CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
Application Number(s)	022320/004
Priority or Standard	Standard
Submit Date(s)	April 3, 2012
Received Date(s)	April 4, 2012
PDUFA Goal Date	February 4, 2013
Division / Office	DDDP/OND
Reviewer Name(s)	Jane Liedtka
Review Completion Date	Nov 14, 2012
Established Name	adapalene and benzoyl peroxide Gel, 0.1%/2.5%
(Proposed) Trade Name	Epiduo Gel
Therapeutic Class	retinoid/oxidizing agent
Applicant	Galderma Laboratories LP
Formulation(s)	gel
Dosing Regimen	once per day
Indication(s)	Acne Vulgaris
Intended Population(s)	ages 9 and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 22-320, Epiduo gel (adapalene 0.1%/benzoyl peroxide 2.5 %) was approved for the indication of topical treatment of acne vulgaris in patients 12 years of age and older in Dec of 2008. The applicant has submitted a supplemental new drug application (efficacy supplement) to the drug product Epiduo gel for the use of the product in the pediatric population 9 to 11 years of age. The trial performed, #18155 is also submitted as the response to a post-approval commitment made on Dec 8, 2008 for a pediatric trial in this age group. The post-approval commitment is presented below:

> A multi-center, randomized, placebo-controlled double blind trial 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.

The applicant conducted the required multi-center, randomized, placebo-controlled double blind trial which was submitted on Feb 20, 2012 and is reviewed in this document.

This reviewer recommends that Epiduo Gel be approved for the topical treatment of acne vulgaris in patients 9 years and older. The sponsor has fulfilled the post-approval commitment to establish the safety and efficacy of Epiduo Gel for the treatment of acne vulgaris in the 9 to 11 year old age group.

1.2 Risk Benefit Assessment

This reviewer concludes that Adapalene/Benzoyl Peroxide Gel has a favorable benefit/risk profile for the treatment of acne vulgaris in patients 9 years and older. Trial 18155 demonstrated the efficacy of Adapalene/Benzoyl Peroxide Gel in the age group 9 to 11 years. No safety signals were detected in Trial 18155.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for REMS or additional risk management steps beyond product labeling.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

The drug product, Adapalene 0.1%/Benzoyl Peroxide 2.5 % Gel (Epiduo), is a fixed-dose combination of adapalene 0.1% (w/w) and benzoyl peroxide 2.5% (w/w) currently approved for the treatment of acne vulgaris in patients 12 and older. It is a white to very pale yellow opaque gel, containing 0.1% w/w (1 mg/g) of adapalene and 2.5% w/w (25 mg/g) of benzoyl peroxide, as the drug substances, dispersed in an aqueous gel dosage form, for the topical treatment of acne vulgaris. It is packaged in plastic tubes [redacted] with a [redacted] screw closure cap from two suppliers [redacted] Epiduo is supplied as 45 gm tube and 45 gm pump.

Adapalene is a naphthoic acid derivate and retinoid analogue with actions similar to those of retinoids. Benzoyl peroxide is commonly used as an antimicrobial and keratolytic agent in the commercial production of topical drug products, with more than 20 different prescription or over-the-counter drug products currently marketed worldwide.

Epiduo is intended for once daily application. The duration of treatment in the pivotal clinical trials was 12 weeks.

2.2 Currently Available Treatments for Proposed Indications

There are a number of products approved for treatment of acne vulgaris. Pharmacologic categories of approved therapies for acne vulgaris include oral and topical antibiotics (e.g. erythromycin, clindamycin), topical retinoids (e.g. tretinoin, tazarotene) and systemic hormonal therapies (e.g. ethinyl estradiol/norgestimate). The oral formulation of isotretinoin is also available for severe, recalcitrant, nodulo-cystic acne.

2.3 Availability of Proposed Active Ingredient in the United States

Adapalene is widely used in the commercial production of prescription topical drug products. Four different formulations are currently marketed in the USA: Differin® gel 0.1% (NDA# 020380), Differin® cream 0.1% (NDA# 020748), Differin® gel 0.3% (NDA# 021753) and Epiduo® (NDA#022320).

Benzoyl peroxide is widely available, with more than 20 different prescription or over the counter drug products currently marketed worldwide (e.g. Cutacnyl® [benzoyl peroxide] 2.5% gel, Benzac® AC [benzoyl peroxide] gel, marketed by Galderma in US).

2.4 Important Safety Issues With Consideration to Related Drugs

Adapalene, though structurally distinct from retinoic acid is considered a "retinoid" since it acts at retinoic acid receptors. Retinoids are irritants and known teratogens. Use of these products may also make for heightened sun sensitivity because topical retinoids may decrease the number of layers in the stratum corneum.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program for the original approval of Epiduo was conducted under IND 67,801. (See clinical review under NDA 22-320 in DARRTS for details of Presubmission Regulatory Activity related to the original approval).

As part of the original NDA submission for Epiduo, the Applicant had requested a waiver of the requirement to assess the use of the drug in pediatric patients less than 12 year of age. As their reason for this waiver request they stated:

> Since acne vulgaris usually develops after the onset of puberty and largely affects teenagers and young adults, the Applicant certifies that adequate and well-controlled studies to evaluate the drug in patients less than 12 years of age would be highly impractical.

The applicant had not submitted any references or data to substantiate this statement. According to the Guidance "How to Comply with the Pediatric Research Equity Act" the applicant should have provided evidence of a lack of adequate numbers of patients with acne in the age group less than 12 years.

In Fitzpatrick's "Dermatology in General Medicine" in chapter 78 entitled "Acne Vulgaris and Acneiform Eruptions" it states:

> In girls, the occurrence of acne may precede menarche by more than one year…..The age of onset of acne varies considerably. It may start as early as 6 to 8 years of age or it may not appear until the age of 20 years or later.

In the article "Age at Menarche and Racial Comparisons in US Girls" by Chumlea et al. published in Pediatrics (2003)111, 110-113 the author states

> From NHANES III data collected between 1988 and 1994….that mean age of menarche was 12.43 years

By extrapolation this would put the mean age of acne onset at 11.43 years with 50% of patients having onset at an earlier time. This reviewer recommended deferral of studies in subjects under 12 years and waiver of subjects below the age of 8 years.

The approval letter for Epiduo contained the following comments:

> We are waiving the pediatric trial requirement for up to 9 years of age, because necessary studies are impossible or highly impractical in that age group.
>
> We are deferring submission of your pediatric studies for ages 9 to 11 years for this application because this product is ready for approval for use in patients 12 years and older.
>
> Your deferred pediatric studies required by section 505B (a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B (a) (3)(B) of the Federal Food, Drug and Cosmetic Act. These required studies are listed below.
>
> A multi-center, randomized, placebo-controlled double blind trial 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 required pediatric assessments contained in the approval letter for Epiduo, the sponsor submitted on April 25, 2008 a protocol, # RD.06.SPR.18155, entitled “A Multi-center, Randomized, Vehicle-Controlled, and Double-Blind Trial to Evaluate the Safety and Efficacy of Epiduo (adapalene and benzoyl peroxide) Gel 0.1 %/2. 5% administered once daily for the treatment of subjects 9-11 years of age with acne vulgaris.

On Nov 6, 2009 an advice letter was sent containing the following comments:

1. Include an appropriate Investigator Global Assessment (IGA). The inclusion criteria should define an appropriate severity on the IGA for enrollment.
2. Define the primary efficacy endpoints as success on the IGA (clear or almost clear with at least 2 grades reduction from baseline), and absolute change in lesions.
3. Include sensitivity analyses for the handling of missing data to ensure that the conclusions are not driven by the method of handling missing data.

4. Exclude subjects with an acne nodule (even one) from the trial. Nodular acne may require more aggressive treatment than topicals alone to prevent scarring.
5. Identify the principal investigator and the Institutional Review Board before the trial begins.

Reviewer's Comment

The recommendations above were all incorporated into the final protocol used for trial 18155.

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Division of Scientific Investigators (DSI) was not consulted to review the conduct of the single trial (18155). The clinical team, in consultation with the biostatistics reviewer, concluded that there were no irregularities in the data requiring DSI consultation.

3.2 Compliance with Good Clinical Practices

In section 5.2 of the trial report for trial #18155 the applicant states that

> The trial procedures outlined in the protocol were to be conducted in accordance with the ethical principles originating from the Declaration of HELSINKI revised version (SOMERSET WEST, 1996), the International Conference on Harmonization (ICH) Good Clinical Practice (GCP), and in compliance with local regulatory requirements.

3.3 Financial Disclosures

With regard to financial disclosures the following investigators submitted disclosable arrangements:

(b) (6), MD	Preceptorship grant of $15,000 Grants totaling $300,000 to (b) (6) Dept.of Dermatology
(b) (6), MD	Speaking fees of $5,000 Dermatology research chair endowment fee of $40,000 Educational and advisory board fees totaling $59,745

Table 1: Table of Investigators with Financial Disclosures

Investigator name	# of patients	% of patients
(b) (6), MD	(b) (6)	(b) (6) %
(b) (6), MD	(b) (6)	(b) (6) %

Trial (b) (6) was a (b) (6) clinical trial which involved (b) (6) investigational sites and enrolled (b) (6) subjects. It is unlikely given the small number of subjects enrolled by Drs. (b) (6) and (b) (6) that significant bias was introduced.

The statistical reviewer performed an analysis of success rates by analysis centers (smaller investigational sites were combined into analysis centers). Dr. (b) (6) site was analysis center (b) (6), Dr. (b) (6) site was combined with (b) (6) other sites to form analysis center (b) (6) The statistical reviewer performed a sensitivity analysis where each analysis center was systematically removed to explore the possible source of an interaction effect. Removal of either analysis center (b) (6) still resulted in Epiduo® gel being statistically superior to vehicle gel.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No chemistry, microbiology, clinical pharmacology or animal pharmacology/toxicology data were contained in the submission.

4.1 Chemistry Manufacturing and Controls

Not applicable (See review for original application for Epiduo Gel)

4.2 Clinical Microbiology

Not applicable (See review for original application for Epiduo Gel)

4.3 Preclinical Pharmacology/Toxicology

Not applicable (See review for original application for Epiduo Gel)

4.4 Clinical Pharmacology

Pharmacokinetic (PK) assessment was not carried out in trial RD.06.SRE.18155. The sponsor was asked to provide a rationale to justify why systemic bioavailability information would not be needed in this population to support the systemic safety of Epiduo Gel.

The sponsor provided data from evaluation of PK for other products that include adapalene as an active moiety. Only adapalene plasma concentrations were evaluated. Benzoyl peroxide plasma concentrations were not assessed because of its complete and rapid metabolism to benzoic acid in the skin. Since benzoic acid is an endogenous compound and it is also widely used as a food additive (that is considered safe in humans), the applicant stated that it would be difficult to accurately evaluate treatment-related exposure of benzoic acid. Our clinical pharmacology reviewer agreed with this assessment.

The sponsors' response regarding adapalene PK was reviewed by the clinical pharmacology reviewer and a summary table of available historical data on the adapalene moiety (all obtained from trials in adults) is presented below:

Table 2: 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 ± 0.46 ng/mL and mean AUC_{0-24} = 8.37 ± 8.46 ng*h/mL

Source: Clinical Pharmacology Review, pg 6

The clinical pharmacology reviewer noted that

> During 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… PK assessment was done on Day 1, 15 and 28 and data was quantifiable in 5/14 subjects. On day 28, the mean Cmax = 0.13 ± 0.05 ng/mL and mean AUC0-24 = 3.07 ± 1.21 ng*h/mL.

The clinical pharmacology reviewer concluded

> 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 observation based on the PK data in the table). Furthermore, in another trial adapalene exposures appeared to be comparable when administered as a combination of 0.1% adapalene and 2.5% benzoyl peroxide Gel and 0.1% adapalene Gel…. In conclusion, additional PK assessments in subjects 9 - 11 years old will not be requested at this time.

Reviewer's Comment

I agree with the recommendation of the clinical pharmacology reviewer. I do not feel that additional PK assessments in the 9 to 11 year age group are needed at this time.

4.4.1 Mechanism of Action

See review for original application for Epiduo Gel

4.4.2 Pharmacodynamics

See review for original application for Epiduo Gel

4.4.3 Pharmacokinetics

See review for original application for Epiduo Gel

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3: Table of Studies for this Efficacy Supplement

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 4 Safety, Efficacy	RD.06.SRE.18155	To evaluate the safety and efficacy of Epiduo® Gel administered once daily for up to 12 weeks in subjects 9 to 11 years of age with *acne vulgaris*.	Multi-center, randomized, vehicle-controlled, double-blind study	Study Drugs: Epiduo® Gel and Gel Vehicle Dose: Once daily application in the evening to the face and trunk, if needed. Route: Topical	285	Subjects with *acne vulgaris*	12 weeks	Complete; Full

Source: Sponsor's Synopsis of Individual Studies, pg 2.

Table 4: Table of Studies from original Epiduo NDA Submission

Study No.	Population (subjects)	Study Type	Adapalene/Benzoyl Peroxide Gel	Adapalene Gel, 0.1%	Benzoyl Peroxide Gel, 2.5%	Gel Vehicle
Clinical Pharmacology Studies - Healthy Subjects						
RD.03.SRE.2674	Healthy	Dose finding Study with Separate Products	31[a]	-	15[a]	-
RD.03.SRE.2687	Healthy	Cumulative Irritation Potential Study	25[b]	25	25[b]	25
RD.03.SRE.2683	Healthy	Cutaneous Sensitization Potential Study	251	251	251	251[c]
RD.03.SRE.2681	Healthy	Phototoxic Potential Study	25	25	25	25
RD.03.SRE.2682	Healthy	Photosensitization Potential Study Photoallergy Potential Study	33	33	33	33
		Total Exposure in Healthy Subjects	**365**	**334**	**349**	**334**
Pharmacokinetics Studies - Subjects with Acne Vulgaris						
RD.03.SRE.2685	Acne vulgaris	Ten-Day PK Study	8	8	-	-
RD.03.SRE.18097	Acne vulgaris	Thirty-Day PK Study	12	12	-	-
		Total Exposure in pharmacokinetics studies	**20**	**20**	0	0
Efficacy and Safety Studies - Subjects with Acne Vulgaris						
RD.06.SRE.18094	Acne vulgaris	Efficacy and Safety Study (12 weeks treatment)	149	148	149	71
RD.06.SRE.18087	Acne vulgaris	Efficacy and Safety Study (12 weeks treatment)	415	420	415	418
RD.06.SRE.18089	Acne vulgaris	Long-Term Safety and Efficacy Study (12 months treatment)	452	-	-	-
		Total Exposure in Efficacy and Safety Studies	**1016**	**568**	**564**	**489**
		Total Exposure in Subjects with Acne Vulgaris	**1036**	**588**	**564**	**489**
		Total Subjects Exposed to Formulations	**1401**	**922**	**913**	**823**

[a] In Study RD.03.SRE.2674, the following treatment arms were tested: Adapalene 0.1% /Benzoyl peroxide 2.5% gel, Adapalene 0.1%/benzoyl peroxide 5% gel, benzoyl peroxide 2.5% gel (Cutancyl® 2.5), benzoyl peroxide 5% gel (Cutancyl® 5), benzoyl peroxide 10% gel (Benzac AC in the US and Cutancyl® 10 in the EU). The study was performed in 60 subjects: 31 subjects received Adapalene/Benzoyl Peroxide Gel. 2.5%.
[b] In Study RD.03.SRE.2687, the following other treatments were also tested: benzoyl peroxide 10% gel (Cutancyl® 10) and tazarotene 0.1% gel (Zorac®).
[c] In Study RD.03.SRE.2683, the following other treatment was also tested: white petrolatum.

Source: ISS, original Epiduo NDA 22-320, pg 11.

In the combined pivotal studies SRE 18094 and SRE 18087, 68.3% (1492 out of 2185) of the subjects were between the ages of 12-17.

5.2 Review Strategy

Efficacy and safety of Epiduo Gel in ages 9-11 is derived from the conduct of one safety and efficacy trial (Protocol Number RD.06.SPR.18155) conducted at sites across the US (20 sites) and Canada (5 sites).

Efficacy and safety is supported by the entire clinical development program for NDA 22-320 for Epiduo Gel for Acne vulgaris in ages 12 and above including the two previously submitted pivotal trials (SRE 18094 and SRE 18087). In addition, safety is supported by the two PK studies (SRE.2685 and subsection of SRE.18097) and the long term safety trial (SRE.18089).

Safety is also supported by the literature and postmarketing database for each of the monads, adapalene gel 0.1% and benzoyl peroxide 2.5% and for Epiduo Gel.

5.3 Discussion of Individual Studies/Clinical Trials

Clinical Trial: Protocol Number RD.06.SPR.18155

Title: A multi-center, randomized, vehicle-controlled, double-blind, trial to evaluate the safety and efficacy of Epiduo® (adapalene and benzoyl peroxide) Gel 0.1%/2.5% administered once daily for the treatment of subjects 9 to 11 years of age with acne vulgaris

Objective: The primary objective was to evaluate the safety and efficacy of Epiduo® (adapalene and benzoyl peroxide) Gel 0.1%/2.5% administered once daily for up to 12 weeks in subjects 9 to 11 years of age with acne vulgaris.

Principal Investigator(s):

RD.06.SPR.18155 PRINCIPAL INVESTIGATORS		
Name/Address/Tel./Fax	**Dates of Participation**	**Subject Identifier Series**
Boni Elewski, MD UAB Dermatology Clinical Research 2000 6th Avenue South 3rd Floor Birmingham, AL 35233 Tel: 205-502-9960 Fax: 205-502-9963	Oct. 21, 2010-Sep. 20. 2011	8005-001 to 8005-008
Lawrence Eichenfield, MD Rady Children's Hospital, San Diego Division of Pediatric and Adolescent Dermatology 8010 Frost Street, Suites 600, 602 San Diego, CA 92123 Tel: 858-966-6795 Fax: 858-576-9260	Jul. 29, 2010-Sep. 07, 2011	8008-001 to 8008-8036
Charles Lynde, MD Lynderm Research, Inc. 5762 Highway #7 East Suite 201 Markham, Ontario Canada L3P 1A8 Tel: 905-471-8011 Fax: 905-471-8182	Aug. 04, 2010-Sep. 26, 2011	8026-001 to 8026-011
William Werschler, MD Premier Clinical Research 104 West 5th Avenue Suite 320 Spokane, WA 99204 Tel: 509-343-3710 Fax: 509-242-1799	Jun. 15, 2010-Sep. 14, 2011	8039-001 to 8039-020
Joel Schlessinger, MD Skin Specialists, PC 2802 Oak View Mall Drive Omaha, NE 68144 Tel: 402-697-6599 Fax: 402-334-8627	Aug. 10, 2010-Sep. 19, 2011	8048-001 to 8048-007
Patricia Westmoreland, MD Palmetto Clinical ITrial Services, LLC 920 Woodruff Road Greenville, SC 29607 Tel: 864-467-1557 Fax: 864-467-1558	Jun. 17, 2010-Sep. 08, 2011	8056-001 to 8056-015
Joseph Fowler, MD Dermatology Specialists Research 501 South Second Street Louisville, KY 40202 Tel: 502-583-7546 Fax: 502-585-9708	Jun. 07, 2010-Sep. 20, 2011	8069-001 to 8069-012

Linda Stein Gold, MD Henry Ford Health Systems Department of Dermatology New Center One 3031 W. Grand Boulevard Detroit, MI 48202-2608 Tel: 313-916-1984 Fax: 313-916-9857	Aug. 17, 2010- Sep. 27, 2011	8094-001 to 8094-010
Zoe Draelos, M.D. 2444 North Main Street High Point, NC 27262 Tel: 336-841-2040 Fax: 336-841-2044	Jun. 09, 2010- Sep. 07, 2011	8110-001 to 8110-018
Rodion Kunynetz, MD Ultranova Skincare 125 Bell Farm Road Suite 104 Barrie, Ontario, Canada L4M 6L2 Tel: 705-722-4930 Fax: 705-722-6578	Aug. 16, 2010- Sep. 13, 2011	8132-001 to 8132-002
Leslie Andrew Rosoph, MD North Bay Dermatology Centre 500 Cassells Street 2nd Floor North Bay, Ontario Canada P1B 3Z7 Tel: 705-476-4539 Fax: 705-476-3967	Aug. 17, 2010- Sep. 13, 2011	8135-001 to 8135-003
Steven Kempers, MD Minnesota Clinical Study Center A Division of Associated Skin Care Specialists, P.A. 7205 University Avenue, N.E. Fridley, Minnesota 55432 Tel: 763-571-4200 Fax: 763-571-7202	Jun. 10, 2010- Sep. 29, 2011	8140-001 to 8140-017
Ian Landells, MD Nexus Clinical Research 120 Stavanger Drive Suite 102 St. John's, NL Canada A1A 5E8 Tel: 709-726-3386 Fax: 709-726-5898	Jul. 15, 2010- Sep. 08, 2011	8147-001 to 8147-004
George Murakawa, MD Dermcenter PC Somerset Skin Centre 255 Kirts Boulevard Troy, MI 48084 Tel: 248-244-8448 Fax: 248-244-8766	Jun. 15, 2010- Sep. 28, 2011	8155-001 to 8155-005

Lorne Albrecht, MD Guildford Dermatology Specialists 15300 105th Avenue, Suite 20 Surrey, British Columbia Canada V3R 6A7 Tel: 604-585-1110 Fax: 604-585-1170	Aug. 18, 2010- Sep. 27, 2011	8161-001 to 8161-006
Adelaide Hebert, MD The University of Texas Health Science Center at Houston 665 Travis Suite #600 Houston, TX 77030 Tel: 713-500-8266 Fax: 713-524-3432	Jul. 30, 2010- Sep. 22, 2011	8183-001 to 8183-008
Alan Fleischer, MD Department of Dermatology Wake Forest University Health Sciences 4618 Country Club Road Winston-Salem, NC 27104 Tel: 336-713-4114 Fax: 336-713-4255	Oct. 28, 2010- Sep. 26, 2011	8186-001 to 8186-020
David Kaplan, MD Adult & Pediatric Dermatology 4601 West 109th Street Suite 116 Overland Park, KS 66211 Tel: 913-663-3030 X112 Fax: 913-469-9192	Jun. 30, 2010- Sep. 27, 2011	8187-001 to 8187-007
Andrea Zaenglein, MD Penn State Milton S. Hershey Medical Center Penn State College of Medicine Department of Dermatology, HU-14 500 University Drive Room 2010 Hershey, PA 17033-0850 Tel: 717-531-1513 Fax: 717-531-5088	Jul. 22, 2010- Sep. 06, 2011	8188-001 to 8188-022
Robert Haber, MD Haber Dermatology Clinical Research Center 14077 Cedar Road Suite 200 South Euclid, OH 44118 Tel: 216-932-5200 Fax: 216-932-5212	Jun. 23, 2010- Sep. 21, 2011	8195-001 to 8195-020
Michael Heffernan, MD Central Dermatology, PC 1034 South Brentwood Boulevard Suite 600 St. Louis, MO 63117 Tel: 314-721-5565 Fax: 314-721-6122	Jul. 07, 2010- Sep. 21, 2011	8198-001 to 8198-011

Francisco Flores, MD FXM Research Miramar 3000 SW 148th Avenue Suite 216 Miramar, FL 33027 Tel: 954-430-1097 Fax: 305-675-3152	Jun. 17, 2010- Sep. 15, 2011	8259-001 to 8259-037
Russell Mader, MD Dermatology Associates of Kingsport, PC 2300 W. Stone Drive Kingsport, TN 37660 Tel: 423-230-3133 (M-W) Tel: 423-989-3105 (Th-F) Fax: 423-989-3693	Jul. 28, 2010- Sep. 21, 2011	8294-001 to 8294-006
Jeffrey Sugarman, MD Redwood Family Dermatology 2725 Mendocino Avenue Santa Rosa, CA 95403 Tel: 707-545-4537 Fax: 707-545-6726	Jun. 23, 2010- Sep. 29, 2011	8297-001 to 8297-012
Michael Spigarelli, MD Cincinnati Children's Hospital 3333 Burnet Avenue ML 7004 Cincinnati, OH 45229 Tel: 513-636-8597 Fax: 513-636-0168	Jan. 25, 2011- Sep. 16, 2011	8299-001 to 8299-010

Institutional Review Board: (b) (4) IRB (b) (4)

Drug Development Phase: Phase 4 Post Marketing Commitment

Trial Design: multi-center, randomized, vehicle-controlled, double-blind trial

Number of Subjects: 284 subjects were planned (142 in each arm), 285 were enrolled

Ages of Subjects for Inclusion: 9-11 years

Inclusion Criteria:

1. Male and female subjects 9 to11 years of age (inclusive) at Baseline.
2. A clinical diagnosis of acne vulgaris with facial involvement.
3. A score of 3 (moderate) on the IGA scale
4. A minimum of 20 but not more than 100 total lesions (Noninflammatory and/or Inflammatory) on the face (including the nose).

5. All females of childbearing potential (including pre-menstrual subjects) with a negative urine pregnancy test (UPT).
6. Willingness and ability for protocol compliance (as subjects were under the Age of Majority, the parent/legal representative must have been also willing and able to comply with trial requirements).
7. Consent to participate verified by assent form signature by the subject AND Informed Consent Signature by the parent/legal representative.
8. For U.S. subjects only; subjects were apprised of the Health Insurance Portability and Accountability Act (HIPAA). Willingness to share personal information and data as applicable was verified by the parent/legal representative signing a written authorization

Exclusion Criteria:

1. Any acne nodule.
2. Any acne cyst.
3. Acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), or severe acne requiring systemic treatment.
4. Underlying diseases and/or dermatologic conditions that required the use of interfering topical or systemic therapy or that might interfere with trial assessments. This included clinically significant abnormal findings or conditions, which might, in the opinion of the Investigator, interfere with trial evaluations or pose a risk to subject safety during the trial.
5. Use of hormonal contraceptives
6. Use of prohibited medications prior to the trial or unwillingness to refrain from use during the trial.

Specified washout period(s) up to Baseline for TOPICAL treatments on the face:

■ Devices and procedures, which include: ● Phototherapy devices for acne (e.g., ClearLight™ and lasers); ● Adhesive cleansing strips (e.g., Pond® and Biore®); and ● Cosmetic procedures (i.e., facials, peeling, comedone extraction)	1 Week
■ Anti-inflammatory drugs (e.g., salicylic acid, Clearasil®, and Clean & Clear®)	2 Weeks
■ Corticosteroids; and	2 Weeks
■ Antibiotics, including antibacterials like benzoyl peroxide containing products (e.g. Benzamycin®), retinoids, zinc, topical dapsone, and azelaic acid.	2 Weeks

Note: no washout was required for zinc oxide containing products

Specified washout period(s) up to Baseline for SYSTEMIC medications:

● Anti-inflammatory drugs	2 Weeks
● Corticosteroids	4 Weeks

● Antibiotics (except plain penicillin)	4 Weeks
● Other oral acne treatments (e.g., isotretinoin, anti-androgens)	6 Months

No washout was required for alpha hydroxy acid products, astringents, preparations with alcohol, but their application was forbidden during trial.
Note: All medications and treatments requiring a washout period were prohibited during the trial.

Oral vitamin A up to the recommended daily dose, 2,000 IU, and plain penicillin were acceptable. Systemic anti-inflammatory medication up to 14 total days of treatment were acceptable.

7. Known sensitivities to the trial preparations (see Package Insert), including paraben preservatives (i.e. methylparaben).
8. Participation in another investigational drug or device research trial within 30 days prior to Baseline.

Trial Plan:

Male and female subjects, 9 to 11 years of age meeting the inclusion/exclusion criteria at Baseline were randomized. Although acne lesions were only evaluated on the face, subjects presenting with facial and truncal acne vulgaris did participate in the trial. Subjects were randomized 1:1 to Epiduo® (adapalene and benzoyl peroxide) Gel 0.1%/2.5% or Topical Gel Vehicle.

Subjects not requiring a washout period completed both the Screening and Baseline procedures on the same day and were treated for a period of up to 12 weeks. All subjects were instructed to use a moisturizer throughout the trial. Subjects returned to the trial center for evaluations at Weeks 1, 2, 4, 8 and 12/Early Termination. A urine pregnancy test was required at both Baseline and Week 12/Early Termination visits for all female subjects. If a subject needed a 2-week washout for medication specified in Exclusion Criterion 6, the subjects were consented and the Screening Visit was performed. After the completed washout period and not later than two weeks (14 days +3 days) the subject returned to the site for the Baseline visit.

Complete physical examination and vital signs (blood pressure, heart rate and temperature) and assessment for preexisting signs and conditions were performed. Acne was evaluated using the IGA scale (see below). Facial Lesion Counts were performed. The Baseline Local Tolerability Assessment (Erythema, Dryness, Scaling, Stinging/Burning) was performed. Photographs of facial acne were performed (for selected sites only). The “Children’s Dermatology Life Quality Index” was completed. Verbal and written instructions on when and how to properly apply the trial medication were given. No other topical medication treatment, other than the trial drug,

moisturizer, and sunscreen was permitted on the face. The trial drug was to be applied daily in the evening after washing.

Interim visits occurred at weeks 1, 2, 4 and 8. IGA evaluation, facial lesion counts and recording of severity of signs and symptoms of local tolerability were performed at each visit. Adverse events were assessed at each visit by asking an open ended question such as "Have you had any new symptoms, injuries, illness or side effects or worsening of pre-existing conditions?" The number of missed applications and compliance to treatment were obtained and recorded prior to the subject leaving the clinic. At Weeks 4 and 8 the subject returned the trial medication and new medication (2 tubes) was dispensed.

Table 5: IGA Scale

Investigator's Global Assessment Scale			
SUCCESS	0	Clear	No comedones, papules or pustules. Residual hyperpigmentation and erythema may be present.
	1	Almost Clear	Rare comedones. No more than a few small papules and pustules might be present.
	2	Mild	Easily recognizable comedones in limited numbers, with or without the presence of some small papules or pustules.
	3	Moderate	Many comedones. Easily recognizable small and medium sized papules or pustules may be present. No nodules or cysts.
	4	Severe	Widespread and numerous comedones with many small, medium sized and large papules and pustules. Nodules or cysts may or may not be present.

Source: Sponsors' protocol pg 37

Reviewer's Comment on Protocol

This scale differs slightly from that used in the pivotal studies for Epiduo. According to the sponsors these adjustments were made in order to better "reflect the severity, distribution and predominance of lesion types seen in the younger population." The main difference lies in the descriptors for the mild and moderate categories which place more emphasis on noninflammatory lesions (and less on papules and pustules) for the scale designed for younger subjects. This seems reasonable.

Safety:

Safety was assessed via:

- Adverse Events (AEs) reported after the Informed Consent and at each following visit
- Local Tolerability Assessments (Erythema, Scaling, Dryness, and Stinging/Burning)

assessed on scales ranging from 0 (none) to 3 (severe)

An eCRF AE page was completed if the severity of the signs and symptoms was such that:

- The subject's participation in the trial was interrupted at his/her request or at the Investigator's request (Note: Temporary change (less than 2 weeks) from daily dosing to an alternate day treatment regimen did not constitute an interruption of trial.)
- The subject permanently discontinued the treatment at his/her request or at the Investigator's request.
- The subject required concomitant prescription or OTC therapy other than moisturizers.

Physical examination and vital signs were performed. There were no laboratory safety tests for this trial. Adverse events of special interest (AESI) is a noteworthy event for the particular trial drug that it can be appropriate to monitor carefully. The AESIs for this trial were defined as:

- Suspected sensitization with cutaneous signs (allergic contact dermatitis)
- Cutaneous AEs related to the trial product and leading to discontinuation

Table 6 : Trial 18155 Flow Chart

Table 2 Study flow chart/time and events schedule

	Adapalene/Benzoyl Peroxide Topical Gel Protocol 18155 Scheduled Visits [a]						
Procedures	Screening Visit [b]	Baseline[b,c]	Week 1	Week 2	Week 4	Week 8	Week 12 / Early Termination Visit [d]
Informed Consent / Assent	X						
Investigator's Global Assessment[m] (face)	X	X	X	X	X	X	X
Photography Consent, HIPAA [e]	X						
Demographics	X						
Medical History	X						
Previous Medications	X	(X)[b]					
Vital Signs/Physical Examination	X						X
Inclusion/Exclusion Criteria	X	(X)[b,l]					
Pregnancy Testing [f]		X					X
Parent/Legal Representative Assessment of Acne							X
Lesion Counts (face)	X	X	X	X	X	X	X
Local Tolerability Assessment [g]		X[h]	X	X	X	X	X
C-DLQI [i]		X					X
Photographs (face) [e]		X					X
Treatment Dispensed		X			X	X	
Treatment Returned					X	X	X
Dosing Calendar Dispensed		X			X	X	
Dosing Calendar Returned & Reviewed			X	X	X	X	X
Concomitant Therapy/ Procedure [j]	X	X	X	X	X	X	X
Adverse Event [k]		X	X	X	X	X	X
Exit Form							X

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protocol-or-amendment

Table 2 Study flow chart/time and events schedule

a. To assist subject compliance, a study visit window of plus or minus 3 days will be allowed for Week 1, and Week 2. A study visit window of plus or minus 7 days will be allowed for Week 4, Week 8 and Week 12.
b. Screening Visit and Baseline Visit will be performed the same day if no washout of medication is needed. Maximum time window allowed between Screening Visit and Baseline Visit is 14 days+3 days.
c. Instruct all subjects to use moisturizer beginning at Baseline. Study staff should use moisturizer to demonstrate application of study medication.
d. Should be conducted earlier if subject discontinues prior to Week 12.
e. Selected sites only HIPAA for U.S. sites only.
f. Pregnancy testing is mandatory for all females at Baseline and final visits. The Investigator will decide whether or not to conduct additional pregnancy tests during the course of the study.
g. The Investigator must grade and record the severity of the signs (Erythema, Dryness and Scaling) and record the subjects' assessment of symptoms (Stinging/Burning) of local tolerability on the Local Tolerability Assessment Form at each visit.
h. Evaluate the signs and symptoms of local tolerability at Baseline prior to the first application of study medication.
i. Children's Dermatology Life Quality Index (C-DLQI) (see section 12.2)
j. Medication that continues after Screening should be recorded on the eCRF Therapy Form. Medical or surgical procedures occurring after the Screening Visit should be recorded on the Procedures page of the eCRF.
k. Events occurring after the Informed Consent Form has been signed should be recorded as Adverse Events in the eCRF.
l. Complete or Reevaluate in case of Screening Visit and Baseline Visit on different days.
m. Evaluate IGA prior to conducting the Lesion Counts assessment.

Data Analysis:

Primary efficacy criteria:

- Success Rate was defined as the percentage of subjects rated Clear or Almost Clear with at least 2 grades reduction from Baseline on the Investigator's Global Assessment (IGA) at Week 12 (LOCF, ITT)
- Change from Baseline in Total Lesion Counts at Week 12 (LOCF, ITT)

Secondary efficacy criteria

- Percent Change in Lesion Counts - Percent Change from Baseline in Total Lesion Count at Week 12 (LOCF, ITT)
- Change in Lesion Counts
  - Change from Baseline in Noninflammatory Lesion Counts at Week 12 (LOCF, ITT).
  - Change from Baseline in Inflammatory Lesion Counts at Week 12 (LOCF, ITT).

Success Rate at Week 12 (LOCF, ITT) was analyzed by the Cochran-Mantel-Haenszel test stratified by analysis center, using general association. The change from baseline in total lesion count at week 12 analysis was performed using two-way ANCOVA model including Baseline Lesion Counts as a covariate, treatment, analysis center, and treatment-by-Baseline as factors.

Reviewer's Comment on Protocol

As noted under "Presubmission Regulatory Activity" the sponsor was asked to include the following in the protocol for the PMC trial of Epiduo in 9-11 yr olds:

- *Include an appropriate Investigator Global Assessment (IGA). The inclusion criteria should define an appropriate severity on the IGA for enrollment.*
- *Define the primary efficacy endpoints as success on the IGA (clear or almost clear with at least 2 grades reduction from baseline), and absolute change in lesions.*
- *Include sensitivity analyses for the handling of missing data to ensure that the conclusions are not driven by the method of handling missing data.*
- *Exclude subjects with an acne nodule (even one) from the trial. Nodular acne may require more aggressive treatment than topicals alone to prevent scarring.*
- *Identify the principal investigator and the Institutional Review Board before the trial begins.*

The sponsor complied with each of the above requests in the protocol for trial 18155.

The protocol for trial 18155 was very similar to the protocol for the pivotal trial 18087 except for the requested change in age of the participants. Trial 18094 was a phase 2 trial that the sponsor presented as a pivotal trial. DDDP did not have input into the design of that trial and as a result it differed somewhat from trial 18087. The table below highlights some of the differences across the studies designed to demonstrate efficacy.

Table 7: Comparison and Analysis Across Studies

Study Parameter	SRE.18094	SRE.18087	SRE.18089	SRE.18155
Study Design Parameters				
Randomized, double blind, parallel group study	Yes	Yes	No	Yes
Open-label, non comparative study	No	No	Yes	No
Randomization	2:2:2:1	1:1:1:1	NA	1:1
Treatment duration	12 weeks	12 weeks	1 year	12 weeks
Inclusion/exclusion criteria				
Males and females 12 years of age or older	Yes	Yes	Yes	No
Males and females 9 to 11 years of age	No	No	No	Yes
20 to 50 Inflammatory Lesions	Yes	Yes	Yes	
30 to 100 Noninflammatory Lesions	Yes	Yes	Yes	
20 to 100 Total Lesions	No	No	No	Yes
IGA score of 3 (moderate)	Not specified	Yes	Not specified	Yes
Presence of nodules and cysts	No	1 nodule allowed	No	No
Use of hormonal contraceptives solely for acne control prohibited	No	Yes	No	Yes
Third party confirmation of eligibility	Yes	No	No	No
Primary Efficacy Endpoints				
Success Rate (IGA)	Yes	Yes	No	Yes
Absolute change in lesion counts	No[a]	Yes	No	Yes
Percent change in lesion counts	Yes	No[a]	No	No[b]

[a] Absolute change in lesion counts, secondary endpoints in study SRE.18094 and additional analysis using SRE.18087 methodology are presented to facilitate comparison to absolute change in lesion counts in study SRE.18087, which defined absolute change in lesion counts primary. Vice versa, percent change in lesion counts, secondary endpoints in study SRE.18087, are presented to facilitate comparison to percent change in lesion counts in study SRE.18094, which defined percent change in lesion counts primary.
[b] Secondary endpoint.
IGA = Investigator's Global Assessment

Source: Sponsor's Summary of Clinical Efficacy, Section 2.7.3, pg18.

For trial 18155, total lesion counts rather than inflammatory vs noninflammatory lesion counts were used. No nodules (versus one allowed in trial 18087) were permitted.

6 Review of Efficacy

Efficacy Summary

The efficacy of Epiduo Gel was demonstrated in the 9-11 year old age group in a single phase 4 clinical trial (18155) conducted in the US and Canada,. The results are supported by the statistical determination of efficacy with the Epiduo Gel in the original review cycle.

The demographics for trial 18155 revealed a majority of female subjects (76.1%), a majority of Caucasian subjects (58.9%) and a mean age of 10.4 years. All enrolled subjects had a baseline severity of moderate with a mean total lesion count of 54 (≈68% comedonal). With regard to disposition, 94% of the Epiduo subjects completed the trial versus 88% of the vehicle subjects.

Efficacy versus vehicle was demonstrated for both co-primary endpoints; Success Rate and Change from Baseline in Total Lesion Count in trial 18155. The success rate for subjects treated with Epiduo was 47.2% (clear or almost clear) at the end of the 12 week treatment period vs 15.4% for vehicle. The change in total lesion count for subjects treated with Epiduo was -27.6 at the end of the 12 week treatment period vs -3.6 for vehicle.

The treatment effect (%success for Epiduo- %success for vehicle) for success rate for the original pivotal trial 18094 was 15.9%, for the original pivotal trial 18087 was 18.8% and for trial 18155 was 31.8%. The treatment effect for total lesion count change (sum of mean change in inflammatory lesion count and noninflammatory lesion count – mean change in vehicle total lesion count) for trial 18094 was -16.7, for trial 18087 was -20 and for trial 18155 was -24.

Epiduo achieved all of the secondary endpoints with a statistically (and clinically) meaningful advantage over the vehicle gel in subjects aged 9-11 years, thus supporting the findings of the primary analyses. All subgroups showed a statistically significant advantage for the Epiduo arm vs vehicle.

6.1 Indication

The current indication for Epiduo Gel is the topical treatment of acne vulgaris in patients 12 years of age and older. The proposed indication for Epiduo Gel is the topical treatment of acne vulgaris in patients 9 years of age and older.

6.1.1 Methods

A single trial, #18155 was submitted and has been reviewed in depth for this efficacy supplement.

6.1.2 Demographics

Of the 285 subjects enrolled in trial #18155, 76.1% were female, 58.9% of subjects were Caucasian and the mean age was 10.4 years (53% of the subjects were 11 years of age, 33% were 10 years of age, and 14% were 9 years of age).

Table 8: Summary of Subject Demographics in Trial SRE.18155 (ITT Population)

Demographics	Epiduo® Gel N=142 n (%)	Gel Vehicle N=143 n (%)	Total (N=285) n (%)	p-value
Gender n (%)				
Male	33 (23.2)	35 (24.5)	68 (23.9)	0.768
Female	109 (76.8)	108 (75.5)	217 (76.1)	
Age (Years)				
Mean	10.3	10.4	10.4	0.175
SD	0.76	0.68	0.72	
Median	11.0	11.0	11.0	
Min, Max	9, 11	9, 11	9, 11	
Subgroups n (%)				
9 years old	25 (17.6)	15 (10.5)	40 (14.0)	0.280
10 years old	45 (31.7)	49 (34.3)	94 (33.0)	
11 years old	72 (50.7)	79 (55.2)	151 (53.0)	
Race n (%)				
Caucasian	81 (57.0)	87 (60.8)	168 (58.9)	0.935
Black	36 (25.4)	32 (22.4)	68 (23.9)	
Asian	2 (1.4)	1 (0.7)	3 (1.1)	
Hispanic	6 (4.2)	5 (3.5)	11 (3.9)	
Other	17 (12.0)	18 (12.6)	35 (12.3)	
Skin Type n (%)				
I	10 (7.0)	8 (5.6)	18 (6.3)	0.144
II	30 (21.1)	48 (33.6)	78 (27.4)	
III	43 (30.3)	43 (30.1)	86 (30.2)	
IV	23 (16.2)	13 (9.1)	36 (12.6)	
V	26 (18.3)	18 (12.6)	44 (15.4)	
VI	10 (7.0)	13 (9.1)	23 (8.1)	

Source: Sponsor's Summary of Clinical Efficacy, pg31.

Reviewer's Comment

For the demographic data, no significant differences were observed in the ITT Population between the treatment groups. The higher percentage of female subjects versus the pivotal studies (40.2 % female in trial 18094 and 51.3% female in trial 18087) is to be expected in this younger age group. Females enter puberty earlier than their male counterparts and therefore also develop acne earlier. Trial 18155 also enrolled slightly fewer Hispanic subjects and slightly more African-american subjects versus the pivotal studies.

With regard to baseline severity of acne all subjects enrolled were graded moderate (IGA = 3). The baseline lesion counts are presented below:

Table 9: Summary of baseline lesion counts for Trial 18155 (ITT Population)

Acne Characteristics	Epiduo® Gel N=142	Gel Vehicle N=143	Total N=285	p-value
Baseline Lesion Count				
Inflammatory Lesions				
Mean	13.8	16.6	15.2	0.083
Median	12.0	13.0	12.0	
NonInflammatory Lesions				
Mean	36.7	39.9	38.3	0.104
Median	32.0	37.0	34.0	
Total Lesion Count				
Mean	50.5	56.4	53.5	0.015
Median	48.0	55.0	54.0	

Source: Source: Sponsor's Clinical Trial Report Trial 18155, pg 51.

Reviewer's Comment

The baseline lesion counts are somewhat lower in trial 18155 than those seen for the pivotal studies in the older age group. For example, total median lesion counts were 54.0 for the 9-11 age group in trial 18155 versus 74-79 for the older population in the pivotal studies. This is not suprising as acne often presents initially as mostly comedonal lesions distributed predominantly in the t-zone. For both mean and median scores the comedonal acne represented about 2/3 of the total lesions in trial 18155.

6.1.3 Subject Disposition

There were 285 subjects randomized and all were included in the ITT and Safety population. Of the 285 subjects randomized, 25 prematurely discontinued the trial; 8 subjects in the Epiduo treatment group and 17 in the vehicle group. The reasons for discontinuation are presented in the table below:

Table 10: Summary of Subject Disposition, ITT Population

Completion Status, n (%)	Epiduo Gel (N=142)	Vehicle Gel (N=143)	Total (N=285)
Normal Completion	134 (94.4)	126 (88.1)	260 (91.2)
Premature Discontinuation	8 (5.6)	17 (11.9)	25 (8.8)
Adverse Event	2 (1.4)	0	2 (0.7)
Subject's Request	3 (2.1)	7 (4.9)	10 (3.5)
Lost to Follow-up	3 (2.1)	9 (6.3)	12 (4.2)
Other	0	1 (0.7)	1 (0.4)

Data source: Table 14.1.2.1

Source: Sponsor's Clinical Trial Report Trial 18155, pg 48.

Reviewer's Comment

The rate for discontinuation for the trial was 8.8% of subjects. Only 2 subjects discontinued the trial secondary to an adverse event (See section 7 for details). The rest of the discontinuations were related to subject's request and lost to follow-up, both of which were more significant in the vehicle group.

There were 51 subjects (17.9%) who had major protocol violations and were therefore excluded from the Per Protocol (PP) population. These violations included entrance criteria deviations, use of prohibited medications, noncompliance and administrative error. Both the percentage and the types of violations seen are similar to the major protocol violations in the pivotal studies; 20% for trial 18087 and 18.6% for trial 18094.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints for trial 18155 were:

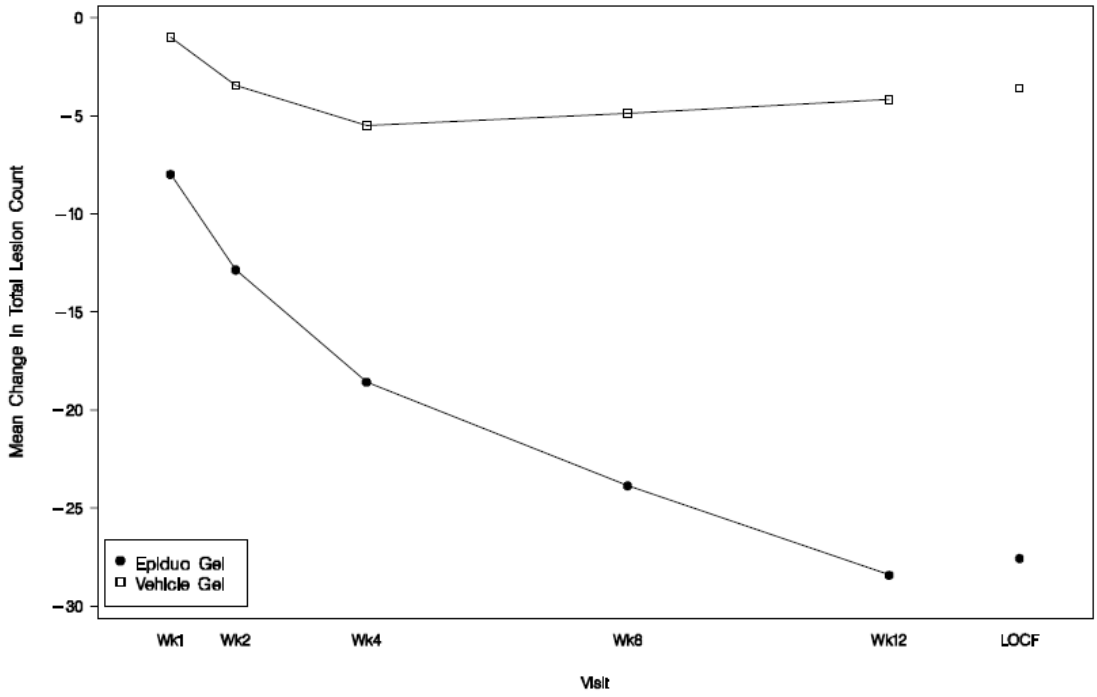
- Success Rate defined as the percentage of subjects with IGA rated 'Clear' or 'Almost Clear' with at least 2-grade improvement at Week 12 (LOCF, ITT)
- Change from Baseline in Total Lesion Counts at Week 12 (LOCF, ITT).

Table 11: Summary of the Primary Efficacy Analyses-Trial 18155

Efficacy Parameters	Epiduo Gel N=142	Vehicle Gel N=143	p-value
Primary Analyses (ITT Population; Week 12 LOCF)			
Success rate[a]: n (%)	67 (47.2%)	22 (15.4%)	<0.001[a]
Clear: n (%)	16 (11.3%)	1 (0.7%)	
Almost Clear: n (%)	51 (35.9%)	21(14.7%)	
	Mean (SD)	**Mean (SD)**	
Change in Total Lesion Count[b] (SD)	-27.6 (22.43)	-3.6 (24.44)	<0.001[b]

[a] P-values were based on CMH test general association statistic, controlling for center
[b] P-values were based on ANCOVA model with ranked changes as dependent variable, ranked Baseline as a covariate, and treatment and center as main effects
SD=Standard deviation.
Source: Reviewers table

Figure 1: Mean change in Total Lesion Count, ITT Population



LOCF = Week 12 (LOCF): The last available data observed during the study. Baseline value was used if no Post-baseline data were available.
Data source: Figure 14.4.2.1a

Source: Sponsor's Clinical Trial Report Trial 18155, pg 61.

Reviewer's Comment

As can be seen from Table 11, Epiduo achieved both primary endpoints with a statistically (and clinically) meaningful advantage over the vehicle gel in subjects aged 9-11 years.

Comparing the results of trial 18155 to the two pivotal studies reveals that subjects in the 9-11 year age group experienced a larger overall effect than their older counterparts. The treatment effect (%success for Epiduo- %success for vehicle) for success rate for trial 18094 was 15.9%, for trial 18087 was 18.8% and for trial 18155 was 31.8%. The treatment effect for total lesion count change (sum of mean change in inflammatory lesion count and noninflammatory lesion count – mean change in vehicle total lesion count) for trial 18094 was -16.7, for trial 18087 was -20 and for trial 18155 was -24. This may reflect the greater % of subjects who were naïve to treatment for trial 18155 vs the pivotal studies (72.3 % vs 50-54%). Many dermatologists believe that acne can become more resistant (at least to certain types of therapy) over time.

The statistical reviewer provided their analysis of the primary endpoint with the lesion counts broken down into inflammatory and non-inflammatory lesions (as was done in the original pivotal trials for approval). This information, since it mirrors that obtained in the pivotal trials, may be most appropriate for inclusion in labeling. The statistical reviewer's table from the statistical review is presented below:

Table 12: Efficacy Endpoints at Week 12 (ITT, LOCF)

Endpoints	Epiduo® Gel (N=142)	Vehicle Gel (N=143)	p-value
IGA Success(1), n (%)	67 (47.2%)	22 (15.4%)	<0.001(2)
Change in Inflammatory Lesion Count: Mean Absolute (%)	7.4 (36.0%)	0.7 (-13.2%)	<0.001(3)
Change in Non-Inflammatory Lesion Count: Mean Absolute (%)	20.2 (54.7%)	2.9 (2.3%)	<0.001(3)

(1) Success is defined as achieving an IGA score of 0 (Clear) or 1 (Almost Clear)
(2) p-value calculated from CMH test stratified by analysis centers
(3) p-value calculated based on an ANCOVA model using rank data with baseline, treatment, and analysis center as factor
ITT: Intent-to-treat, defined as all randomized subjects.
LOCF: Last observation carried forward
Source: Statistical Review, pg 3

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints for trial 18155 were:

- % Change in Total Lesion Count
- Change in Inflammatory Lesion Count
- Change in Noninflammatory Lesion Count

Table 13: Summary of the Secondary Efficacy Analyses-Trial 18155

	Epiduo® Gel	Vehicle Gel	
Secondary Analyses (ITT Population; Week 12 LOCF)			
	Mean (SD)	**Mean (SD)**	
% Change in Total Lesion Count[c] (SD)	-55.5%(38.99)	-9.3% (48.00)	**<0.001**[c]
Change in Inflammatory Lesion Count[b] (SD)	-7.4 (12.46)	-0.7 (12.46)	**<0.001**[b]
Change in Noninflammatory Lesion Count[b] (SD)	-20.2 (18.20)	-2.9 (19.60)	**<0.001**[b]

[b] P-values were based on ANCOVA model with ranked changes as dependent variable, ranked Baseline as a covariate, and treatment and center as main effects
[c] P-values were based on CMH test row mean difference, RIDIT transformed score, controlling for center (Table 14.2.3).
SD=Standard deviation
Source: Reviewers table

Reviewer's Comment

Epiduo achieved all of the secondary endpoints with a statistically (and clinically) meaningful advantage over the vehicle gel in subjects aged 9-11 years, thus supporting the findings of the primary analyses.

6.1.6 Other Endpoints

The sponsor performed analyses on the Per Protocol (PP) population, and in addition performed sensitivity analyses on the ITT population. All of the results were statistically significant ($p < 0.001$) in favor of the Epiduo arm in trial 18155 at week 12.

6.1.7 Subpopulations

Subjects in trial 18155 were examined by subgroups of gender, race and age. The findings for success rate at week 12 are presented in the Table below:

Table 14: Success Rate by Gender, Race, and Age year, ITT Population

Success Rate at Week 12 (LOCF)	Epiduo Gel		Vehicle Gel	
	Total number subjects	N (%)	Total number subjects	N (%)
Gender				
Male	33	15 (45.5%)	35	7 (20.0%)
Female	109	52 (47.7%)	108	15 (13.9%)
Race				
Caucasian	81	35 (43.2%)	87	14 (16.1%)
Non-Caucasian	61	32 (52.5%)	56	8 (14.3%)
Age year				
9 Years Old	25	14 (56.0%)	15	5 (33.3%)
10 Years Old	45	21 (46.7%)	49	7 (14.3%)
11 Years Old	72	32 (44.4%	79	10 (12.7%)

Success was defined as 'Clear' or 'Almost Clear' on the Investigator's Global Assessment.
Week 12 (LOCF): The last available data observed during the study. Baseline value was used if no Post-baseline data were available.
Data source: Table 14.2.12.1.1, Table 14.2.12.1.2, Table 14.2.12.2.1, Table 14.2.12.2.2, Table 14.2.12.3.1, Table 14.2.12.3.2, Table 14.2.12.3.3

Source: Sponsor's Clinical Trial Report Trial 18155, pg 72.

Reviewer's Comment

All subgroups showed a statistically significant advantage for the Epiduo arm vs vehicle. Success rate was comparable between male and female. Non-caucasians did slightly better than caucasians. Efficacy increased as age decreased. Improved efficacy in younger subjects may reflect the greater percentage of younger subjects who were naïve to treatment.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable, a single fixed dose of Epiduo Gel was used in trial 181855.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable, a 12 week treatment course was used for all subjects in trial 181855.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

A single clinical trial, #18155 was conducted to evaluate the safety of Epiduo gel in subjects with acne vulgaris ages 9-11 years. A total of 285 subjects (142 of whom were exposed to Epiduo gel) were enrolled. The results of the phase 2 and phase 3 studies that were conducted for the original approval of Epiduo gel are supportive. There were 1492 (out of 2185) of the subjects in the original development program between the ages of 12-17.

Topical safety was adequately evaluated in trial 18155 and included an assessment for local tolerability. A majority of subjects in the Epiduo arm initially had stinging/ burning (62.1%), dryness (56.4%), and scaling (55.7%). A significant minority had erythema (42.9%). For most subjects however, these signs and symptoms were of mild severity and resolved despite continued treatment.

The incidence of adverse events in trial 18155 was higher in the Epiduo arm (47.2 % of subjects) vs the vehicle arm (31.5% of subjects). No deaths occurred. No serious adverse events occurred in the Epiduo arm. The majority of the adverse events in both arms were rated as mild; 53/67 (79%) for the Epiduo arm and 32/45 (71%) for the vehicle arm. One event for each group was rated as severe; this event was related for the Epiduo arm (facial skin irritation) and unrelated for the vehicle arm (vascular malformation). For adverse events assessed by the investigators as drug related, all were in the skin and subcutaneous tissue disorder category. Related adverse events occurring in greater than 1% of subjects included skin burning sensation, skin irritation, skin discomfort, dry skin and erythema.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A single trial, #18155 was submitted and has been reviewed in depth for this efficacy supplement.

7.1.2 Categorization of Adverse Events

Adverse events were recorded at each visit. In addition, signs and symptoms of local tolerability (Erythema, Scaling, Dryness, and Stinging/Burning) were evaluated at each visit using a score ranging from “0” (none) to “3” (severe) in Trial 18155.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable since only a single trial was reviewed.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The mean treatment duration for trial 18155 was 77.6 days for the vehicle arm and 82.3 days for the Epiduo arm. The mean daily amount of Epiduo Gel used per subject in trial 18155 was 0.46 g/day. This is lower than the average daily amount used in the pivotal studies for the original approval for Epiduo Gel which was 0.7 to 0.8 g/day.

Reviewer's Comment

A lower mean amount of product applied daily would be expected in this trial of younger (and therefore in most cases smaller) subjects.

7.2.2 Explorations for Dose Response

Not applicable, a single fixed dose of Epiduo Gel was used in trial 181855.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable, no special animal or in vitro testing was included in this submission.

7.2.4 Routine Clinical Testing

Urine pregnancy testing (upt) was the only laboratory test performed in trial 18155. All results were negative.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable, no metabolic, clearance or drug interaction studies were included in this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See original clinical review for Epiduo Gel.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in trial 18155.

7.3.2 Nonfatal Serious Adverse Events

One subject in the vehicle gel arm of trial 18155 (# 8186-004) was discovered to have an arteriovenous malformation. This was considered a Serious Adverse Event (SAE) but was classified by the investigator as unrelated.

Reviewer's Comment

I agree with the investigator's assessment that this was an unrelated SAE.

7.3.3 Dropouts and/or Discontinuations

There were 2 subjects in trial 18155 (both in the Epiduo arm, #8155-001 and # 8297-006) who discontinued the trial because of a related adverse event, one classified as erythema (which occurred on day 31) and one as skin irritation (which occurred on day 10). Both events were rated as mild. Both subjects discontinued at the parents request.

7.3.4 Significant Adverse Events

Two subjects (both in the vehicle gel arm) experienced adverse events classified as irritant contact dermatitis.

One subject in the Epiduo arm experienced severe facial skin irritation that was considered related by the investigator.

Reviewer's Comment

This is expected with a product that combines two monads known to be irritants.

7.3.5 Submission Specific Primary Safety Concerns

No cases of sensitization were reported in trial 18155.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Signs and symptoms of local tolerability (Erythema, Scaling, Dryness, and Stinging/ Burning) were evaluated at each visit using a score ranging from “0” (none) to “3” (severe) in Trial 18155. These signs and symptoms were considered adverse events under the following circumstances:

- The subject’s participation in the trial was interrupted at his/her request or at the Investigator’s request. Temporary change (less than 2 weeks) from daily dosing to an alternate day treatment regimen did not constitute an interruption of trial.
- The subject permanently discontinues the treatment at his/her request or at the Investigator’s request.
- The subject requires concomitant prescription or OTC therapy other than moisturizers.

The incidence of adverse events in trial 18155 was higher in the Epiduo arm (47.2 % of subjects) vs the vehicle arm (31.5% of subjects). The majority of the adverse events in both arms were rated as mild; 53/67 (79%) for the Epiduo arm and 32/45 (71%) for the vehicle arm. One event for each group was rated as severe; this event was related for the Epiduo arm (See details in Section 7.3.2) and unrelated for the vehicle arm (See details in Section 7.3.4).

Table 15: Summary of Overall Adverse Events, Safety Population

Category	Epiduo Gel (N=142) n, %	Vehicle Gel (N=143) n, %
Subjects With At Least One Adverse Event	67 (47.2)	45 (31.5)
Related AE	29 (20.4)	1 (0.7)
Unrelated AE	51 (35.9)	44 (30.8)
Subjects With At Least One Serious Adverse Event	0	1 (0.7)
Unrelated AE	0	1 (0.7)
Subjects With At Least One Adverse Event Leading to Discontinuation	2 (1.4)	0
Related AE	2 (1.4)	0
Subjects With At Least One Mild Adverse Event	53 (37.3)	32 (22.4)
Related AE	22 (15.5)	1 (0.7)
Unrelated AE	37 (26.1)	31 (21.7)
Subjects With At Least One Moderate Adverse Event	24 (16.9)	16 (11.2)
Related AE	7 (4.9)	0
Unrelated AE	18 (12.7)	16 (11.2)
Subjects With At Least One Severe Adverse Event	1 (0.7)	1 (0.7)
Related AE	1 (0.7)	0
Unrelated AE	0	1 (0.7)
Subjects With At Least One Adverse Event of Special Interest	2 (1.4)	0
Related AE	2 (1.4)	0

Subjects may be counted twice, once in Related AE category and once in Unrelated AE category for having more than one AE.
MedDRA dictionary version 11.0.
Data source: Table 14.3.3.2

Source: Sponsor's Clinical Trial Report Trial 18155, pg.93.

For adverse events assessed as drug related the difference between the Epiduo arm (20.4%) and the vehicle arm (0.7%) was substantial. When looked at by System Organ Class, all of the events that were considered related were in the skin and subcutaneous tissue disorder category as shown in the table below:

Table 16: Adverse Events Related to Trial Drug by System Organ Class and Preferred Term, Safety Population Trial 18155

System Organ Class/Preferred Term[a]	Epiduo Gel (N=142) n, %	Vehicle Gel (N=143) n, %
Total Number of AE(s)	**48**	**1**
Total Number (%) of Subjects with AE(s)[b]	**29 (20.4)**	**1 (0.7)**
Skin and subcutaneous tissue disorders	**29 (20.4)**	**1 (0.7)**
Skin burning sensation	13 (9.2)	0
Skin irritation	8 (5.6)	0
Skin discomfort	5 (3.5)	0
Dry skin	4 (2.8)	0
Erythema	3 (2.1)	0
Skin hypopigmentation	1 (0.7)	0
Dermatitis	1 (0.7)	0
Sunburn	1 (0.7)	1 (0.7)

[a] Multiple occurrences within a System Organ Class by a subject were counted once per System Organ Class. Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.

[b] A subject was counted once even if the subject experienced more than one adverse event during the study.

MedDRA dictionary version 11.0.

Data source: SRE.18155, Table 14.3.3.6.1

Source: Sponsor's Clinical Overview, pg 62.

Reviewer's Comment

The spectrum of adverse events seen in trial 18155 (skin burning sensation, skin irritation, dry skin, erythema, dermatitis) were very similar to that seen in the pivotal studies. Skin irritation was seen more commonly in the younger age group, 5.6% for trial 18155 vs 1.2% for the pooled pivotal studies. Dry skin and dermatitis however were less common in trial 18155, 2.8% and 0.7% vs 7.4% and 3.2% in the pivotal studies. Pruritis, which was seen in 1.2% of subjects in the pivotal studies, was not noted in trial 18155.

Local tolerability assessment

The following table provides a summary for the highest score worse than baseline for each tolerability assessment and breakdown by severity:

Table 17: Summary of Local Tolerability, Safety Population

Highest Score[a]	Epiduo Gel	Vehicle Gel
N	140	142
Erythema	60 (42.9%)	32 (22.5%)
1 = Mild	41 (29.3%)	24 (16.9%)
2 = Moderate	18 (12.9%)	8 (5.6%)
3 = Severe	1 (0.7%)	0
Scaling	78 (55.7%)	18 (12.7%)
1 = Mild	59 (42.1%)	15 (10.6%)
2 = Moderate	18 (12.9%)	3 (2.1%)
3 = Severe	1 (0.7%)	0
Dryness	79 (56.4%)	22 (15.5%)
1 = Mild	62 (44.3%)	21 (14.8%)
2 = Moderate	14 (10.0%)	1 (0.7%)
3 = Severe	3 (2.1%)	0
Stinging/burning	87 (62.1%)	18 (12.7%)
1 = Mild	54 (38.6%)	16 (11.3%)
2 = Moderate	25 (17.9%)	2 (1.4%)
3 = Severe	8 (5.7%)	0

[a] Highest Score during study and worse than Baseline
Source: Table 14.3.2.1, Table 14.3.2.2, Table 14.3.2.3, Table 14.3.2.4

Source: Sponsor's Clinical Trial Report Trial 18155, pg 104.

Reviewer's Comment

A majority of subjects in the Epiduo arm had stinging/burning (62.1%), dryness (56.4%), and scaling (55.7%). A significant minority had erythema (42.9%). For most subjects however, these signs and symptoms were of mild severity and resolved despite continued treatment. Less than 6% had severe signs and/or symptoms at any time during their 12 week treatment course. These are very similar to the numbers noted in the pivotal studies presented below for comparison:

Table 18: Signs and Symptoms of Local Tolerability for Studies 18094 and 18087 Combined

	Adapalene/ Benzoyl Peroxide Gel Na = 553* n (%)	Adapalene Gel N a = 562* n (%)	Benzoyl Peroxide Gel N a = 557* n (%)	Gel Vehicle N a = 481* n (%)
Erythema	**225 (40.7)**	**174 (31.0)**	**104 (18.7)**	**97 (20.2)**
1 = mild	148 (26.8)	121 (21.5)	73 (13.1)	72 (15.0)
2 = moderate	72 (13.0)	51 (9.1)	30 (5.4)	24 (5.0)
3 = severe	5 (0.9)	2 (0.4)	1 (0.2)	1 (0.2)
Scaling	**253 (45.8)**	**211 (37.5)**	**100 (18.0)**	**88 (18.3)**
1 = mild	192 (34.7)	175 (31.1)	89 (16.0)	84 (17.5)
2 = moderate	58 (10.5)	35 (6.2)	11 (2.0)	4 (0.8)
3 = severe	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
Dryness	**302 (54.6)**	**244 (43.4)**	**135 (24.2)**	**87 (18.1)**
1 = mild	224 (40.5)	202 (35.9)	121 (21.7)	80 (16.6)
2 = moderate	74 (13.4)	39 (6.9)	14 (2.5)	7 (1.5)
3 = severe	4 (0.7)	3 (0.5)	0 (0.0)	0 (0.0)
Stinging/Burning	**328 (59.3)**	**178 (31.7)**	**79 (14.2)**	**53 (11.0)**
1 = mild	225 (40.7)	139 (24.7)	72 (12.9)	45 (9.4)
2 = moderate	84 (15.2)	31 (5.5)	5 (0.9)	8 (1.7)
3 = severe	19 (3.4)	8 (1.4)	2 (0.4)	0 (0.0)

Source: Sponsor's Summary of Clinical Safety NDA 22-320 pg 35.

7.4.2 Laboratory Findings

No routine laboratory testing was performed in trial 18155.

7.4.3 Vital Signs

No significant differences were noted comparing the two trial arms with regard to BP or heart rate.

7.4.4 Electrocardiograms (ECGs)

No EKGs were performed in trial 18155.

7.4.5 Special Safety Studies/Clinical Trials

See original clinical review for NDA 22320 for discussion of this subject.

7.4.6 Immunogenicity

Not applicable, as the drug products are small molecule drugs, and not therapeutic proteins.

7.5 Other Safety Explorations

There were no additional safety explorations.

7.5.1 Dose Dependency for Adverse Events

Not applicable, a single fixed dose combination was used in trial 18155.

7.5.2 Time Dependency for Adverse Events

Adverse events were reported during the dosing period. No additional time-dependent safety explorations were conducted. Adverse events decreased in incidence over the 12 week trial period (See Section 7.4.1 for details).

7.5.3 Drug-Demographic Interactions

Subgroup summaries of AE data by gender, race, and age year were provided. There was no obvious discernible pattern in looking at tolerability based on gender, race or age.

7.5.4 Drug-Disease Interactions

All subjects enrolled into trial 18155 had the same disease severity (moderate) so no evaluation of drug-disease interaction was performed.

7.5.5 Drug-Drug Interactions

No specific studies of potential drug interactions were performed. See original clinical review for NDA 22320 for discussion of this subject.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See original clinical review for NDA 22320 for discussion of this subject.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies occurred in trial 18155. See original clinical review for NDA 22320 for discussion of this subject.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessment has been made on the effects of Adapalene/Benzoyl Peroxide Gel on growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

There was no new information relevant to this review supplied in the 120 day update report.

8 Postmarket Experience

In accordance with the Pediatric Research Equity Act (PREA), in August of 2010, the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE) was asked to summarize post-marketing reports of adverse events associated with the use of Epiduo in pediatric patients 16 years of age and younger. The Adverse Event Reporting System (AERS) database search for all reports of adverse events (serious and non-serious) up to the "data lock" date of June 22, 2010 retrieved seven reports for Epiduo. Pediatric reports represented 48% (3/7) of the total post-marketing adverse event reports for Epiduo. There were no cases of death reported in association with the use of Epiduo in adults or pediatrics. DPV recommended consideration of the following changes to the label for Epiduo:

- Update the CONTRAINDICATIONS (Section 4) of the label to reflect that Epiduo Gel should not be administered to individuals who are hypersensitive to adapalene, benzoyl peroxide or any of the components in the vehicle gel.

- Update the POSTMARKETING EXPERIENCE (Section 6.2) of the Epiduo label to include the following adverse events: eyelid edema, conjunctivitis, erythema, pruritus, skin discoloration, rash, eczema, swelling face, and throat tightness.

On Aug 16, 2010 Galderma submitted a Prior Approval Labeling Supplement (PAS) that was administratively split into two supplements. The first (S-1) contained changes to the Adverse Reactions section (as recommended above by DPV) and a new PPI for

Epiduo Gel and was reviewed in a document entered into DARRTS on Dec 16, 2010. This supplement was approved on Feb 18, 2011. S-2 contained information (including additions to the label) regarding the addition of a 45 gram pump. This supplement was approved on Dec 14, 2011.

In addition, Section 505 of the Federal Food, Drug and Cosmetic Act (FDCA), as amended by the Food and Drug Administration Amendments Act of 2007 (FDAAA) directs FDA to improve the transparency of information about drugs by, among other things, "preparing, by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number." The 18 month review of Epiduo conducted by the Agency determined that "No unlabeled or unexpected serious adverse events were identified". This review was completed in May of 2011.

The annual report for Epiduo was most recently submitted on Feb 22, 2012. The estimated US distribution for Epiduo for Dec 2010 to Dec 2011, which was included in that annual report, is shown below:

Table 19: Domestic (US) Distribution-December, 2010 – December, 2011

NDC Number	Package Size	Units Distributed
0299590802	2 gram	(b) (4)
0299590845	45 gram	(b) (4)
0299590845*	45 gram (sample)	15,072

*Distributed to physicians as a sample

In June of 2012, The Division of Pharmacovigilance (DPV) reviewed the literature and Adverse Event Reporting System (AERS) reports for Epiduo (as well as for the other

approved topical retinoids) looking for an association between topical retinoids (tretinoin and adapalene) and idiopathic intracranial hypertension (IIH). They identified 13

pediatric cases (10 from AERS and 3 from the literature) but due to sparse information and confounding they concluded that "…there is insufficient evidence to suggest an association between the topical retinoids and IIH at this time".

9 Appendices

9.1 Literature Review/References

No literature was reviewed for this efficacy supplement.

9.2 Labeling Recommendations

Labeling review is ongoing at the time of this review. Final labeling will be appended to the action letter, if approved.

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this product

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

/s/

JANE E LIEDTKA
11/28/2012

JILL A LINDSTROM
11/29/2012
I concur.