

Clinical Pharmacology Review

NDA #:	022320/S-004
Submission Date:	April 04, 2012
Brand Name:	Epiduo
Generic Name:	Adapalene/ benzoyl peroxide
Dosage Form:	Gel
Dosage Strength:	Adapalene 0.1%/ benzoyl peroxide 2.5%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Galderma Laboratories, LP.
Relevant IND(s):	067,801
Submission Type:	Efficacy supplement
Indication:	Topical treatment of acne vulgaris in patients 9 years of age and older

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1. Executive Summary

The original NDA was approved on December 08, 2008 for the treatment of acne vulgaris in patients 12 years of age and older. At the time of approval, the Sponsor had fulfilled the pediatric study requirements for ages 12 years to 18 years and the Agency issued a waiver for pediatric study in patients up to 9 years of age. Clinical trials in patients aged 9 years to 11 years were deferred to be conducted as a post marketing requirement (PMR). Specifically, the approval letter stated the following trial to be conducted:

“A multi-center, randomized, placebo-controlled double blind study to evaluate the safety and efficacy of Epiduo Gel administered once daily for the treatment of subjects 9 to 11 years of age with acne vulgaris”.

In response to the above PMR, the Sponsor has submitted this efficacy supplement. This supplement contains results of an efficacy and safety trial in pediatric population aged 9 to 11 years (Trial # RD.06.SRE.18155).

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Sponsor.

1.2 Post-Marketing Requirements/ Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

To satisfy the PMR, the Sponsor conducted an efficacy and safety trial in the pediatric population aged 9 to 11 years (Trial # RD.06.SRE.18155). This trial did not evaluate any pharmacokinetics (PK). An information request (IR) was sent on 06/06/2012 asking the Sponsor to provide a rationale to justify why systemic bioavailability in subjects 9 to 11 years of age will not be necessary to support the systemic safety of Epiduo[®] Gel.

The Sponsor responded to the above IR on 06/18/2012 and provided results from an in-vitro study (Study RDS.03.SRE.4781) which showed similar penetration between Epiduo[®] Gel (adapalene monad part) and adapalene (Differin[®]) Gel, 0.1%. This study was not reviewed with the original NDA because in-vitro permeation method is not considered acceptable for assessing exposure of the drug product.

The Sponsor also provided supporting data from previously conducted PK trials with Epiduo[®] Gel and Differin[®] Lotion (adapalene, 0.1%) (NDA 022502), which showed low systemic absorption of adapalene following administration of both of these products. Furthermore, based on cross study comparison, the Sponsor claims that the exposure of adapalene following administration of Differin[®] Lotion in adolescent subjects (12 -17 years) is comparable to adults and due to this the Sponsor does not expect higher absorption in subjects 9 -11 years old. In the opinion of this reviewer, inferences made based on cross study comparison could be used for qualitative assessment but conclusions on relative bioavailability should ideally not be derived from such a comparison.

Finally, the Sponsor also claims that there were no systemic adverse events that were considered related to the study drug in the safety and efficacy Trial # RD.06.SRE.18155) conducted in subjects 9 - 11 years old.

In addition to the above rationale provided by the Sponsor, this reviewer conducted additional analysis where PK information from all adapalene products approved were evaluated. This reviewer identified 2 relative bioavailability (BA) trials in 2 NDAs.

One trial (RD.03.SRE.18115) was a relative BA trial that compared the systemic BA following administration of the 0.3% adapalene Gel and 0.1% adapalene Gel. This trial was conducted as a PMC for NDA 021753 (Differin[®] Gel, 0.3%). The PK results showed that the mean C_{max} and mean AUC₀₋₂₄ were approximately 75% to 85% lower in the 0.1% Gel arm compared to the 0.3% Gel arm.

Another relative BA trial was identified in the original review of this application (NDA 022320 - Epiduo[®] Gel). Specifically, this was a relative BA trial that compared the systemic exposure of adapalene following administration of Epiduo[®] gel and adapalene (Differin[®]) Gel, 0.1% (Trial RD.06.SRE.18097). The results of this study showed that the systemic exposure of adapalene appeared to be comparable and benzoyl peroxide does not appear to affect exposure of adapalene (The systemic exposure of benzoyl peroxide plasma concentrations were not assessed because of its complete and rapid metabolism to benzoic acid in the skin. Furthermore, benzoic acid is an endogenous compound and is widely used as a food additive and is considered safe in humans).

The above relative BA information suggests that exposure to adapalene from Epiduo Gel (adapalene 0.1%/ benzoyl peroxide 2.5%) would be significantly lower than that following application of approved Differin (adapalene) Gel, 0.3%. In addition, there were no systemic adverse events that were considered related to the study drug in the safety and efficacy trial (Trial # RD.06.SRE.18155) conducted in subjects 9 - 11 years old (This reviewer confirmed with the reviewing medical officer Dr. Jane Liedtka regarding the Sponsor's claim of lack of any treatment related systemic side effects in subjects 9 - 11 years old in the clinical trial # RD.06.SRE.18155. Dr. Liedtka concurs with the Sponsor's assessment).

Even though a definitive conclusion could not be made, the available information indicates that the systemic exposure of adapalene in subjects 9 - 11 years old following administration of Epiduo[®] (0.1% adapalene and 2.5% benzoic acid) Gel would likely be lower than the concentrations observed in adults following administration of 0.3% adapalene gel [Differin (adapalene) gel, 0.3% is approved for treatment of acne vulgaris in patients 12 years of age and older].

In conclusion, additional PK assessments in subjects 9 - 11 years old will not be requested at this time.

Clinical Pharmacology Briefing: An optional intra-division level Clinical Pharmacology briefing was conducted on 11/05/2012 with the following in attendance: E. Dennis Bashaw, An-Chi Lu, Doanh Tran and Chinmay Shukla.

2. Question Based Review

2.1 General Attributes of the Drug

2.1.1 Which formulation was used in the new safety and efficacy clinical trial RD.06.SRE.18155?

The Sponsor used approved marketed Epiduo[®] Gel (adapalene 0.1%/ benzoyl peroxide 2.5%) formulation in the new Phase 3 trial (Trial # RD.06.SRE.18155).

2.1.2 What are the proposed mechanism of action and the therapeutic indications?

Mechanism of action: Although the exact mechanism of action is not known, the mechanism of action as per label approved on 12/14/2011 is as follows:

Adapalene

Adapalene binds to specific retinoic acid nuclear receptors but does not bind to cytosolic receptor protein. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes. However, the significance of these findings with regard to the mechanism of action of adapalene for the treatment of acne is unknown.

Benzoyl peroxide

Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects.

Therapeutic indication: Topical treatment of acne vulgaris in patients 9 years of age or older.

2.1.3 What is the proposed route of administration and dosage?

Proposed route of administration: Topical

Proposed dosage: Epiduo Gel is intended to be applied as a thin film to the affected areas of the face and/or trunk once daily after washing.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology studies used to support dosing or claims?

The original NDA was approved on December 08, 2008 for the treatment of acne vulgaris in patients 12 years of age and older with a PMR to conduct a safety and efficacy study in patients aged 9 years to 11 years.

In response to the above PMR, the Sponsor has submitted this efficacy supplement which contains results of the Phase 3 efficacy and safety study in pediatric population aged 9 to 11 years (Trial # RD.06.SRE.18155). The Sponsor did not evaluate any PK in this trial.

An IR was sent on 06/06/2012 asking the Sponsor to provide a rationale to justify why systemic bioavailability in subjects 9 to 11 years of age will not be necessary to support the systemic safety of Epiduo[®] Gel. The Sponsor responded to the above IR on 06/18/2012 and the justification provided by the Sponsor is summarized as follows:

1. The Sponsor referred to the results from the in-vitro permeation study in NDA 022320 (RDS.03.SRE.4781) which showed similar penetration between Epiduo[®] Gel (Adapalene monad part) and Differin[®] Gel, 0.1%. This study was not reviewed with the original NDA because in-vitro permeation method is not considered acceptable for assessing exposure of the drug product (see Clinical Pharmacology review in DARRTS dated 10/27/2008 by Dr. Abimbola Adebowale).
2. The Sponsor also provided supporting data from previously conducted PK trials with Epiduo[®] Gel (adapalene 0.1%/ benzoyl peroxide 2.5%) (NDA 022320) and Differin[®] Lotion (adapalene 0.1%) (NDA 022502). Prior to approval the PK trials with Epiduo[®] Gel and Differin[®] Lotion were conducted only in adult subjects with acne vulgaris. Additional PK information in subjects 12 to 17 years old with acne vulgaris was obtained with Differin[®] Lotion as a PMC. With the results, the Sponsor has shown low systemic absorption of adapalene following administration of Epiduo[®] Gel and Differin[®] Lotion. Furthermore, the Sponsor claims that the exposure of adapalene following administration of Differin[®] Lotion in adolescent subjects (12 -17 years) is comparable to adults (based on cross study comparison) and due to this the Sponsor does not expect higher absorption in subjects 9 -11 years old.

Reviewer comments: *In the opinion of this reviewer, inferences made based on cross study comparison could be used for qualitative assessment and any conclusions should ideally not be derived.*

3. The Sponsor also claims that there were no systemic adverse events that were considered related to the study drug in this safety and efficacy trial conducted in 9 - 11 years old subjects (Trial # RD.06.SRE.18155).

Reviewer comments: *This reviewer checked with the reviewing medical officer Dr. Jane Liedtka regarding the Sponsor's claim of lack of any treatment related systemic side effects in subjects 9 - 11 years old in this clinical trial and Dr. Liedtka concurs with the Sponsor's assessment.*

Additional data assessment: In addition to the Sponsor's rationale, this reviewer conducted additional analyses as follows.

An analysis of historical data was carried out and Table - 1 provides a summary of all adapalene products approved as a monad and as a combination with benzoyl peroxide. All products are approved for the treatment of acne vulgaris in subjects 12 years of age and older.

Table 1: Summary of all adapalene products approved as a monad and as a combination product

NDA # and approval date	Trade Name	Active ingredients	PK data in the label
NDA 022320 12/08/2008	Epiduo Gel	Adapalene 0.1%/ Benzoyl peroxide 2.5%	2/24 subjects had quantifiable conc. $C_{max} = 0.21$ ng/mL and $AUC_{0-24} = 1.99$ ng*h/mL
NDA 020380 05/31/1996	Differin Gel	Adapalene 0.1%	Trace amounts in the plasma (< 0.25 ng/mL)
NDA 020748 05/26/2000	Differin Cream	Adapalene 0.1%	No quantifiable conc. (LLOQ = 0.35 ng/mL)
NDA 022502 03/17/2010	Differin Lotion	Adapalene 0.1%	2/14 subjects had quantifiable conc. Conc. ranged from 0.102 – 0.131 ng/mL. No PK analysis done due to limited samples.
NDA 021753 06/19/2007	Differin Gel	Adapalene 0.3%	15/16 patients had quantifiable conc. mean $C_{max} = 0.55 \pm 0.46$ ng/mL and mean $AUC_{0-24} = 8.37 \pm 8.46$ ng*h/mL

All the PK data shown above were obtained from trials in adult subjects.

For Differin[®] Lotion (NDA 022502), PK in pediatric subjects 12 - 17 years of age was obtained as a PMC (see Clinical Pharmacology review in DARRTS by Dr. Adebowale 04/14/2012). PK assessment was done on Day 1, 15 and 28 and data was quantifiable in 5/14 subjects. On day 28, the mean $C_{max} = 0.13 \pm 0.05$ ng/mL and mean $AUC_{0-24} = 3.07 \pm 1.21$ ng*h/mL (Results from this trial are not currently in the label and the Agency has asked the Sponsor to submit a labeling supplement with the proposed labeling language with the results of this trial incorporated into the label).

Comparing the data obtained in pediatric subjects (12 - 17 years old) from this trial with the data in adults from the table, the C_{max} values appear to be comparable (this is based on cross study comparison and any observations should be made for qualitative purpose only).

From Table - 1 above, the qualitative inference that can be made is that the exposure of adapalene following administration of 0.1% strength (any formulation) appears to be lower than that obtained following administration of 0.3% strength. However, no quantitative inference can be made with confidence because of cross study comparison.

Relative BA data: In addition to the above, relative BA data is available from 2 NDAs as follows.

NDA 021753 Differin[®] Gel, 0.3%: Trial RD.06.SRE.18060 was reviewed with the original NDA. This was a relative BA trial that compared the systemic BA of adapalene

following administration of the 0.3% Gel and 0.1% Gel. Subjects applied the formulation to the face and optionally to the trunk. All the systemic concentrations were below the LLOQ of 0.25 ng/mL (see Clinical Pharmacology review by Dr. Lei Zhang dated 01/18/05 in DARRTS).

The Sponsor conducted another relative BA trial (RD.03.SRE.18115) as a PMC, which again compared the relative BA following administration of the 0.3% Gel and 0.1% Gel to the face upper chest and upper back and PK data were obtained on Day 1, Day 15 and Day 30. The mean C_{max} and mean AUC_{0-24} were approximately 75% to 85% lower in the 0.1% Gel arm compared to the 0.3% Gel arm (LLOQ 0.1 ng/mL) (see Clinical Pharmacology review by Dr. Seongeun Cho dated 07/28/2009 in DARRTS).

NDA 022320 Epiduo[®] Gel: Trial RD.06.SRE.18097 was a relative BA trial that compared the systemic exposure of adapalene following administration of Epiduo[®] gel and Differin[®] Gel, 0.1% (see Clinical Pharmacology review by Dr. Abimbola Adebowale dated 10/27/2008 in DARRTS). The results of this trial showed that the systemic exposure of adapalene appeared to be comparable and benzoyl peroxide did not appear to affect the exposure of adapalene. However, Dr. Adebowale concluded that definitive conclusions could not be made due to few subjects with plasma levels.

Based on the available relative BA data, adapalene exposure following administration of 0.1% Gel was approximately 75% to 85% lower than 0.3% Gel (this confirms our earlier qualitative observation based on the PK data in Table - 1). Furthermore, in another study adapalene exposures appeared to be comparable when administered as a combination of 0.1% adapalene and 2.5% benzoyl peroxide Gel (Epiduo[®] Gel) and 0.1% adapalene Gel (Differin[®] Gel).

Overall reviewer conclusion: There are no adapalene PK data in subjects 9 - 11 years of age. Based on the available data, adapalene systemic exposure following administration of 0.1% adapalene Gel is approximately 75% to 85% lower than 0.3% Gel. Results from another study showed that systemic adapalene exposures observed following administration of 0.1% adapalene as a monad in a Gel formulation and administration of 0.1% adapalene as a combination with 2.5% benzoyl peroxide in a Gel formulation, appeared to be comparable.

This reviewer also checked with the reviewing medical officer Dr. Jane Liedtka regarding the Sponsor's claim of lack of any treatment related systemic side effects in subjects 9 - 11 years old in the clinical trial # RD.06.SRE.18155. Dr. Liedtka concurs with the Sponsor's assessment. Based on this, any additional PK assessment in subjects 9 - 11 years old will not be requested at this time.

Based on the available data (excluding the in-vitro permeation data which was not reviewed as this method is not considered acceptable for assessing exposure of a drug product), the systemic exposure of adapalene in subjects 9 - 11 years old following administration of 0.1% adapalene and 2.5% benzoic acid Gel would likely

be lower than the concentration observed in adults following administration of 0.3% Gel. However, any definitive conclusions can not be made.

2.2.2 What is the Sponsor's pediatric development plan?

The Sponsor has submitted this supplement to their NDA in order to fulfill Pediatric Research Equity Act (PREA) PMR.

2.3 Intrinsic Factors and Extrinsic Factors

No new information provided in this sNDA.

2.4 General Biopharmaceutics

No new information provided in this sNDA.

2.5 Analytical Section

The Sponsor did not assess any PK in this application and hence did not carry out any bioanalysis.

3. Detailed Labeling Recommendations

The following changes are recommended in the Sponsor's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

12.3 Pharmacokinetics

A pharmacokinetic study was conducted in ^(b)₍₄₎ **adult** subjects with acne vulgaris who were treated once daily for 30 days with 2 grams/day of EPIDUO gel applied to 1000 cm² of acne involved skin, (face, chest, and upper back).

Two subjects (20%) had quantifiable adapalene plasma concentrations above the limit of quantification (LOQ = 0.1ng/mL). The highest adapalene C_{max} and AUC_{0-24h} was 0.21 ng/mL and 1.99 ng•h/mL, respectively. Excretion of adapalene appears to be primarily by the biliary route. **Pharmacokinetics of EPIDUO Gel in pediatric subjects has not been evaluated.**

Benzoyl peroxide is absorbed by the skin where it is converted to benzoic acid and eliminated in the urine.

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/s/

CHINMAY SHUKLA
11/09/2012

DOANH C TRAN
11/09/2012