CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-320

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	13 November 2008
From	Jill Lindstrom, MD
Subject	Cross-Discipline Team Leader Review
NDA #	22-230
Applicant	Galderma Laboratories
Date of Submission	8 February 2008
PDUFA Goal Date	8 December 2008
Proprietary Name / Established (USAN) names	Epiduo Adapalene/benzoyl peroxide
Dosage forms / Strength	Gel; adapalene 0.1%, benzoyl peroxide 2.5%
Proposed Indication(s)	Acne vulgaris
Recommended:	*Approval*

1. Introduction

EPIDUO (adapalene and benzoyl peroxide) Gel, 0.1%/2.5%, is a fixed-dose combination drug product for which the applicant seeks approval for the topical treatment of acne vulgaris in patients 12 years of age and older.

2. Background

EPIDUO Gel is not currently marketed in any jurisdiction. However, the applicant markets Differin Gel, 0.1%, and Differin Cream, 0.1%, which contain adapalene at the same concentration as the proposed product, and Differin Gel, 0.3%, which contains adapalene at a greater strength than the proposed product. Additionally, benzoyl peroxide is marketed for topical treatment of acne at strengths ranging from 2.5% to 10%, in both single-active (over-the-counter) and combination (prescription) products.

3. CMC

Epiduo Gel is a combination product containing two active ingredients, adapalene and benzoyl peroxide. Adapalene is a naphthoic acid derivative that acts on retinoid receptors; it is marketed in three formulations: Differin Gel 0.1%, Differin Cream 0.1%, and Differin Gel 0.3%. Benzoyl peroxide is an oxidizing agent; it is marketed in multiple prescriptiona dn nonprescription topical drug formulations. Adapalene and benzoyl peroxide were demonstrated to be chemically compatible in the formulation under normal conditions of storage.

The drug product is a white to pale yellow opaque aqueous gel. It is packaged in ——— b(4)
plastic tubes with ⌜ ⌟ screw cap closures. Proposed tube
sizes for marketing are — 45g, ⌜ ⌟
Submitted stability data supports an expiry of 24 months.

The drug product contains a novel excipient, Simulgel 600PHA, a copolymer of acrylamide
and sodium acryloyldimethyltaurate ——————— with isohexadecane, polysorbate 80, b(4)
and sorbitan oleate. ⌜
⌟ Simulgel 600PHA was fully characterized by the applicant.

Facilities inspections have been completed, and did not identify deficiencies that would preclude reliance upon the data submitted in this application.

Pending a favorable recommendation from the Office of Compliance (now completed), the CMC reviewer, Ms Maria Ysern, recommended *Approval* of this application from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

The applicant conducted six non-clinical studies with Epiduo gel:

- 4 week dermal toxicology study in rats
- 4 week dermal toxicology study in dogs
- rabbit primary irritation assay
- guinea pig sensitization assay
- guinea pig photallergenicity/phototoxicity assay
- 13 week dermal toxicology study in mini-pigs

Essentially no systemic toxicity was identified. The drug product was demonstrated to be an irritant and sensitizer, but it did not demonstrate photoallergenicity or phototoxicity.

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, although benzoyl peroxide is a tumor promoter in several species. Adapalene is teratogenic at high doses in rats and rabbits, however these effects were seen at doses 135 and 270 times the daily maximum recommended human dose. These issues are addressed in labeling.

The formulation included a novel excipient, Simulgel 600 PHA. This excipient contains acrylamide/sodium acryloyldimethyltaureate copolymer (Simulgel 600), isohexadecane, polysorbate 80 and sorbitan oleate. Simulgel 600 is a high molecular weight (~10 million Daltons) molecule used in cosmetics and dietary supplements. Because of it's high molecular weight, Simulgel 600 is unlikely to be absorbed. The maximal systemic exposure of Simulgel 600 from Epiduo gel, assuming 100% absorption, would be 1.3mg/kg/day. The oral LD_{50} in rats is 2gm/kg.

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.

5. Clinical Pharmacology/Biopharmaceutics

Epiduo gel is a fixed combination product containing adapalene 0.1% and benzoyl peroxide 2.5%. Both actives are marketed at higher concentrations in single-active products.

The applicant conducted a Maximal Use Systemic Exposure (MUSE) study using the to-be-marketed formulation and the monad adapalene 0.1%. 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 was detected in 2 of 10 subject in the Epiduo arm and 3 of 10 subjects in the adapalene monad arm; plasma concentrations were similar between the two arms (EPIDUO and adapalene monad), and for all samples were less than the maximum concentrations measured in the MUSE study with the marketed 0.3% adapalene gel product (Differin Gel 0.3%).

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 higher concentrations. 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. The drug product is topical with low systemic exposure. For these reasons, a TQT study would not likely be informative.

6. Clinical Microbiology

The applicant did not conduct microbiologic studies.

7. Clinical/Statistical- Efficacy

The applicant submitted data from two pivotal trials, a Phase 2 study (18094) and a Phase 3 study (18087), to establish the effectiveness of their product used once daily for 12 weeks in the treatment of acne. The applicant did not seek formal agreements with the Agency regarding the design, endpoints, or statistical analysis plan for Study 18094, which was conducted prior to the EOP2 meeting. A special protocol assessment of Study 18087 did not result in agreements.

Both studies (18094 and 18087) included four arms (the combination product, both monads, and vehicle), and enrolled subjects with 20-50 inflammatory and 30-100 non-inflammatory lesions at baseline. However, the studies differed in that Study 18087 required IGA score of 3 (moderate) or greater as an entry criterion whereas Study 18094 had no IGA threshold as entry

criterion; this allowed enrollment of subjects with an IGA score of 2 (mild) in Study 18094 and meant that Success on the IGA, defined as a score of 0 (clear) or 1 (minimal) could involve a 1-grade change for subjects who had an IGA score of 2 at enrollment. Additionally, the studies also differed in size, randomization ratios, primary analysis of lesion counts, and number of lesions allowed at entry (0 vs. 1).

Study 18094

Study 18094 was a Phase 2, multi-center, prospective, randomized, double-blind, parallel group study with four arms: EPIDUO gel, adapalene 0.l% in vehicle, benzoyl peroxide 2.5% in vehicle, and vehicle. After randomization in a 2:2:2:1 ratio, 517 subjects applied their respective study drug once daily for twelve weeks. The primary endpoints were the Investigator's Global Assessment (IGA) score dichotomized to success (ie, "Clear" or "Almost Clear") and failure, and lesion counts, assessed week 12. Table 1, below, describes the results for the IGA, and Table 2, below, describes the results for lesion counts.

Table 1: Investigator Global Assessment Results (ITT_LOCF) – Study 18094

	EPIDUO N=149	Adapalene N=148	Benzoyl Peroxide N=149	Vehicle N=71
Clear or Almost Clear				
Success (%)	41 (27.5)	23 (15.5)	23 (15.4)	7 (9.9)
p-value		0.0079	0.0034	0.0015
Two Grade Improvement				
Success (%)	33 (22.1)	19 (12.8)	18 (12.1)	4 (5.6)
p-value		0.0309	0.0056	0.0016
Clear or Almost Clear *and* Two Grade Improvement				
Success (%)	32 (21.5)	18 (12.2)	18 (12.1)	4 (5.6)
p-value		0.0291	0.0088	0.0023

Source: Statistical Review and Evaluation of NDA 22-320, p.20, Mat Soukup, PhD

The applicant's analysis (Clear or Almost Clear, above) considered as successes those subjects who achieved "Clear" or "Almost Clear" at week 12, but did not require a two-grade improvement; thus subjects enrolled with an IGA score of "Mild" at baseline who achieved "Almost Clear" at week 12 (one grade improvement) were counted as successes. Because the IGA represents a categorical scale overlying a "continuous reality," one grade of improvement on the IGA may not represent a clinically-meaningful difference.

The second analysis above, Two Grade Improvement, increases the likelihood that the measured change represents a clinically-meaningful difference by eliminating from the definition of success those subjects who achieved only a one grade improvement. However, because subjects enrolled with an IGA score of "Severe" at baseline who achieved "Mild" at week 12 were counted as successes, it is likely that those subjects, who per the category descriptor for "Mild" still had "easily recognizable" disease, would not find the improvement clinically meaningful.

The third analysis above, Clear or Almost Clear *and* Two Grade Improvement, is both the most rigorous and the most likely to represent a clinically-meaningful difference, as it eliminates from the definition of success both those subjects who only achieve one grade of improvement and those subjects who do not achieve Clear or Almost Clear. This is the analysis favored by this reviewer and recommended for inclusion in labeling.

In all three analyses of the IGA, EPIDUO Gel is statistically superior to vehicle and to both of its monads.

Table 2: Change in Lesion Counts (ITT_LOCF) – Study 18094

	EPIDUO N=149	Adapalene N=148	Benzoyl Peroxide N=149	Vehicle N=71
Inflammatory Lesion Counts				
Mean Change	-16.0	-11.4	-10.5	-9.5
Mean % Change	-52.4	-39.9	-35.8	-31.8
p-value		<0.001	<0.001	<0.001
Non-Inflammatory Lesion Counts				
Mean Change	-23.4	-15.2	-13.7	-13/2
Mean % Change	-45.9	-29.6	-32.2	-27.8
p-value		<0.001	<0.001	<0.001
Total Lesion Counts				
Mean Change	-39.3	-26.5	-24.1	-22.6
Mean % Change	-48.5	-34.0	-33.3	-29.7
p-value		<0.001	<0.001	<0.001

Source: Statistical Review and Evaluation of NDA 22-320, p.23-6, Mat Soukup, PhD

EPIDUO was statistically superior to vehicle and each of its monads for reductions in inflammatory, non-inflammatory, and total lesion counts, whether analyzed by absolute change or percent change. The applicant specified absolute change as the primary endpoint and percent change as secondary.

Study 18087

Study 18087 was a Phase 3, multi-center, prospective, randomized, double-blind, parallel group study with four arms: EPIDUO gel, adapalene 0.1% in vehicle, benzoyl peroxide 2.5% in vehicle, and vehicle. After randomization in a 1:1:1:1 ratio, 1668 subjects applied their respective study drug once daily for twelve weeks. The primary endpoints were the Investigator's Global Assessment (IGA) score dichotomized to success (ie, "Clear" or "Almost Clear," by definition a two-grade improvement) and failure, and lesion counts, assessed week 12. Table 3, below, describes the results for the IGA, and Table 4, below, describes the results for lesion counts.

Table 3: Investigator Global Assessment Results (ITT_LOCF) – Study 18087

	EPIDUO N=415	Adapalene N=420	Benzoyl Peroxide N=415	Vehicle N=418
Clear or Almost Clear *and* Two Grade Improvement				

Success (%)	125 (31.1)	83 (19.8)	92 (22.2)	47 (11.3)
p-value		<0.001	0.0062	<0.001

Source: Statistical Review and Evaluation of NDA 22-320, p.34, Mat Soukup, PhD

EPIDUO Gel was superior to vehicle and to both of its monads based on IGA. Unlike study 18094, Study 18087 required a baseline IGA score of 3/Moderate or greater, so achievement of 0/Clear or 1/Almost Clear represented a 2-grade improvement by definition.

Table 2: Change in Lesion Counts (ITT_LOCF) – Study 18087

	EPIDUO N=415	Adapalene N=420	Benzoyl Peroxide N=415	Vehicle N=418
Inflammatory Lesion Counts				
Mean Change	-15.4	-12.3	-13.7	-8.7
Mean % Change	-53.4	-41.7	-47.6	-30.2
p-value		<0.001	*0.068*	<0.001
Non-Inflammatory Lesion Counts				
Mean Change	-24.6	-21.0	-19.2	-11.3
Mean % Change	-48.1	-40.8	-37.2	-23.2
p-value		0.048	<0.001	<0.001
Total Lesion Counts				
Mean Change	-39.9	-33.3	-33.0	-20.0
Mean % Change	-50.0	-41.3	-41.2	-26.1
p-value		0.0003	0.0004	<0.001

Source: Statistical Review and Evaluation of NDA 22-320, p.36-8, Mat Soukup, PhD

EPIDUO was superior to vehicle and each of its monads for reductions in inflammatory, non-inflammatory, and total lesion counts, whether analyzed by absolute change or percent change, however the comparison against benzoyl peroxide in vehicle for inflammatory lesion counts failed to be significant at the 0.05 level. However, when the data was analyzed using unranked data, significance was achieved (see Dr. Soukup's Statistical Review, p.36). The totality of the evidence supports the contribution of adapalene to the effectiveness of the product.

✓ pos thon

In summary, Study 18094 and 18087 demonstrate that EPIDUO Gel is superior to vehicle and to each monad in the treatment of acne. I concur with the conclusions of the Clinical and Statistical Reviewers, Drs. Jane Liedtka and Mat Soukup, respectively, that the data support a determination of effectiveness.

8. Safety

The safety database is adequate. No unexpected safety signals emerged.
There were no deaths or SAEs attributable to EPIDUO Gel during the development program. The most frequently reported adverse event was dry skin. Collection of adverse events and assessment of local tolerance did not reveal unexpected safety signals. In the provocative dermal safety studies, irritation and sensitization were observed, but the active ingredients are

known to be irritants and benzoyl peroxide is a known allergen. The potential for irritation and sensitization are addressed in labeling.

The reader is referred to the Clinical Review by Jane Liedtka, MD, for full discussion.

No postmarketing commitments or requirements to address safety concerns are warranted.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

The applicant conducted studies in subjects 12 years of age and older. The applicant's pediatric assessment included a request for waiver below 9 years of age, and deferral for 9 to 11 years of age. The waiver and deferral request were presented to PeRC, who concurred with the requests and the proposed plan.

The onset of acne coincides with adrenarche. In girls, this precedes menarche by about 1 year. The average age of menarche in the US is 12 years of age; hence there is a significant population of children younger than 12 years of age with acne. The applicant's pediatric assessment, submitted late in the review cycle, contained a literature review which documented the presence of sizeable population of children younger than 12 years with acne. Because acne is more comedonal in early puberty, it may not be appropriate to extrapolate efficacy from older subjects to those in early puberty (immediately post-adrenarchal). The applicant should study the safety and effectiveness of their product in children aged 9 to 11 as a postmarketing requirement.

11. Other Relevant Regulatory Issues

No DSI audits

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted.
DMEPA did not find the tradename EPIDUO Gel to be vulnerable to name confusion that could lead to medication errors, and did not object to its use.

12. Labeling

Labeling negotiations are ongoing at the time of completion of this review.

13. Recommendations/Risk Benefit Assessment

I concur with the recommendations of the multi-disciplinary review team for approval of NDA 22-320, EPIDUO Gel, pending agreement of the applicant with the recommended labeling revisions. The risk-benefit calculus for this product is appropriate for the indication of topical treatment of acne in patients 12 years of age and older. Postmarketing risk management

beyond professional labeling, prescription status, and routine pharmacovigilance is not needed. However, to fulfill the requirements of PREA, the applicant will need to conduct a study of the safety and effectiveness of EPIDUO Gel in pediatric subjects aged 9 to 11 years of age.

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

/s/

Jill Lindstrom
11/28/2008 05:19:49 PM
MEDICAL OFFICER