:
- DFD-06-CD-007: Phase 2 HPA axis suppression/ maximal use PK trial
- CDS1002: Pilot Phase 2 HPA axis suppression trial
- DFD-06-CD-003a: Phase 1 vasoconstrictor potency study

Trial DFD-06-CD-007 (HPA axis suppression trial)
This was a randomized, parallel group, open label, multicenter trial to assess the potential for adrenal suppression and systemic drug absorption, following multiple dosing with DFD-06 cream or Temovate E® cream (clobetasol propionate 0.05%), in subjects with moderate to severe plaque psoriasis. Approximately 50 subjects with normal ACTH test at baseline, who had moderate to severe psoriasis covering 20% to 50% body surface area (BSA), were included in this trial. Subjects were instructed to apply the study drug twice daily, for 15 days.

The results of HPA axis suppression assessment revealed that the proportion of subjects with HPA axis suppression was lower in DFD-06 treatment arm, compared to Temovate treatment arm.

Table: Proportion of Subjects with Abnormal ACTH Stimulation Test on Day 15

Statistics	DFD-06 Cream	Temovate Cream	p-value
N	24	22	
Number (%) of Subjects with Abnormal Results	3 (12.5%)	8 (36.4%)	0.086

Source: Clinical Pharmacology review by Dr. Shukla, Table 6, page 9.

Study CDS1002 (Pilot HPA axis suppression trial)
This was a 28-day prospective, randomized, active-controlled, investigator blind, parallel group three arm pilot trial. Eighty-eight adult subjects with moderate to severe psoriasis, were randomized to treatment with either, Clobetasol Propionate 0.025% Formulation 5, Clobetasol Propionate 0.025% Formulation 13 or, Temovate E emollient cream 0.05%. Subjects were instructed to apply study drug to the psoriatic lesions, twice daily, and cover 25% of body surface area (BSA) at each application.

The results of HPA axis suppression assessment revealed that the proportion of subjects with HPA axis suppression was similar between the treatment arms.

Table: Proportion of Subjects with Abnormal ACTH Stimulation Test on Day 28

	ACTH stimulation test result	Test 1(N=26) n(%)	Test 2(N=29) n(%)	Reference(N=26) n(%)	p-value
VISIT 6 – Day 28	ABNORMAL	8 (30.8)	6 (20.7)	9 (34.6)	0.4932
	NORMAL	18 (69.2)	23 (79.3)	17 (65.4)	
Test1= Clobetasol propionate 0.025% formulation 5 ; Test2= Clobetasol propionate 0.025% formulation 13 ; Reference = Temovate E® 0.05% cream n (%) = Number (percentage) of patients with the given characteristics					

Source: Clinical Pharmacology review by Dr. Shukla, Table 28, page 34.

Vasoconstriction (VCA) study
The single point VCA study using both visual assessment (primary endpoint) and chromameter assessment (secondary endpoint) indicated that DFD-06 cream is a potent topical corticosteroid belonging to Class 2.

TQT waiver request
The applicant submitted a request for waiver of TQT assessment. The applicant based their request on the results from pivotal HPA axis suppression trial, DFD-06-CD-007, showing that the mean systemic exposure of DFD-06 cream was lower than Temovate E cream and, the absence of any cardiovascular adverse events in the two Phase 3 trials. In addition, the applicant presented literature support suggesting that neither hERG channel study nor, clinical experience with other approved topical clobetasol products with higher strengths, produced any clinically meaningful QT prolongation.

The clinical pharmacology reviewer, Shinmay Shukla, Ph.D. made the following conclusion regarding this NDA: "From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the applicant."

I agree with Dr. Shukla's conclusion.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted data from two Phase 3 trials (Trials DFD-06-004 and DFD-06-005) to establish the effectiveness of their product in the treatment of moderate to severe psoriasis. These were identically design, randomized, double-blind, multicenter, vehicle-controlled, parallel-group, Phase 3 trials. Adult subjects 18 years of age and older with diagnosis of stable (at least 3 months) moderate to severe plaque-type psoriasis, defined by Investigator's Global Assessment (IGA) score of 3 (moderate) or 4 (severe); and body surface area (BSA) involvement of at least 3%, not including the face, scalp, groin, axillae, or other intertriginous areas. Subjects were instructed to apply thin layer of study product, twice daily, for 14 consecutive days.

The primary efficacy endpoint was the proportion of subjects with treatment success at Day 15, where treatment success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade reduction from baseline. The pre-specified secondary endpoints were the percent change from baseline in BSA at Day 15 and, the proportion of subjects with treatment success at Day 8.

In both trials, DFD-06 cream was statistically superior to vehicle cream for all endpoints. Because the percent change from baseline in BSA is not considered clinically meaningful, the results for this endpoint were not presented below and will not be considered for inclusion in labeling. The efficacy results are presented in Table 1 below.

Table 1: Results of the Primary and Secondary Endpoints for Trials 004 and 005

	Trial DFD-06-004			Trial DFD-06- 005		
	DFD-06 N=178	**Vehicle** N=89	**p-value**	**DFD-06** N=176	**Vehicle** N=89	**p-value**
Primary Endpoint Treatment success at Day 15	30.2%	9.0%	<0.001	30.1%	9.7%	0.001
Secondary Endpoint Treatment success at Day 8	15.7%	5.6%	0.006	14.2%	1.6%	0.001

Source: statistical reviewer Rebecca Hager, PhD.

Because the applicant changed the conduct of randomization midway through the trials without informing the Agency, Dr. Hager conducted sensitivity analyses evaluating the impact of this change. The results of sensitivity analyses for the primary and secondary endpoints supported the superiority of DFD-06 cream compared to vehicle cream.

The reader is referred to the biostatistics reviews by Rebecca Hager, Ph.D., for detailed review of the Phase 3 trials and additional analyses.

8. Safety

The applicant conducted two identical randomized, vehicle controlled, Phase 3 trials (Trials DFD-06-004 and FDD-06-005) in subjects 18 years of age and older, with moderate to severe psoriasis. Pooled data from trials DFD-06-004 and DFD-06-005 and Phase 2 trial (DFD-06-CD-007) comprised the primary safety database.

The primary safety population was comprised of subjects who took part in two pivotal Phase 3 trials and one Phase 2 trial including a total of 378 subjects who were treated with clobetasol propionate cream, 0.025% twice daily for 14 days.

No deaths were reported during the development program for DFD-06 drug product.

Three serious adverse events (SAEs), metastatic lymphoma, stab wound and cellulitis, were reported during the development program for DFD-06. The event of metastatic lymphoma and stab wound were reported in DFD-06 treatment arms. These two SAEs were not considered treatment related. The SAE of cellulitis was reported in subject treated with vehicle.

Local adverse reactions were consistent with local adverse reactions seen with other topical corticosteroids, including other clobetasol propionate topical products.

The only adverse reaction (AR) that occurred in ≥1% of subjects, and at a higher incidence in DFD-06 treatment arms, was the application site discoloration (2% in DFD-06 treatment arms and 1% in the vehicle treatment arms).

As discussed in the section **5. Clinical Pharmacology/Biopharmaceutics** of this review, HPA axis suppression occurred in approximately one third of subjects exposed to DFD-06 cream, compared to Temovate cream, 0.05%, when treated for 14 days. However, if the exposure to DFD-06 cream or Temovate cream, 0.05% was for 28 days, the proportion of subjects with HPA suppression was similar between treatment arms. For the recommended treatment duration of 2 weeks, it is expected that treatment with DFD-06 cream, will have a lower potential for HPA axis suppression compared to clobetasol propionate cream, 0.05%.

To evaluate dermal safety, the applicant conducted the following provocative dermal safety studies: Phototoxicity study DFD-06-CD-008; Photoallergenicity study DFD-06-CD-009 and Cumulative Irritancy/Contact Sensitization study DFD-06-CD-010. The results of these studies showed that DFD-06 was not phototoxic, photoallergenic, irritating of or sensitizing.

9. Advisory Committee Meeting

Not applicable; this application was not presented to the Advisory Committee as the application did not raise novel or controversial issues that would merit outside discussion.

10. Pediatrics

Clinical trials submitted in support of this application were conducted in adult subjects. The Applicant had an Agreed Initial Pediatric Study Plan (iPSP) dated 10/7/2015. The Agreed iPSP includes studies in children ages down to 6 years of age. The planned study will evaluate PK, safety and HPA axis suppression of clobetasol propionate cream, 0.025% in subjects 6 years of age and not more than16 years and 11 months with moderate to severe plaque psoriasis under maximal use conditions. The proposed study timeline is as follow:

- Estimated protocol submission date: September 31, 2016
- Estimated study initiation date: January 10, 2017
- Estimated final report submission date: January 10, 2020

Trials in children younger than 6 years have been waived because of the following reason: The prevalence of psoriasis in pediatric population in this age group is low that the studies would be “impossible or highly impracticable (because, for example, the number of patients in that age group is so small or the patients in that age group are geographically dispersed).”

For children and adolescents 6 to 17 years of age, the applicant submitted a request for deferral. The reason for deferral is that "the drug or biologic product is ready for approval for use in adults".

The planned pediatric study will be listed Pediatric Research Equity Act (PREA) postmarketing requirement (PMRs).

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.
We have completed our review of the proposed proprietary name Impoyz and, found to be acceptable.

12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding the contents are ongoing at the time of closure of this review.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Approval
This reviewer recommends that clobetasol propionate cream, 0.025% be approved for the treatment of patients ages 18 years of age and older with moderate to severe plaque psoriasis

Risk Benefit Assessment: The applicant established the efficacy and safety of clobetasol propionate cream, 0.025% in the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older in two adequate and well-controlled trials, and provided sufficient information in their application to support product labeling.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
No postmarketing risk evaluation and mitigation strategies are recommended for this product.

Recommendation for other Postmarketing Requirements and Commitments
For pediatric patients, ages 6 to (b) (4) years, information is needed on pharmacokinetic, safety and HPA axis suppression of clobetasol propionate cream, 0.025% for the treatment of moderate to severe psoriasis. Deferred pediatric studies in pediatric patients ages 6 to (b) (4) years will be conducted as required by PREA.

Under PREA, the following study is recommended as a PMR:

- A safety pharmacokinetic, hypothalamic-pituitary-adrenal (HPA) axis suppression study under maximal use conditions in children and adolescents in the age group of 6 years to 16 year and 11 months old.

Recommended Comments to Applicant
None

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/s/

SNEZANA TRAJKOVIC
10/19/2017