CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207917Orig1s000

SUMMARY REVIEW

CDTL and Summary Review for Regulatory Action

Date	15 July 2015
From	Jill A Lindstrom, MD
Subject	CDTL and Acting Deputy Division Director Summary Review
NDA #	207917
Applicant Name	Galderma Research and Development, LLC
Date of Submission	17 September 2014
PDUFA Goal Date	17 July 2015
Proprietary Name / Established (USAN) Name	Epiduo Forte Adapalene and benzoyl peroxide
Dosage Forms / Strength	Gel, 0.3%/2.5%
Proposed Indication(s)	Topical treatment of acne vulgaris
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jane Liedtka, MD
Statistical Review	Matthew Guerra, PhD
Pharmacology Toxicology Review	Kumar Mainingi, PhD
CMC Review	Gene Holbert, PhD
CMC Microbiology	Erika Pfeiler, PhD
Clinical Pharmacology Review	Chinmay Shukla, PhD
DPP	Melinda McLawhorn
OSE/DMEPA	Carlos Mena-Grillasca, RPh
PLT	Nathan Caulk, MS BSN RN

OND=Office of New Drugs
DPP=Division of Professional Promotion (formerly part of Division of Drug Marketing, Advertising and Communication)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
PLT=Patient Labeling Team (formerly part of DRISK)

1. Introduction

Epiduo Forte (adapalene and benzoyl peroxide) gel, 0.3%/2.5% is a topical fixed-dose combination drug product for which the applicant seeks approval under Section 505(b)(2) of the Federal Food Drug and Cosmetic Act for the treatment of acne vulgaris. The applicant markets a lower strength topical fixed-dose combination product, Epiduo (adapalene and benzoyl peroxide) gel, 0.1%/2.5%, also for the treatment of acne. Adapalene is also marketed as a single-active gel (Differin gel, 0.3% and 0.1% strengths), lotion (Differin lotion, 0.1%) and cream (Differin cream, 0.1%) by the applicant, as well as by ANDA holders. Benzoyl peroxide is marketed in multiple products at concentrations from 2.5% to 10%, as a single

active ingredient and as part of fixed-dose combinations. The applicant relied on published literature to supply nonclinical information about benzoyl peroxide, but owns the remainder of the data provided to support the safety and effectiveness of Epiduo Forte gel. This memo, which serves as my summary review as well as the cross-discipline team leader review (a role which I fulfilled during the review cycle), will summarize the findings of the multi-disciplinary review team and provide the rationale for my decision.

2. Background

Acne vulgaris is a disease of the pilosebaceous unit that affects the face, chest and back of adolescents and adults. Clinical manifestations include closed and open comedones, inflammatory papules and nodules, cysts, and scars. Onset typically follows adrenarche. Prevalence is highest among adolescents, although the disease can persist into adulthood. The topical therapeutic armamentarium for acne includes topical retinoids (e.g., adapalene, tazarotene, tretinoin,), topical antibiotics (e.g., clindamycin, erythromycin, sulfacetamide), other topicals (e.g., azelaic acid, benzoyl peroxide, dapsone), as well as fixed-dose combination topical products. The oral therapeutic armamentarium includes antibiotics (e.g., tetracycline, doxycycline, minocycline), oral contraceptives, and isotretinoin.

Epiduo (adapalene and benzoyl peroxide) gel, 0.1%/2.5% was approved for marketing on December 8, 2008. The development program for Epiduo gel included a four-arm trial to establish the contributions of the monads to product efficacy. In this new product, Epiduo Forte gel, the applicant increased the concentration of adapalene from 0.1% to 0.3%, and maintained the same concentration of benzoyl peroxide (b) (4) To provide evidence of effectiveness for the higher strength combination product, the applicant conducted a single, three-arm trial with Epiduo Forte gel, Epiduo gel, and vehicle gel. The design elements of the trial—population, measurement scale, efficacy endpoints—mirrored those of the pivotal trials for Epiduo gel. The applicant also conducted a maximal use pharmacokinetic study and a cumulative irritancy study with Epiduo Forte gel.

3. CMC

The combination product contains two drug substances: adapalene and benzoyl peroxide. Their molecular formulas (and weights) are $C_{28}H_{28}O_3$ (412.52) and $C_{14}H_{10}O_4$ (242.23, anhydrous), respectively. Adapalene, a napthoic acid derivative, is a white to off-white powder that is practically insoluble in ethanol or water. Benzoyl peroxide, an oxidizing agent, is a white (b) (4) powder that is soluble in alcohol but not in water.

The drug product, Epiduo Forte gel, is white to very pale yellow in color and contains 0.3% (3mg/gm) of adapalene and 2.5% (25mg/gm) of benzoyl peroxide. The composition of the drug product is described in the following table:

Ingredient	Function	% w/w
Adapalene	Drug Substance	0.30
Benzoyl peroxide	Drug Substance	2.50
(b) (4)	(b) (4)	
Docusate sodium		
Edetate Sodium		
Glycerin		
Poloxamer 124		
Propylene glycol		
Purified water		

* (b) (4) acrylamide and sodium acryloyldimethyltaurate, isohexadecane, polysorbate 80, sorbitan oleate

Source: adapted from NDA 207917 section 3.2.P.1 p2.

There are no novel excipients in the drug product. Though the product contains water, benzoyl peroxide has antimicrobial properties and, as with Epiduo (adapalene and benzoyl peroxide) gel, 0.1/2.5%, it was found to provide adequate antimicrobial activity for the product. Microbial limits testing is included in the finished product specifications.

The drug product is packaged into an (b) (4) pump comprised of a white (b) (4) high density polyethylene bottle and a white (b) (4) pump/overcap, which will be marketed in 15 gram, 30 gram, 45 gram, 60 gram and 70 gram sizes. The pumps are not intended to dispense a metered dose. In addition, (b) (4) tubes (b) (4) in 2 gram and 5 gram sizes will be manufactured for use as physician samples. Stability data support an expiry of 24 months.

The Office of Compliance completed facilities inspections and issued an overall "Acceptable" recommendation.

The CMC reviewer, Dr. Gene Holbert, 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.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

The applicant conducted the following non-clinical studies with Epiduo Forte gel:

- 13 week dermal toxicology study in mini-pigs
- rabbit primary irritation assay
- bovine corneal opacity and permeability test
- Buehler test for sensitization (guinea pig sensitization assay)

Essentially no systemic toxicity was identified. The drug product was demonstrated to be a cutaneous irritant and sensitizer, but it did not elicit ocular irritancy or opacity.

The applicant submitted data from the literature and that for which they have right of reference for benzoyl peroxide, and data that they own for adapalene, to address carcinogenicity and reproductive toxicity. Neither BP nor adapalene appear to be mutagenic. There was no dermal carcinogenicity signal for either active. Adapalene is teratogenic at high doses in rats and rabbits, however these effects were seen at doses 41 and 82 times the daily maximum recommended human dose, respectively. These issues are addressed in labeling.

The pharmacology/toxicology reviewer, Dr. Kumar Mainigi, recommended *Approval* of this application from a pharmacology/toxicology perspective; he did not identify the need for any non-clinical postmarketing commitments or requirements.

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

5. Clinical Pharmacology/Biopharmaceutics

Epiduo Forte (adapalene and benzoyl peroxide) gel, 0.3%/2.5%, is a fixed-dose combination product for the treatment of acne vulgaris that is intended to be applied topically to the affected areas of the face and/or trunk once daily.

The to-be-marketed formulation was used in the clinical trial and maximum use pharmacokinetic study; there is no manufacturing site change.

The applicant conducted Study RD.06.SRE.18229, a parallel-group maximum use pharmacokinetic study, to investigate the relative bioavailability of adapalene from repeated (4 weeks) once daily topical application of Epiduo Forte gel or Differin (adapalene) gel, 0.3%, in adult and adolescent subjects with severe acne. Study drug was applied once daily in a thin film to the face, chest, shoulders and back. Blood samples for pharmacokinetic analysis were obtained at hours 2, 4, 6, 8, 10, 12, and either 14 (subjects 12-17 years old) or 16 hours (subjects 18-35 years old) post dose on days 1, 15 and 29, as well as at a single pre-dose timepoint on days 2, 10 (adults only), 16, and 22 (adults only), and in the post-treatment period on days 30 and 31. Benzoyl peroxide was not assayed, as it is rapidly metabolized to benzoic acid in the skin; benzoic acid is an endogenous compound and an approved food additive, so assay for this metabolite was also not performed. Adapalene serum concentrations were below the level of quantitation in 50% and 38% of subjects in the Epiduo Forte gel arm on days 1 and 29, respectively, and 67% and 53% of the subjects treated with Differin gel, 0.3%, on days 1 and 29, respectively. Based on subjects for whom serum adapalene concentrations were measurable, on Day 29 the mean ($\pm$standard deviation) value for C_{max} was 0.16 ($\pm$0.08) ng/mL, and for AUC_{0-24} was 2.49 ($\pm$1.21) ng-h/mL. Comparative analysis found that systemic exposure to adapalene was similar between the Epiduo Forte gel and Differin gel, 0.3% arms.

A thorough QT/QT_c study was not performed. Neither benzoyl peroxide nor adapalene is a new molecular entity; both active ingredients are marketed at the same (adapalene) or higher

(benzoyl peroxide) concentrations compared to those found in Epiduo Forte gel. Benzoyl peroxide is metabolized in the skin to benzoic acid, an endogenous compound which is unlikely to affect cardiac repolarization. Adapalene is a retinoid, a class which are not known to prolong the QT interval. Topical administration of the drug product results in low systemic exposure to adapalene, similar to that seen with the marketed product Differin gel, 0.3%. For these reasons, a TQT study is not needed.

The Clinical Pharmacology/Biopharmaceutics reviewer, Dr. Chinmay Shukla, found that the applicant met the requirements for approval from a clinical pharmacology perspective, and recommended *Approval* from a clinical pharmacology/biopharmaceutics perspective.

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

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant submitted data from one pivotal trial, Study RD.06.SRE.18240, to establish the effectiveness of their product applied once daily in the treatment of acne vulgaris. The study was multi-center, randomized, double-blind, and active- and vehicle-controlled with parallel groups.

Enrolled subjects were 12 years of age or older with an Investigators Global Assessment (IGA) score of 3 (moderate) or 4 (severe) at baseline, and 20-100 inflammatory lesions and 30 to 50 non-inflammatory lesions on the face. Randomization was stratified by center and severity, such that 50% of subjects had baseline IGA score of 3/moderate (IGA 3) and 50% of subjects had a baseline IGA score of 4/severe. The primary time point was at twelve weeks. The primary efficacy measures were Investigator Global Assessment score and lesion counts. The co-primary endpoints were i) success rate, defined as the proportion of subjects who scored “Clear” or “Almost Clear” (score of 0 or 1) on the IGA scale at week 12, ii) absolute change in inflammatory lesion count from baseline to week 12, and iii) absolute change non-inflammatory lesion count from baseline to week 12 .

The applicant was granted a Special Protocol Assessment, and a letter with agreements was issued on 3 November 2013. Agreements included:

- enrollment population of subjects with moderate to severe acne
- co-primary efficacy endpoints
    - proportion of subjects who achieve clear or almost clear and a 2-grade improvement on the 5-point IGA scale at week 12
    - absolute change in inflammatory lesion count from baseline to week 12
    - absolute change in non-inflammatory lesion count from baseline to week 12

- secondary efficacy endpoints:
  - percent change in inflammatory lesion counts from baseline to week 12
  - percent change in non-inflammatory lesion counts from baseline to week 12
- ITT population as primary analysis population
- primary endpoint analyses and variables for stratification

The results for the co-primary efficacy endpoints are presented in the following table:

Co-primary Endpoints	Epiduo Forte gel (N=217)	Epiduo gel (N=217)	Vehicle gel (N=69)	p-value[1]
IGA Success n (%)	73.2 (33.7%)	59.2 (27.3%)	7.6 (11.0%)	<0.001
Absolute change in inflammatory lesion counts: Mean	27.8	26.5	13.2	<0.001
Absolute change in inflammatory lesion counts: Mean	40.5	40.0	19.7	<0.001

[1]Epiduo Forte gel versus vehicle gel
Source: Adapted from Statistical Review and Evaluation NDA 207917, Matthew Guerra, PhD, archived 5/14/2015, p.10.

In Study RD.06.SRE.18240, Epiduo was superior to vehicle for the co-primary endpoints of i) success on the IGA, ii) absolute change in inflammatory lesions, and iii) absolute change in non-inflammatory lesions. In addition, the efficacy trend favored Epiduo Forte over Epiduo.

The reader is referred to the biostatistical and clinical reviews by Matthew Guerra, PhD, and Jane Liedtka, MD, respectively, for detailed review of the pivotal trial and additional analyses, including post hoc explorations of the data and sensitivity analysis.

I concur with Drs. Guerra and Liedtka that the clinical trial data support a determination of efficacy.

8. Safety

Two hundred and forty-five subjects with acne were exposed to Epiduo Forte gel during the development program, including 217 in the pivotal trial. In addition, the applicant presented safety data from the Epiduo and Differin development programs. In the pivotal trial, Study RD.06.SRE.18240, the mean treatment duration of subjects exposed to Epiduo Forte gel was 79 days, and mean daily medication use was 0.92 grams.

There were no deaths reported in the development program. One serious adverse event (SAE), generalized anxiety reaction, was reported during the development program of Epiduo Forte, which occurred in a subject in the active arm; both the investigator and the medical reviewer, Dr. Jane Liedtka, considered the SAE to be unlikely to be related to study drug.

In the pivotal trial, adverse events were reported by a slightly greater percentage of subjects in the Epiduo Forte arm (23%) than in the Epiduo and vehicle arms (19% each). Adverse reactions (adverse events attributable to study drug and occurring more commonly in the active than the vehicle group) that occurred at a frequency of greater than 1% include skin irritation, eczema, atopic dermatitis, and skin burning sensation; these will be included in labeling.

Local tolerance is a special safety concern that was evaluated in the pivotal trial. Erythema, scaling, dryness and stinging/burning were assessed using four-point scales. Each occurred with slightly greater frequency in subjects treated with Epiduo Forte gel than those treated with Epiduo, and in greater frequency in those treated with either active than those treated with vehicle. These results will be addressed in labeling.

The reader is referred to the clinical review by Dr. Jane Liedtka for a full review of the safety database, as well as to the biostatistical review by Dr. Matthew Guerra.

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

The applicant conducted studies in subjects 12 years of age and older, consistent with their Agreed initial Pediatric Study Plan. The applicant requested a waiver for patients nine to eleven years of age because the product does not represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients in this age group, and for patients less than 9 years of age because necessary studies would be highly impractical because the number of pediatric patients in this age group is so small. On June 10, 2015, the application was presented to the Pediatric Review Committee, who agreed with the applicant's waiver request.

Pediatric studies are waived for patients nine to eleven years of age and less than nine years of age for the reasons stated above.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The proposed proprietary name, Epiduo Forte, was reviewed by Carlos Mena-Grillasca, RPh, on February 3, 2014, and found acceptable.

All components of labeling were reviewed. The applicant was requested to consider a single package insert for Epiduo Forte (adapalene and benzoyl peroxide) gel, 0.3%/2.5% and Epiduo (adapalene and benzoyl peroxide) gel, 0.1%/2.5% in order to i) reduce the risk of medication errors, ii) inform prescribers and patients of the available product strengths, and iii) facilitate postmarketing labeling updates; the applicant declined to combine the information from these two products into a single package insert, (b) (4) Professional labeling conforms to the standards of the Physicians Labeling Rule. Patient labeling was proposed and is appropriate for this product in order to inform patients about product application and the risk of local skin reactions.

13. Decision/Action/Risk Benefit Assessment

Regulatory action: *Approval*

I concur with the recommendations of the multi-disciplinary review team regarding approval of NDA 207917 Epiduo Forte (adapalene and benzoyl peroxide) gel, 0.3%/2.5% for the treatment of the acne vulgaris.

Risk-benefit assessment: The applicant established the efficacy and safety of Epiduo Forte gel in the treatment of acne vulgaris in one adequate and well-controlled trial, and provided sufficient information in their application to support product labeling. The robust efficacy of the product justifies the modest risks, the most significant of which appears to be the risk for local skin reactions.

Postmarketing Risk Evaluation and Management Strategies: Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

Postmarketing requirements (PMR) and commitments (PMC): none

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

/s/

JILL A LINDSTROM
07/15/2015