

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 22-320/S-002**

***Trade Name:*** Epiduo

***Generic Name:*** adapalene and benzoyl peroxide

***Sponsor:*** Galderma Laboratories LP

***Approval Date:*** December 14, 2011

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 22-320/S-002**

## CONTENTS

### Reviews / Information Included in this NDA Review.

<b>Approval Letter</b>	<b>X</b>
<b>Other Action Letter(s)</b>	<b>X</b>
<b>Labeling</b>	<b>X</b>
<b>Summary Review</b>	
<b>Officer/Employee List</b>	
<b>Office Director Memo</b>	
<b>Cross Discipline Team Leader Review</b>	
<b>Medical Review(s)</b>	<b>X</b>
<b>Chemistry Review(s)</b>	<b>X</b>
<b>Environmental Assessment</b>	
<b>Pharmacology Review(s)</b>	
<b>Statistical Review(s)</b>	
<b>Microbiology Review(s)</b>	
<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	<b>X</b>
<b>Risk Assessment and Risk Mitigation Review(s)</b>	
<b>Proprietary Name Review(s)</b>	
<b>Other Review(s)</b>	<b>X</b>
<b>Administrative/Correspondence Document(s)</b>	<b>X</b>

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 22-320/S-002**

**APPROVAL LETTER**



NDA 022320/S-002

**SUPPLEMENT APPROVAL**

Galderma Laboratories, L.P.  
Attention: Richard Almond, MBA, RAC  
Manager Regulatory Affairs  
14501 North Freeway  
Forth Worth, TX 76177

Dear Mr. Almond:

Please refer to your Supplemental New Drug Application (sNDA) dated and received June 14, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Epiduo (adapalene and benzoyl peroxide) Gel, 0.1%/2.5%.

We acknowledge receipt of your amendments dated October 26, November 18, and December 2, 2011.

The June 14, 2011, submission constituted a complete response to our February 16, 2011, action letter.

This "Prior Approval" supplemental new drug application proposes an alternate container closure system, a 45 gm pump.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effectuated" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container label as soon as they are available, but no more than 30 days after they are printed.

### **POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of the postmarketing commitment:

- 1847-1 To develop and validate a revised method for the proposed Epiduo pump, which avoids unwarranted reporting of adapalene degradation products, during the first 6 months after the supplement (S-002) approval date. You will submit within 6 months after the S-002 approval date, a revised HPLC method with a complete method validation report for adapalene degradants in the drug product.

The timetable you submitted on December 2, 2011, states that you will conduct this study according to the following schedule:

Final Method Submission: 06/2012

Final Report Submission: 06/2012

Submit clinical protocols to your IND 067801 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

### **ENCLOSURES:**

Content of Labeling  
Carton and Container Labeling

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

/s/  
-----

STANKA KUKICH  
12/14/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-320/S-002**

**OTHER ACTION LETTER(S)**



NDA 022320/S-002

**COMPLETE RESPONSE**

Galderma Laboratories, L.P.  
Attention: Richard Almond  
Manager, Regulatory Affairs  
14501 North Freeway  
Fort Worth, Texas 76177

Dear Mr. Almond:

Please refer to your Supplemental New Drug Application (sNDA) dated August 16, 2010, received August 19, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Epiduo<sup>®</sup> (adapalene and benzoyl peroxide) Gel, 0.1%/2.5% indicated for the treatment of acne vulgaris in patients 12 years of age and older.

This Prior Approval supplemental new drug application provides for an alternate container closure system.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**Deficiencies**

(b) (4)

## OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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

/s/  
-----

STANKA KUKICH  
02/16/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 22-320/S-002**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use EPIDUO Gel safely and effectively. See full prescribing information for EPIDUO Gel.**

**EPIDUO® (adapalene and benzoyl peroxide) Gel 0.1% / 2.5%  
For topical use**

**Initial U.S. Approval: 2008**

**INDICATIONS AND USAGE**

EPIDUO gel is a combination of adapalene, a retinoid, and benzoyl peroxide, and is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older. (1)

**DOSAGE AND ADMINISTRATION**

EPIDUO gel is not for oral, ophthalmic, or intravaginal use. (2)  
Apply a thin film of EPIDUO gel to affected areas of the face and/or trunk once daily after washing. Use a pea sized amount for each area of the face (e.g., forehead, chin, each cheek). Avoid the eyes, lips and mucous membranes. (2)

**DOSAGE FORMS AND STRENGTHS**

Each gram of EPIDUO gel contains 1 mg (0.1%) adapalene and 25 mg (2.5%) benzoyl peroxide. (3)

**CONTRAINDICATIONS**

None. (4)

**WARNINGS AND PRECAUTIONS**

Ultraviolet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided. (5.1)

Erythema, scaling, dryness, stinging/burning, irritant and allergic contact dermatitis may occur with use of EPIDUO gel and may necessitate discontinuation. (5.2)

**ADVERSE REACTIONS**

-Most commonly reported adverse events ( $\geq 1\%$ ) in patients treated with EPIDUO gel were dry skin, contact dermatitis, application site burning, application site irritation and skin irritation. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved product labeling.**

**Revised: 06/2011**

**FULL PRESCRIBING INFORMATION: CONTENTS\***

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
  - 5.1 Ultraviolet Light and Environmental Exposure
  - 5.2 Local Cutaneous Reactions
- 6 ADVERSE REACTIONS
  - 6.1 Clinical Studies Experience
  - 6.2 Postmarketing Experience
- 7 DRUG INTERACTIONS
- 8 USE IN SPECIFIC POPULATIONS
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers
  - 8.4 Pediatric Use
  - 8.5 Geriatric Use

- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
  - 12.1 Mechanism of Action
  - 12.2 Pharmacodynamics
  - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
  - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION

**\*Sections or subsections omitted from the full prescribing information are not listed.**

**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

EPIDUO gel is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

**2 DOSAGE AND ADMINISTRATION**

For topical use only; EPIDUO gel is not for oral, ophthalmic, or intravaginal use.

Apply a thin film of EPIDUO gel to affected areas of the face and/or trunk once daily after washing. Use a pea sized amount for each area of the face (e.g., forehead, chin, each cheek). Avoid the eyes, lips and mucous membranes.

**3 DOSAGE FORMS AND STRENGTHS**

Each gram of EPIDUO gel contains 1 mg (0.1%) adapalene and 25 mg (2.5%) benzoyl peroxide in a white to very pale yellow, opaque, aqueous based gel.

**4 CONTRAINDICATIONS**

None

**5 WARNINGS AND PRECAUTIONS**

**5.1 Ultraviolet Light and Environmental Exposure**

Exposure to sunlight, including sunlamps, should be minimized during the use of EPIDUO gel. Patients with high levels of sun exposure and those with inherent sensitivity to sun should exercise particular caution. Use of sunscreen products and protective apparel, (e.g., hat) are recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, may be irritating to patients under treatment with EPIDUO gel.

**5.2 Local Cutaneous Reactions**

Erythema, scaling, dryness, and stinging/burning may be experienced with use of EPIDUO gel. These are most likely to occur during the first four weeks of treatment, are mostly mild to moderate in intensity, and usually lessen with continued use of the medication. Irritant and allergic contact dermatitis may occur. Depending upon the severity of these adverse reactions, patients should be instructed to use a moisturizer, reduce the frequency of the application of EPIDUO gel, or discontinue use. The product should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, use of “waxing” as a depilatory method should be avoided on skin treated with EPIDUO gel. Avoid concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have strong skin drying effect and products with high concentrations of alcohol, astringents, spices, or limes).

**6 ADVERSE REACTIONS**

**6.1 Clinical Studies Experience**

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

During clinical trials, 1401 subjects were exposed to EPIDUO gel. A total of 1036 subjects with acne vulgaris, 12 years and older, were treated once daily for 12 weeks to 12 months. Related adverse events reported within 12 weeks of treatment and in at least 1% of subjects treated with EPIDUO gel and those reported in subjects treated with the vehicle gel are presented in Table 1:

**Table 1 Drug Related Adverse Events Reported in Clinical Trials by At Least 1% of Patients Treated For 12 Weeks**

System Organ Class/ Preferred Term	EPIDUO gel N = 564	Vehicle gel N = 489
Subjects with AE (s)	14%	4%
Dry Skin	7%	2%
Contact dermatitis	3%	<1%
Application site burning	2%	<1%
Application site irritation	1%	<1%
Skin irritation	1%	0%

Local tolerability evaluations, presented in Table 2, were conducted at each study visit in clinical trials by assessment of erythema, scaling, dryness, burning, and stinging.

**Table 2 Incidence of Local Cutaneous Irritation in Controlled Clinical Trials (N = 553)**

	Maximum Severity During Treatment			End of Treatment Severity (12 Weeks)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	27%	13%	1%	8%	2%	1%
Scaling	35%	11%	1%	9%	1%	<1%
Dryness	41%	13%	1%	10%	2%	<1%
Stinging/burning	41%	15%	3%	7%	2%	1%

Analysis over the 12 week period showed that local tolerability scores for erythema, scaling, dryness, and stinging/burning peaked at Week 1 of therapy and decreased thereafter.

**6.2 Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of EPIDUO Gel: eyelid edema, sunburn, blister, pain of skin, pruritus, swelling face, conjunctivitis, skin discoloration, rash, eczema, throat tightness and allergic contact dermatitis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**7 DRUG INTERACTIONS**

Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

No formal drug drug interaction studies were conducted with EPIDUO gel.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. There are no well controlled trials in pregnant women treated with EPIDUO gel. Animal reproduction studies have not been conducted with the combination gel or benzoyl peroxide. Furthermore, such studies are not always predictive of human response; therefore, EPIDUO gel should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day, up to 25 times (mg/m<sup>2</sup>/day) the maximum recommended human dose (MRHD) of 2 grams of EPIDUO gel. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of ≥ 25 mg adapalene/kg/day representing 123 and 246 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele and skeletal abnormalities in rats; and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6 to 6.0 mg adapalene/kg/day [25 to 59 times (mg/m<sup>2</sup>) the MRHD] exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

### 8.3 Nursing Mothers

It is not known whether adapalene or benzoyl peroxide is excreted in human milk following use of EPIDUO gel. Because many drugs are excreted in human milk, caution should be exercised when EPIDUO gel is administered to a nursing woman.

### 8.4 Pediatric Use

Safety and effectiveness of EPIDUO gel in pediatric patients under the age of 12 have not been established.

### 8.5 Geriatric Use

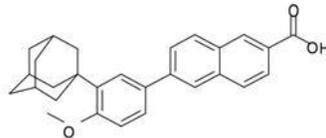
Clinical studies of EPIDUO gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

## 11 DESCRIPTION

EPIDUO (adapalene and benzoyl peroxide) gel, 0.1%/2.5% is a white to very pale yellow, opaque gel for topical use containing adapalene 0.1% and benzoyl peroxide 2.5%.

Adapalene, a synthetic retinoid, is a naphthoic acid derivative with retinoid like properties. The chemical name for adapalene is (6 [3 (1 adamantlyl) 4 methoxyphenyl] 2 naphthoic acid). It has the following structural formula:

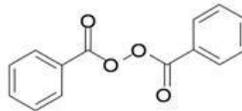
Adapalene:



Molecular formula: C<sub>28</sub>H<sub>28</sub>O<sub>3</sub> Molecular weight: 412.5

Benzoyl Peroxide is a highly lipophilic oxidizing agent that localizes in both bacterial and keratinocyte cell membranes. The chemical name for benzoyl peroxide is dibenzoyl peroxide. It has the following structural formula:

Benzoyl Peroxide:



Molecular formula: C<sub>14</sub>H<sub>10</sub>O<sub>4</sub> Molecular weight: 242.23

EPIDUO gel contains the following inactive ingredients: acrylamide/sodium acryloyldimethyltaurate copolymer, docusate sodium, edetate disodium, glycerin, isohexadecane, poloxamer 124, polysorbate 80, propylene glycol, purified water, and sorbitan oleate.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

#### 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.

### 12.2 Pharmacodynamics

Pharmacodynamics of EPIDUO gel is unknown.

### 12.3 Pharmacokinetics

A pharmacokinetic study was conducted in 24 subjects with acne vulgaris who were treated once daily for 30 days with 2 grams/day of EPIDUO gel applied to 1000 cm<sup>2</sup> 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<sub>max</sub> and AUC<sub>0-24h</sub> was 0.21 ng/mL and 1.99 ng•h/mL, respectively. Excretion of adapalene appears to be primarily by the biliary route.

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

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No carcinogenicity, photocarcinogenicity, genotoxicity, or fertility studies were conducted with EPIDUO gel. Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m<sup>2</sup>/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m<sup>2</sup>/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of EPIDUO gel. In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed.

No significant increase in tumor formation was observed in rodents topically treated with 15 25% benzoyl peroxide carbopol gel (6 10 times the concentration of benzoyl peroxide in EPIDUO gel) for two years. Rats received maximum daily applications of 138 (males) and 205 (females) mg benzoyl peroxide/kg. In terms of body surface area, these levels are 27 40 times the MRHD. Similar results were obtained in mice topically treated with 25% benzoyl peroxide carbopol gel for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide carbopol gel for rest of the 2 years study period, and in mice topically treated with 5% benzoyl peroxide carbopol gel for two years.

The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. However, the significance of this finding in humans is unknown.

In a photocarcinogenicity study conducted with 5% benzoyl peroxide carbopol gel, no increase in UV induced tumor formation was observed in hairless mice topically treated for 40 weeks.

No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects *in vitro* (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or *in vivo* (mouse micronucleus test).

Bacterial mutagenicity assays (Ames test) with benzoyl peroxide has provided mixed results, mutagenic potential was observed in a few but not in a majority of investigations. Benzoyl peroxide has been shown to produce single strand DNA breaks in human bronchial epithelial and mouse epidermal cells, it has caused DNA protein cross links in the human cells, and has also induced a dose dependent increase in sister chromatid exchanges in Chinese hamster ovary cells.

In rat oral studies, 20 mg adapalene/kg/day (120 mg/m<sup>2</sup>/day; 98 times the MRHD based on mg/m<sup>2</sup>/day comparison) did not affect the reproductive performance and fertility of F<sub>0</sub> males and females, or growth, development and reproductive function of F<sub>1</sub> offspring.

No fertility studies were conducted with benzoyl peroxide.

**14 CLINICAL STUDIES**

The safety and efficacy of EPIDUO gel applied once daily for the treatment of acne vulgaris were assessed in two 12 week, multicenter, controlled clinical studies of similar design, comparing EPIDUO gel to the gel vehicle in acne subjects. Treatment response was defined as the percent of subjects who had a two grade improvement and rated 'Clear' and 'Almost Clear' at Week 12 based on the Investigator's Global Assessment (IGA) and mean absolute change from baseline at Week 12 in both inflammatory and non-inflammatory lesion counts. An IGA score of 'Clear' corresponded to residual hyperpigmentation and erythema may be present. An IGA score of 'Almost Clear' corresponded to a few scattered comedones and a few small papules.

In Study 1, 517 subjects were randomized to EPIDUO gel, adapalene 0.1% in vehicle gel, benzoyl peroxide 2.5% in vehicle gel, or vehicle gel. The median age of these 517 subjects was 15 years old and 60% were males.

At baseline subjects had between 20 to 50 inflammatory lesions and 30 to 100 non-inflammatory lesions. The majority of subjects had a baseline IGA score of 'Moderate' which corresponded to more than half of the face is involved, many comedones, papules and pustules. The efficacy results at week 12 are presented in Table 3.

In Study 2, 1668 subjects were randomized to EPIDUO gel, adapalene 0.1% in vehicle gel, benzoyl peroxide 2.5% in vehicle gel, or vehicle gel. The median age of subjects was 16 years old and 49% were males. At baseline subjects had between 20 to 50 inflammatory lesions and 30 to 100 non-inflammatory lesions as well as an Investigator Global Assessment score of 'Moderate'. The efficacy results at week 12 are presented in Table 3.

**Table 3: Clinical Efficacy of EPIDUO Gel at Week 12**

<b>Study 1</b>				
	EPIDUO gel (N 149)	Adapalene 0.1% in Vehicle gel (N 148)	Benzoyl Peroxide 2.5% in Vehicle gel (N 149)	Vehicle gel (N 71)
IGA: Two Grade Improvement and Clear or Almost Clear	32 (21.5%)	18 (12.2%)	18 (12.1%)	4 (5.6%)
Inflammatory Lesions: Mean Absolute (Percent) Change	16.0 (52.4%)	11.4 (39.9%)	10.5 (35.8%)	9.5 (31.8%)
Non-inflammatory Lesions: Mean Absolute (Percent) Change	23.4 (45.9%)	15.2 (29.6%)	13.7 (32.2%)	13.2 (27.8%)

<b>Study 2</b>
----------------

	EPIDUO gel (N 415)	Adapalene 0.1% in Vehicle gel (N 420)	Benzoyl Peroxide 2.5% in Vehicle gel (N 415)	Vehicle gel (N 418)
IGA: Two Grade Improvement and Clear or Almost Clear	125 (30.1%)	83 (19.8%)	92 (22.2%)	47 (11.3%)
Inflammatory Lesions: Mean Absolute (Percent) Change	15.4 (53.4%)	12.3 (41.7%)	13.7 (47.6%)	8.7 (30.2%)
Non inflammatory Lesions: Mean Absolute (Percent) Change	24.6 (48.1%)	21.0 (40.8%)	19.2 (37.2%)	11.3 (23.2%)

In both Studies 1 and 2 the treatment effect was smaller in subjects with a small number of baseline lesions than in subjects with a large number of baseline lesions.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

EPIDUO (adapalene and benzoyl peroxide) gel 0.1% / 2.5% is white to very pale yellow in color and opaque in appearance, and is supplied as follows:

- 45 gram tube NDC 0299 5908 45
- 45 gram pump NDC 0299 5908 25

Storage and handling

- Store at 25°C; excursions permitted to 15° 30°C (59° 86°F).
- Protect from light.
- Keep out of reach of children.
- Keep away from heat.
- Keep tube tightly closed.

**17 PATIENT COUNSELING INFORMATION**

[See FDA Approved Patient Labeling (Patient Information)]

Information for Patients

Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply EPIDUO gel as a thin layer, avoiding the eyes, lips and mucous membranes.

Advise patients not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.

EPIDUO gel may cause irritation such as erythema, scaling, dryness, stinging or burning.

Advise patients to minimize exposure to sunlight, including sunlamps.

Recommend the use of sunscreen products and protective apparel, (e.g., hat) when exposure cannot be avoided.

EPIDUO gel may bleach hair and colored fabric.

Patient Information  
EPIDUO® (Ep-E-Do-Oh)  
(adapalene and benzoyl peroxide)  
gel 0.1%/2.5%

**Important:** For use on the skin only (topical). Do not use EPIDUO gel in or on your mouth, eyes, or vagina.

Read this Patient Information leaflet about EPIDUO gel before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your treatment or your medical condition. If you have any questions about EPIDUO gel, talk with your doctor or pharmacist.

**What is EPIDUO gel?**

EPIDUO gel is a prescription medicine for skin use only (topical) used to treat acne vulgaris in people 12 years of age and older.

Acne vulgaris is a condition in which the skin has blackheads, whiteheads and pimples.

It is not known if EPIDUO gel is safe and effective in children younger than 12 years old.

**What should I tell my doctor before using EPIDUO gel?**

Before you use EPIDUO gel, tell your doctor if you:

- have other skin problems, including cuts or sunburn
- have any other medical conditions
- are pregnant or planning to become pregnant. It is not known if EPIDUO gel can harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if EPIDUO gel passes into your breast milk and if it can harm your baby. Talk to your doctor about the best way to feed your baby if you use EPIDUO gel.

**Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements.

Especially tell your doctor if you use any other medicine for acne. Using EPIDUO gel with topical medicines that contain sulfur, resorcinol or salicylic acid may cause skin irritation.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

**How should I use EPIDUO gel?**

- Use EPIDUO gel exactly as your doctor tells you to use it. EPIDUO gel is for skin use only. Do not use EPIDUO gel in or on your mouth, eyes, or vagina.
- Apply EPIDUO gel 1 time a day.
- Do not use more EPIDUO gel than you need to cover the treatment area. Using too much EPIDUO gel or using it more than 1 time a day may increase your chance of skin irritation.

**Applying EPIDUO gel:**

- Wash the area where the gel will be applied with a mild cleanser and pat dry.
- EPIDUO gel comes in a tube and a pump. If you have been prescribed the:
  - Tube: Squeeze a small amount (about the size of a pea) of EPIDUO gel onto your fingertips and spread a thin layer over the affected area.
  - Pump: Depress the pump to dispense a small amount (about the size of a pea) of EPIDUO gel and spread a thin layer over the affected area.

**What should I avoid while using EPIDUO gel?**

- You should avoid spending time in sunlight or artificial sunlight, such as tanning beds or sunlamps. EPIDUO gel can make your skin sensitive to sun and the light from tanning beds and sunlamps. You should wear sunscreen and wear a hat and clothes that cover the areas treated with EPIDUO gel if you have to be in sunlight.
- You should avoid weather extremes such as wind and cold as this may cause irritation to your skin.
- You should avoid applying EPIDUO gel to cuts, abrasions and sunburned skin.
- You should avoid skin products that may dry or irritate your skin such as harsh soaps, astringents, cosmetics that have strong skin drying effects and products containing high levels of alcohol.
- You should avoid the use of “waxing” as a hair removal method on skin treated with EPIDUO gel.
- EPIDUO gel may bleach your clothes or hair. Allow EPIDUO gel to dry completely before dressing to prevent bleaching of your clothes.

**What are the possible side effects of EPIDUO gel?**

EPIDUO gel may cause serious side effects including:

- Local skin reactions. Local skin reactions are most likely to happen during the first 4 weeks of treatment and usually lessen with continued use of EPIDUO gel. Signs and symptoms of local skin reaction include:
  - Redness
  - Dryness
  - Swelling
  - Scaling
  - Stinging or burning

Tell your doctor right away if these side effects continue for longer than 4 weeks or get worse, you may have to stop using EPIDUO gel.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of EPIDUO gel. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to GALDERMA LABORATORIES, L.P. at 1-866-735-4137

**How should I store EPIDUO gel?**

- Store EPIDUO gel at room temperature, 68° – 77° F (20° – 25° C)
- Keep EPIDUO gel inside container and out of light and away from heat.

**Keep EPIDUO gel and all medicines out of the reach of children.**

**General information about EPIDUO gel**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use EPIDUO gel for a condition for which it was not prescribed. Do not give EPIDUO gel to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about EPIDUO gel. If you would like more information, talk with your doctor. You can also ask your doctor or pharmacist for information about EPIDUO gel that is written for health professionals.

**What are the ingredients in EPIDUO gel?**

Active ingredient: adapalene and benzoyl peroxide

Inactive ingredients: acrylamide/sodium acryloyldimethyltaurate copolymer, docusate sodium, edetate disodium, glycerin, isohexadecane, polaxamer 124, polysorbate 80, propylene glycol, purified water and sorbitan oleate

Revised: June 2011

Marketed by:  
GALDERMA LABORATORIES, L.P., Fort Worth, Texas 76177 USA  
Manufactured by:  
Galderma Production Canada Inc., Baie d’Urfé, QC, H9X 3S4 Canada  
Made in Canada.  
GALDERMA is a registered trademark.  
XXXXX X

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-320/S-002**

**MEDICAL REVIEW(S)**

## Third Addendum to Medical Officer's Review of NDA 22-320

**Supporting Document #:** 20  
**Correspondence date:** Aug 16, 2010  
**CDER Stamp date:** Aug 19, 2010  
**Sponsor:** Galderma  
**Drug:** Epiduo Gel  
**Route of Administration:** topical  
**Active Ingredient(s):** Adapalene 0.1% /  
Benzoyl peroxide 2.5% Topical Gel  
**Dosage Form:** gel

**Pharmacologic Category:**  
retinoid/oxidizing agent  
**Proposed Indication:** Acne Vulgaris  
**Review start date:** Dec 5, 2011  
**Review completion date:** Dec 6, 2011  
**Reviewer:** Jane Liedtka  
**Team Leader:** Jill Lindstrom  
**Project Manager:** Dawn Williams

### REGULATORY BACKGROUND

Epiduo Gel, a new combination of Adapalene 0.1% and Benzoyl peroxide 2.5% was originally approved for the topical treatment of acne vulgaris in patients 12 years of age and older on Dec 8, 2008.

This document reviews S-2, a Prior Approval Labeling Supplement (PAS) [REDACTED] (b) (4)

[REDACTED] The first (S-1) contained changes to the Adverse Reactions section 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 contains information (including additions to the label) regarding the addition of a 45 gram pump. S-2 received a CR letter on Feb 16, 2011 which contained 9 deficiencies. A Type A Teleconference meeting was held on April 12, 2011 to discuss the CR letter. A complete response letter was received from the applicant on June 15, 2011. An IR letter was sent to the applicant on Oct 7, 2011, requesting further information. A response letter was received from the applicant on Oct 20, 2011. A teleconference was held on Nov 4, 2011 to discuss CMC's "concern about [REDACTED] (b) (4) [REDACTED]. A response letter was received from the applicant on November 18, 2011 addressing CMC's concerns. Another teleconference was held on Dec 1, 2011 to clarify this response.

### REVIEW

The annotated label provided by the sponsor for S-2 includes the addition of the 45 gram pump with its associated NDC number to Section 16 HOW SUPPLIED/STORAGE AND HANDLING.

The addition of the following statement is made to the Patient Information handout:

Pump: Depress the pump to dispense a small amount of EPIDUO Gel (about the size of a pea) and spread a thin layer over <sup>(b) (4)</sup> affected area <sup>(b) (4)</sup>

Reviewer's Comments

*These labeling changes are acceptable.*

CMC Review

The CMC review is pending at the time my review is closed.

DMEPA Review

The DMEPA reviewer recommended adding instructions for <sup>(b) (4)</sup> to the carton labeling, container labeling and the Patient Information section of the label.

Reviewer's Comments

<sup>(b) (4)</sup>

**Recommendation**

I recommend approval of this supplement pending a recommendation for approval by the CMC reviewer.

Jane Liedtka, M.D.  
Medical Officer/Dermatology

APPEARS THIS WAY IN ORIGINAL

-----  
**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  
12/14/2011

JILL A LINDSTROM  
12/16/2011

## Third Addendum to Medical Officer's Review of NDA 22-320

**Supporting Document #:** 20  
**Correspondence date:** Aug 16, 2010  
**CDER Stamp date:** Aug 19, 2010  
**Sponsor:** Galderma  
**Drug:** Epiduo Gel  
**Route of Administration:** topical  
**Active Ingredient(s):** Adapalene 0.1% /  
Benzoyl peroxide 2.5% Topical Gel  
**Dosage Form:** gel

**Pharmacologic Category:**  
retinoid/oxidizing agent  
**Proposed Indication:** Acne Vulgaris  
**Review start date:** Feb 1., 2011  
**Review completion date:** Feb 10, 2011  
**Reviewer:** Jane Liedtka  
**Team Leader:** Jill Lindstrom  
**Project Manager:** Dawn Williams

### REGULATORY BACKGROUND

This document reviews S-2, a Prior Approval Labeling Supplement (PAS) (b) (4)

The first (S-1) contained changes to the Adverse Reactions section and a new PPI for Epiduo Gel and was reviewed in a document entered into DARRTS on Dec 16, 2010. S-2 contains information (including additions to the label) regarding the addition of a 45 gram pump.

Epiduo Gel, a new combination of Adapalene 0.1% and Benzoyl peroxide 2.5% was originally approved for the topical treatment of acne vulgaris in patients 12 years of age and older on Dec 8, 2008.

### REVIEW

In Section 16 HOW SUPPLIED/STORAGE AND HANDLING the addition of a 45 GM pump NDC 0299-5908-25 is noted. In the patient information (FDA-Approved Patient labeling) the following sentences regarding the pump are included:

Pump: Depress the pump to dispense a small amount of EPIDUO Gel (about the size of a pea) and spread a thin layer over (b) (4) affected area (b) (4)

*Reviewer's Comments:*

*These additions to the labeling are acceptable.*

### CMC Review

The CMC reviewer stated the following "Critical deficiencies have been identified. Specifically, (b) (4) This supplement (S-002) is recommended as "not approval" with the outstanding deficiencies outlined in this review."

*Reviewer's Comments:*

*Though the clinical additions to the labeling are acceptable, given the deficiencies cited by the CMC reviewer I concur with their conclusion and recommend a complete response to this supplement.*

**Recommendation**

I recommend complete response for this supplement.

Jane Liedtka, M.D.  
Medical Officer/Dermatology

NDA 22-320

APPEARS THIS WAY IN  
ORIGINAL

-----  
**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  
02/10/2011

JILL A LINDSTROM  
02/15/2011

## Addendum to Medical Officer's Review of NDA 22-320

**Supporting Document #:** 20  
**Correspondence date:** Aug 16, 2010  
**CDER Stamp date:** Aug 19, 2010  
**Sponsor:** Galderma  
**Drug:** Epiduo Gel  
**Route of Administration:** topical  
**Active Ingredient(s):** Adapalene 0.1% /  
Benzoyl peroxide 2.5% Topical Gel  
**Pharmacologic Category:**  
retinoid/oxidizing agent  
**Dosage Form:** gel

**Proposed Indication:** Acne Vulgaris  
**Review start date:** Sept 29, 2010  
**Review completion date:** Sept 30, 2010  
**Review Revised:** Oct 13, 2010  
**Addendum date:** Nov 30, 2010  
**Reviewer:** Jane Liedtka  
**Team Leader:** Jill Lindstrom  
**Project Manager:** Dawn Williams

This document adds an addendum with additional changes to a Prior Approval Labeling Supplement (PAS) submitted by Galderma on Aug 16, 2010 that contained changes to the Adverse Reactions section and a new PPI for Epiduo Gel.

### **REGULATORY BACKGROUND**

Epiduo Gel, a new combination of Adapalene 0.1% and Benzoyl peroxide 2.5% was originally approved for the topical treatment of acne vulgaris in patients 12 years of age and older on Dec 8, 2008.

### **REVIEW**

All of the capitalized "GEL"s were changed to "gel" throughout the label.

### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

Under the "Highlights" section the following changes occurred since my original review (dated 10/13/10 in DARRTS):

1. EPIDUO gel is not for oral, ophthalmic, or intravaginal use. (2) was added to the DOSAGE AND ADMINISTRATION SECTION.
2. The phrases "irritant and allergic contact dermatitis" and "and may necessitate discontinuation" were added to the WARNINGS AND PRECAUTIONS section.
3. The phrase "and FDA-approved product labeling" was added to the last sentence.
4. The sentence "Observed local adverse reactions in patients treated with EPIDUO Gel were erythema, scaling, dryness, stinging, and burning" was replaced with the sentence "Most commonly reported adverse events ( $\geq 1\%$ ) in patients treated with EPIDUO gel were dry skin, contact dermatitis, application site burning, application site irritation and skin irritation. (6)" in the ADVERSE REACTIONS section.

5. The words [REDACTED] (b) (4) were removed from the ADVERSE REACTIONS section.
6. The section DRUG INTERACTIONS which read “Exercise caution in using preparations containing sulfur, resorcinol, or salicylic acid in combination with EPIDUO Gel. (7.1) Concomitant use of topical products with a strong drying effect can increase irritation. Use with caution. (7.1)” was removed from HIGHLIGHTS.

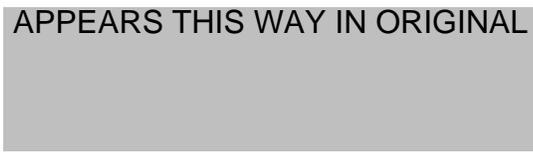
### **FULL PRESCRIBING INFORMATION**

Under the “FULL PRESCRIBING INFORMATION” section the following changes occurred since my original review (dated 10/13/10 in DARRTS):

1. Section [REDACTED] (b) (4) was removed from CONTENTS.
2. “For topical use only” was added to the DOSAGE AND ADMINISTRATION section.
3. “EPIDUO gel is not for oral, ophthalmic, or intravaginal use.” Was moved to the top of the DOSAGE AND ADMINISTRATION section.
4. The words “a white opaque” were added to the DOSAGE FORMS AND STRENGTHS section.
5. The sentence “Irritant and allergic contact dermatitis may occur.” was added to subsection 5.2.
6. The words “side effects” was changed to “adverse reactions” in subsection 5.2.
7. The word “studies” was changed to “trials” in the title of Table 2 under subsection 6.1.
8. The words “conjunctivitis, skin discoloration, rash, eczema, throat tightness” were added to subsection 6.2.
9. The sentence “EPIDUO Gel is a combination product for topical use containing adapalene (a synthetic retinoid) and benzoyl peroxide” was changed to “EPIDUO (adapalene and benzoyl peroxide) gel, 0.1%/2.5% is a white, opaque gel for topical use containing adapalene 0.1% and benzoyl peroxide 2.5%.” in section 11 DESCRIPTION.
10. The phrase “a synthetic retinoid” was added to section 11 DESCRIPTION.
11. The phrase “white and opaque in appearance, and is” was added to the HOW SUPPLIED/STORAGE AND HANDLING section.
12. The phrase “[See FDA Approved Patient Labeling (Patient Information)]” was added to the PATIENT COUNSELING INFORMATION section.
13. “Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents” was removed from the DRUG INTERACTIONS section.
14. Subsection [REDACTED] (b) (4) was removed.

### **PATIENT INFORMATION**

APPEARS THIS WAY IN ORIGINAL



-----  
**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  
11/30/2010

JILL A LINDSTROM  
12/16/2010

## Medical Officer's Review of NDA 22-320

**Supporting Document #:** 20  
**Correspondence date:** Aug 16, 2010  
**CDER Stamp date:** Aug 19, 2010  
**Sponsor:** Galderma  
**Drug:** Epiduo Gel  
**Route of Administration:** topical  
**Active Ingredient(s):** Adapalene 0.1% /  
Benzoyl peroxide 2.5% Topical Gel

**Pharmacologic Category:**  
retinoid/oxidizing agent  
**Proposed Indication:** Acne Vulgaris  
**Review start date:** Sept 29, 2010  
**Review completion date:** Sept 30, 2010  
**Review Revised:** Oct 13, 2010  
**Reviewer:** Jane Liedtka  
**Team Leader:** Jill Lindstrom  
**Project Manager:** Dawn Williams

**Dosage Form:** gel

This document reviews a BPCA safety review by OSE dated Aug 30, 2010 that contains labeling recommendations for Epiduo Gel. This document also includes review of a Prior Approval Labeling Supplement (PAS) [REDACTED] (b) (4)

### REGULATORY BACKGROUND

Epiduo Gel, a new combination of Adapalene 0.1% and Benzoyl peroxide 2.5% was originally approved for the topical treatment of acne vulgaris in patients 12 years of age and older on Dec 8, 2008.

### REVIEW

#### I. BPCA Safety Review by OSE

In accordance with the Pediatric Research Equity Act (PREA), 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. DPV was also asked to note any unlabeled events and to assess how the adverse events found in pediatrics compare to adults. In addition, DPV was asked to perform a literature review searching for case reports describing the use of benzoyl peroxide products and the adverse events of serious cutaneous reactions including severe local edema and possible anaphylaxis. DPV also performed a literature review searching for case reports describing the use of adapalene and the adverse events of serious cutaneous reactions including severe local edema and possible anaphylaxis.

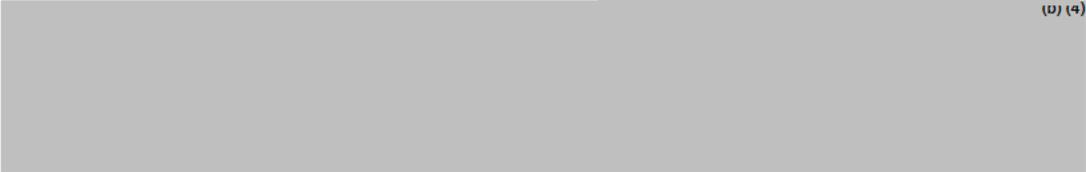
The Adverse Event Reporting System (AERS) database search for all reports of adverse events (serious and non-serious) up to the "data lock" date of June 22, 2010 retrieved

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.

There were three cases of hypersensitivity in pediatrics using Epiduo®, three cases of hypersensitivity in adults using Epiduo®, and one case of worsening acne in an adult using Epiduo®. There were three case reports of hypersensitivity reaction associated with benzoyl peroxide in the literature. (See Appendix A for details on these reports.)

DPV made the following recommendations for labeling changes for Epiduo based on this information:

1. Update the CONTRAINDICATIONS (Section 4) of the label to reflect that (b) (4)  

2. Update the POSTMARKETING EXPERIENCE (Section 6.2) of the Epiduo® label to include the following adverse events: (b) (4)  
(u) (4)  


*Reviewer's Comments:*

*I agree with DPV that information regarding the* (b) (4)  
(b) (4)  


II. Prior Approval Supplement

On Aug 16, 2010 Galderma submitted a PAS for Epiduo Gel (NDA22-320, SD#20) that contained CMC information regarding the addition of an alternate container closure system and Clinical information consisting of the following changes:

- The “HOW SUPPLIED” section of the revised package insert includes both the currently approved “45 gram (b) (4) tube” and the proposed “45 gram (b) (4)
- The trademark symbol “™” has been changed to a registered trademark ®
- Addition of a “FDA Approved Labeling” section
- Addition of section 6.2 on “Postmarketing Experience”
- Minor formatting changes

The terms (b) (4) have been added to the list of events in the ADVERSE REACTIONS section of highlights.

The “Postmarketing Experience” section of the label (I have highlighted in **BOLD** the events that are new to the ADVERSE REACTIONS section of this proposed version of the Epiduo label) includes the following statement:

The following adverse reactions have been identified during postapproval use of EPIDUO Gel: **eyelid edema, sunburn, blister, pain of skin, pruritus, swelling face and allergic contact dermatitis**. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Reviewer’s Comments:*

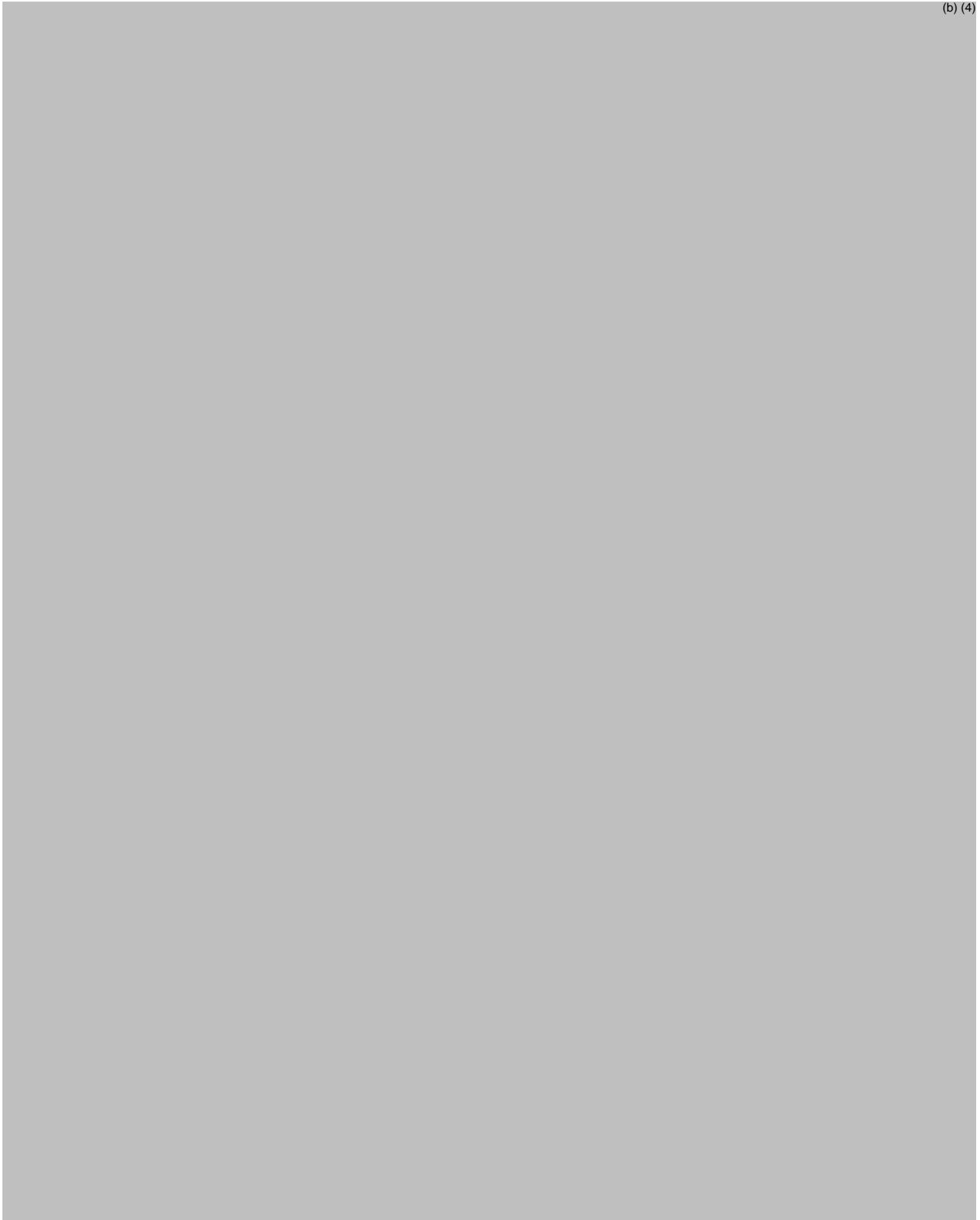
*In addition to the above (and in agreement with the recommendations of DPV) the following should be added to the list of events under the “Postmarketing Experience” subsection of ADVERSE REACTIONS: conjunctivitis, skin discoloration, rash, eczema and throat tightness.*

*Erythema is already listed as an adverse event under the “Clinical Trials” subsection of the ADVERSE REACTION section of the Epiduo label and therefore it is unnecessary to repeat it.*

*Under WARNINGS AND PRECAUTIONS the following statement should be added to highlights and the FPI:*

(b) (4)

The sponsor has added section 17.2 entitled “FDA Approved Labeling” section. I have made some revisions to improve readability which are provided below as “track changes”:



(b) (4)

### **Recommendations**

I recommend approval of the PAS pending sponsor agreement w/the above changes:

1. Including information regarding the (b) (4) in the WARNINGS AND PRECAUTIONS (W&P) and ADVERSE REACTIONS (AR) sections of the label.
2. The ADVERSE REACTIONS section of the Epiduo label should be augmented to include a Postmarketing Experience subsection.
3. The following should be added to the list of events under the “Postmarketing Experience” subsection of ADVERSE REACTIONS: conjunctivitis, skin discoloration, rash, eczema and throat tightness.
4. Under WARNINGS AND PRECAUTIONS the following statement should be added to highlights and the FPI:

(b) (4)

Jane Liedtka, M.D.  
Medical Officer/Dermatology

## **Appendix A**

### **Pediatric Cases**

#### Local Skin reaction/Hypersensitivity Reaction (n= 2)

1. ISR 6028720, Foreign (2009), Expedited: A pharmacist reported that a 15-year old male experienced irritation, itching, and facial erythema after applying Tactuoben (an adapalene and benzoyl peroxide combination available in Spain, produced by Galderma Labs) once daily to his face for two consecutive days for an unspecified indication. The medication was withdrawn and the outcome was resolved within one week “until complete disappearance of the adverse events.” At the time of the report, the patient had restarted the medication and was still suffering from non-severe inflammation. Concomitant medication included Acniben, a cosmetic product administered to decrease irritation.
2. ISR 6528946, Foreign (2009), Expedited: A dermatologist reported that a 16-year old female experienced erythema, papules, yellow erosive reaction, weeping and swelling 14 days after starting Epiduo® gel for acne. The medication was stopped and the patient was treated with Fucidin, a topical antibiotic, and Linola emulsion, a skin care product. Concomitant medications included lymecycline, a tetracycline antibiotic, and Lubex wash, a skin cleanser. The patient improved after five days of treatment.

#### Serious Cutaneous Reactions/Hypersensitivity Reaction (n=1)

3. ISR 6648537, Domestic (2010), Expedited: A consumer reported that a 16-year old female with a history of sensitive skin experienced erythema under her eyes, skin dryness, and increasing size of her pimples (“like boils”) approximately five days after starting Epiduo® gel, minocycline, and Cerave moisturizing lotion to treat acne. Seven days after beginning therapy, the patient experienced facial swelling and throat closing. Epiduo® was discontinued and the patient was treated with an unspecified antihistamine and ice. Her symptoms resolved after an unspecified period of time. The patient tried Epiduo® again on an unknown date and the events reoccurred. The reactions resolved in three days.

On July 19, 2010, The DPV reviewer followed-up with the reporter via telephone. She reported that the patient was not hospitalized as a result of the adverse events. The patient retried Epiduo® in an attempt to determine what may have caused her symptoms. After the retrial, the symptoms reoccurred with increasing severity. The patient was again treated with an unspecified antihistamine and missed days from school. She is presently still taking minocycline without incident.

*Reviewer's Comments:*

*None of the above reports resulted in hospitalization. Though the reports are convincing demonstrations of hypersensitivity (most likely of the Type IV contact hypersensitivity subtype), these reports do not present a compelling case for a "Serious Adverse Event" of the hypersensitivity type.*

Adult Cases

Serious Cutaneous Reactions/Hypersensitivity Reaction (n=3)

4. ISR 6211279, Foreign (2009), Expedited: A dermatologist reported that a 20-year old male applied Epiduo® once for an unspecified indication and developed extensive acute bullous eczema, vesicular eczema, eyelid edema, and an inability to open his eyes within 24 hours. The event abated after the gel was stopped; the patient recovered within one week.
5. ISR 6466138, Domestic (2009), Direct: A 24-year old female reported that she was prescribed Epiduo® application four times daily for acne. She reported sporadic use, but experienced edema and pruritus of her eyelid "within hours" of applying the gel. The symptoms resolved a few days after discontinuing the gel. A couple of weeks later, she reapplied the product and experienced eyelid edema, systemic pruritus, and a chest rash; the eventual outcome was not reported. Concomitant medications included tretinoin gel microsphere.
6. ISR 6510207, Foreign (2009), Expedited: A dermatologist reported that an 18-year old female applied Epiduo® once for acne. On the same day, she developed acute eczema of allergic type with edema associated with weeping and skin induration. Epiduo® was stopped. Three days later, the symptoms continued and the patient was unable to speak or swallow. She was treated with prednisolone, hydrating topical cream (Ictyane), and cold cream (Codexial). Seven days after the first application of Epiduo®, the eczema and edema had resolved with remaining crusts and skin pigmentation. Eight days after the initial application, the facial swelling had completely resolved. At an unspecified time, patch tests revealed a strong positive reaction with Epiduo® and with benzoyl peroxide (erythema, edema, vesicles, weeping, and pruritus) and a negative result with other ingredients including adapalene.

*Reviewer's Comments:*

*None of the above reports resulted in hospitalization. Though the reports are convincing demonstrations of hypersensitivity (most likely of the Type IV contact hypersensitivity subtype), these reports do not present a compelling case for a "Serious Adverse Event" of the hypersensitivity type.*

The seventh case of “worsening acne” is not relevant to this review and will not be discussed further.

Cases from the literature- Benzoyl Peroxide Hypersensitivity

1. Minciullo, P. L. Allergic contact angioedema to benzoyl peroxide. *Journal of Clinical Pharmacy and Therapeutics* (2006) 31, 385–387.

A 26-year-old woman with a history of acne and allergic contact dermatitis to nickel and no history of atopy, presented with an itchy erythematous reaction and strong edema localized to the face. Two weeks before angioedema she had started a new topical treatment with a gel containing 10% BP for acne. The patient was patch-tested to European Standard Series, including BP 1% in white petrolatum, and the 10% BP-containing gel previously used by herself. She showed positivity on day 2 to BP 1% (+++), 10% BP-containing gel (++) , nickel sulphate (+++) and Balsam of Peru (+). The patient showed complete resolution of symptoms after the drug was withdrawn.

2. Shwerek, C. et al. Delayed Type Hypersensitivity to Benzoyl Peroxide. *Journal of Drugs in Dermatology*. 2004. 3(2): 197-199.

A 52 year old man with a history of acne presented with an acute tender facial rash. He had applied for the first time an OTC BP 2.5% cream 48 hours before. He awoke the morning after the application with slight tenderness but applied the product again. Within hours he noted facial swelling and redness extending down his neck. He discontinued the product, self-medicated with oral Benadryl and presented to his physician. He denied shortness of breath, tongue swelling or difficulty swallowing.

3. Edwards, S.A. FRCS et al. Hypersensitivity to Benzoyl Peroxide in a Cemented Total Knee Arthroplasty Cement Allergy. *The Journal of Arthroplasty* Vol. 22 No. 8 2007. pp. 1226-1228.

We report a case history of a patient who developed a systemic reaction and intractable pain after a total knee arthroplasty who was subsequently shown to be hypersensitive to the benzoyl peroxide component of bone cement.

Total knee arthroplasty, without patellar resurfacing, was performed in a 48-year-old woman with end-stage osteoarthritis of the knee. At 6 weeks, the patient was complaining of generalized knee pain; and clinical examination revealed a swollen knee and skin rash over the right lower limb and anterior abdominal wall. The patient was also systemically unwell. Further investigations were carried out to investigate a possible allergy. She was found to have a severe allergy to benzoyl peroxide, an initiating agent that initiates the polymerization process, in the PMMA cement. The allergy was so severe that an ulcer developed under the test

skin patch. Because of continuing symptoms and the confirmation of the allergy, a decision was made to perform revision surgery.

*Reviewer's Comments:*

*None of the above reports resulted in hospitalization. Though the reports are convincing demonstrations of hypersensitivity (most likely of the Type IV contact hypersensitivity subtype), these reports do not present a compelling case for a "Serious Adverse Event" of the hypersensitivity type.*

---

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

---

/s/

---

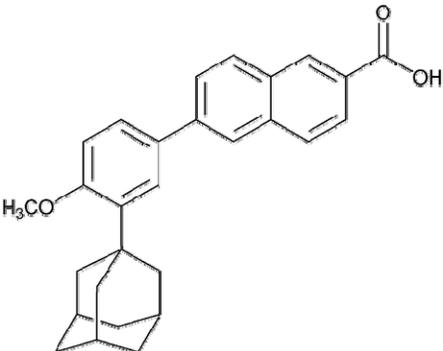
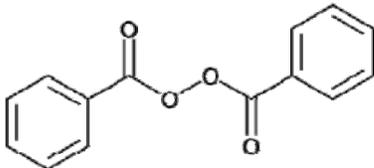
JANE E LIEDTKA  
10/13/2010

JILL A LINDSTROM  
10/27/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-320/S-002**

**CHEMISTRY REVIEW(S)**

<b>CHEMISTS REVIEW #2</b> Jeffrey B. Medwid, Ph.D.		<b>1. ORGANIZATION</b> ONDQA Div II, Branch VI and HFD-540	<b>2. NDA NUMBER</b> 22-320
<b>3. NAME AND ADDRESS OF APPLICANT</b> GALDERMA LABORATORIES, L.P. 14501 North Freeway Fort Worth, TX 76177		<b>4. COMMUNICATION, DATE</b> <b>Supplement #:S-002</b> , Response to 16-Feb-2011 CR Letter from FDA Letter Date: June 15, 2011 Received Date: June 15, 2011 Type: PAS PDUFA DATE: December 14, 2011	
<b>5. PROPRIETARY NAME</b>	<b>6. NAME OF THE DRUG</b>	<b>7. AMENDMENTS, REPORT, DATE</b>	
Epiduo	ADAPALENE 0.1% BENZOYL PEROXIDE 2.5% GEL	See first CMC Review for NDA 22-320 S-002 recommending non-approval by J. Medwid dated 08-Feb-2011. CR Letter sent to Applicant 16-Feb-2011	
<b>8. COMMUNICATION PROVIDES FOR:</b>			
The supplement provides alternate container/closure system – (b) (4)			
<b>9. PHARMACOLOGICAL CATEGORY</b>	<b>10. HOW DISPENSED</b>	<b>11. RELATED IND, NDA, DMF</b>	
ACNE VULGARIS	Rx		
<b>12. DOSAGE FORM</b>	<b>13. POTENCY</b>		
Gel	ADAPALENE 0.1% BENZOYL PEROXIDE 2.5%		
<b>14. CHEMICAL NAME AND STRUCTURE</b>			
<p><b>Adapalene</b> 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid, C<sub>28</sub>H<sub>28</sub>O<sub>3</sub>. 412.52</p>  <p><b>Benzoyl Peroxide</b>, C<sub>14</sub>H<sub>10</sub>O<sub>4</sub> (b) (4). 242.23 (b) (4).</p> 			
<b>15. COMMENTS</b>			

The supplement provides for an alternate container/closure system – (b) (4)

For administratively purposes, (b) (4)

Supplement S-001 provides for labeling changes which include addition of a “FDA Approved Labeling” section, addition of section 6.2 on “postmarketing Experience”, and some formatting changes. Supplement S-002 provides for the addition of an alternate container/closure system – (b) (4)

The first review for this supplement was reviewed and approved on 08-Feb-2011 recommending non approval. A CR letter (nine issues) was sent to the applicant on 16-Feb-2011.

The applicant requested a Type A Teleconference meeting, which was held on April 12, 2011 to discuss the CR letter dated 16-Feb-2011.

A complete response letter was received from the applicant on June 15, 2011. This CR letter was reviewed by this reviewer and it was determined to be a complete response to the 9 questions sent on 08-Feb-2011.

The applicant responses to the 9 questions followed by the reviewer comments are provided in the Reviewer Notes [Section \(A\) Entitled “Galderma June 15, 2011 response”](#) of this review. Not all responses were found to be acceptable and an IR letter was sent on October 7, 2011.

A response to the IR letter was received from the applicant on October 20, 2011. The applicant responses to those questions followed by the reviewer comments are provided in the Reviewer Notes [Section \(B\) Entitled “Galderma October 20, 2011 response”](#) of this review.

The October 20, 2011 response provided by Galderma prompted us to schedule a T-con (November 4, 2011) with Galderma regarding our concern about an (b) (4). A complete response letter was received from the applicant on November 18, 2011 addressing our concerns. The applicant responses to those questions followed by the reviewer comments are provided in the Reviewer Notes Entitled [Section \(C\) “Galderma November 18, 2011 response”](#) of this review.

To address further concerns on the (b) (4), a third T-con was held with Galderma on December 1, 2011 to clarify the November 18, 2011 response. The highlights of that meeting are provided in [Section \(D\) “Highlight Minutes from December 1, 2011 T-con with Galderma”](#).

Based on the applicant’s responses on June 15, 2011, October 20, 2011, November 18, 2011 and a teleconference discussion on December 1, 2011, this supplement was determined to be acceptable from a CMC point of view with acceptance of a post approval commitment (PMC).

**PMC:** The sponsor commits to develop and validate a revised method for the proposed Epiduo pump, which avoids unwarranted reporting of adapalene degradation products, during the first 6 months after the supplement (S-002) approval date. The sponsor will submit within 6 months after the S-002 approval date, a revised HPLC method with a complete method validation report

for adapalene degradants in the drug product.		
<b>16. CONCLUSION AND RECOMMENDATION</b>		
The supplement is recommended for approval from a CMC standpoint. See wording at end of this review for wording for post approval commitment to be added to the AP letter sent to the applicant.		
<b>17. NAME</b>	<b>18. REVIEWERS SIGNATURE</b>	<b>19. DATE COMPLETED</b>
Jeffrey B. Medwid	See appended electronic signature sheet	12-December-2011

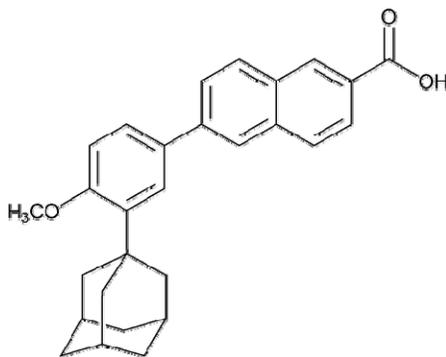
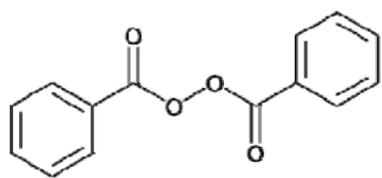
26 pages have been Withheld as b4 (CCI/TS) immediately following this page

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

/s/  
-----

JEFFREY B MEDWID  
12/12/2011

THOMAS F OLIVER  
12/12/2011

<b>CHEMISTS REVIEW #1</b> Jeffrey B. Medwid, Ph.D.		<b>1. ORGANIZATION</b> ONDQA Div II, Branch VI and HFD-540	<b>2. NDA NUMBER</b> 22-320
<b>3. NAME AND ADDRESS OF APPLICANT</b> GALDEMA LABORATORIES, L.P. 14501 North Freeway Fort Worth, TX 76177		<b>4. COMMUNICATION, DATE</b> Supplement #: S-001, S-002 Letter Date: August 16, 2010 Received Date: August 19, 2010 Type: Labeling, CMC CBE-30 PDUFA DATE: February 19, 2011	
<b>5. PROPRIETARY NAME</b>	<b>6. NAME OF THE DRUG</b>	<b>7. AMENDMENTS, REPORT, DATE</b>	
Epiduo	ADAPALENE 0.1% BENZOYL PEROXIDE 2.5% GEL	Amendments dated 09/30/2010 and 10/21/2010	
<b>8. COMMUNICATION PROVIDES FOR:</b>			
The supplement provides alternate container/closure system – (b) (4)			
<b>9. PHARMACOLOGICAL CATEGORY</b>	<b>10. HOW DISPENSED</b>	<b>11. RELATED IND, NDA, DMF</b>	
ACNE VULGARIS	Rx	DMF# (b) (4)	
<b>12. DOSAGE FORM</b>	<b>13. POTENCY</b>	<ul style="list-style-type: none"> <li>• Review of DMF # (b) (4) was reviewed by C. Kim and documented in DARRTS (date August 8, 2010).</li> <li>• Review of DMF (b) (4) was reviewed by A. Schroeder and documented in DARRTS (date November 23, 2010).</li> </ul>	
Gel	ADAPALENE 0.1% BENZOYL PEROXIDE 2.5%		
<b>14. CHEMICAL NAME AND STRUCTURE</b>			
<p><b>Adapalene</b> 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid, C<sub>28</sub>H<sub>28</sub>O<sub>3</sub>, 412.52</p>  <p><b>Benzoyl Peroxide</b>, C<sub>14</sub>H<sub>10</sub>O<sub>4</sub>, (b) (4), 242.23, (b) (4).</p> 			

**15. COMMENTS**

The supplement provides for an alternate container/closure system – (b) (4)

For administratively purposes, (b) (4)

Supplement S-001 provides for labeling changes which include addition of a “FDA Approved Labeling” section, addition of section 6.2 on “postmarketing Experience”, and some formatting changes. Supplement S-002 provides for the addition of an alternate container/closure system – (b) (4) The current approved container/closure system

The proposed alternate container/closure system is a (b) (4)

The proposed fill size for the (b) (4) pump configuration is 45 g. The following information was provided to support this new container/closure system:

(b) (4)

Critical deficiencies have been identified. (b) (4)

(b) (4)

This supplement (S-002) is recommended as “not approval” with the outstanding deficiencies outlined in this review.

**16. CONCLUSION AND RECOMMENDATION**

Recommend COMPLETE RESPONSE from CMC perspective. Project manager is to draft the letter shown at the end of this review.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Jeffrey B. Medwid	See appended electronic signature sheet	08-Feb.-2011

26 pages have been Withheld as b4 (CCI/TS) immediately following this page

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

/s/  
-----

JEFFREY B MEDWID  
02/08/2011

THOMAS F OLIVER  
02/08/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-320/S-002**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology Review

<b>NDA #</b>	22-320 (SDN 20)
<b>Submission Letter date (s)</b>	August 16 <sup>th</sup> , 2010
<b>Brand Name</b>	Epiduo Gel, 0.1 %/2.5 %
<b>Generic Name</b>	Adapalene and Benzoyl Peroxide
<b>Primary Reviewer</b>	Abimbola Adebowale, Ph.D.
<b>Team Leader</b>	Doanh Tran, Ph.D.
<b>Sponsor</b>	Galderma Laboratories
<b>OCP Division</b>	DCP 3
<b>OND division</b>	Division of Dermatology and Dental Products (DDDP)
<b>Submission Type</b>	Prior Approval Labeling Supplement
<b>Approved Indication</b>	Topical Treatment of Acne Vulgaris in Patients 12 Years of Age and Older

### Introduction:

This submission is a Prior Approval Labeling Supplement for the addition of an alternate container closure system and a revision of the labeling of Epiduo gel. Epiduo gel was approved December 8<sup>th</sup>, 2008 with Physician's Labeling Rule (PLR) Prescription Drug labeling. A description of the proposed changes to the label is as follows:

#### Alternate Container Closure System:

(b) (4)

#### Draft Labeling Revisions

- The "HOW SUPPLIED" section of the revised package insert includes both the currently approved "45 gram (b) (4) tube" and the proposed "45 gram (b) (4)
- The trade mark symbol "TM" has been changed to a registered trade mark "®"
- Addition of a "FDA Approved Labeling" section
- Addition of section 6.2 on "Postmarketing Experience"
- Minor formatting changes

It is noted that the applicant added a section (b) (4) as part of the revision to the label.

**Labeling Recommendations:** There are no proposed changes to the clinical pharmacology sections of the label. As per the recommendations of the Study Endpoints and Labeling (SEALD) team, the numbering of labeling subsections (b) (4)

**Signatories:**

\_\_\_\_\_  
Abimbola Adebawale, Ph.D.  
Senior Clinical Pharmacology Reviewer  
Division of Clinical Pharmacology 3  
Office of Clinical Pharmacology

Date: \_\_\_\_\_

\_\_\_\_\_  
Doanh Tran, Ph.D.  
Clinical Pharmacology Team Leader  
Division of Clinical Pharmacology 3  
Office of Clinical Pharmacology

Date: \_\_\_\_\_

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

/s/  
-----

ABIMBOLA O ADEBOWALE  
11/01/2010

DOANH C TRAN  
11/02/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-320/S-002**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: October 20, 2011

Reviewer(s): Cathy A. Miller, MPH, BSN, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, PharmD, Team Leader  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

Drug Name(s): Epiduo (Adapalene and Benzoyl Peroxide) Gel  
0.1%/2.5%

Application Type/Number: NDA 022320/S-002

Applicant/Sponsor: Galderma

OSE RCM #: 2011-2622

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates the addition of a pump delivery system and proposed labels and labeling for Epiduo (Adapalene and Benzoyl Peroxide) Gel, 0.1%/2.5% from a medication error perspective. Epiduo is currently available in the 0.1%/2.5% packaged in 45 gram tube. The proposed pump would be marketed in the same strength. Both containers (pump and tube) will co-exist on the market and have the same directions for use. The Division of Dermatology and Dental Products (DDDP) requested that DMEPA evaluate the proposed label and labeling submitted as a CMC supplement on June 15, 2011.

### 1.1 BACKGROUND OR REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proprietary name and proposed labels and labeling for Epiduo in OSE Review #2009-1395 dated November 26, 2008, finding the name acceptable and providing recommendations for revisions to labels and labeling.

Epiduo Gel 0.1%/2.5% was approved for NDA 022320 on December 8, 2008 incorporating recommendations provided in DMEPA's Epiduo labeling review.

On August 16, 2010, the Applicant submitted a Prior Approval Supplement (PAS) to the approved product, proposing to (b) (4) revise the labeling to add a postmarketing adverse event section to the package insert labeling (S-001). The supplement provides for a 45 gram commercial trade size of Epiduo Gel in an alternate container closure system consisting (b) (4)

On December 21, 2010, the FDA notified the Applicant that (b) (4) Supplement S-001 was (u) (4) to the labeling revision portion of the supplement (b) (4) and Supplement S-002 was (b) (4) to the addition of the 45 gram (u) (4) pump.

The Division of Risk Management (DRISK) conducted a Patient Labeling Review of the patient information section of the insert labeling for the proposed pump in OSE Review #2010-2052 dated November 12, 2010.

On February 22, 2011, Supplement S-001 was approved and a complete response letter for Supplement S-002 was issued citing CMC deficiencies in the submission.

On April 12, 2011 a Type A meeting was held between the Applicant and DDDP to discuss the deficiencies cited in FDA's February 22, 2011 complete response.

On June 15, 2011, the Applicant submitted an amendment to Prior Approval Supplement S-002 incorporating responses to the Agency's complete response deficiencies cited in the February 22, 2011 letter, and adding proposed container labels, carton labeling and revised package insert labeling to include reference to the proposed 45 gram pump.

### 1.2 PRODUCT INFORMATION

Epiduo gel is a combination of 0.1% Adapalene, a retinoid, and 2.5 % Benzoyl Peroxide, and is indicated for the topical treatment of Acne Vulgaris in patients twelve years of age

and older. A thin film of gel should be applied to the affected areas of the face and/or trunk once daily after washing using a pea-sized amount for each area of the face (e.g. forehead, chin and cheek).

Epiduo Gel is white to very pale yellow in color and opaque in appearance. Epiduo is supplied in a 45 gram tube and can be stored at 25°C.

## **2 METHODS AND MATERIALS REVIEWED**

Using Failure Mode and Effects Analysis<sup>1</sup>, the principals of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels and Carton Labeling submitted on June 15, 2011 (See Appendix B and C)
- Insert Labeling submitted on June 15, 2011 (No image)
- Sample of the proposed Epiduo Pump submitted April 14, 2011 (No image)
- Currently marketed Epiduo 45 gram Tube container labels and carton labeling retrieved from March 1, 2011 Annual Report (See Appendix D)

Additionally, DMEPA reviewed DRISK Patient Labeling recommendations provided in OSE Review #2010-2052 to assure our recommendation have been implemented in the revised labeling.

Since Epiduo is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Epiduo. The October 6, 2011 AERS search used the following search terms: active ingredient “Adapalene”, trade name “Epiduo”, and verbatim terms “Epiduo%” and “Adapalene%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. Because other products containing the active ingredients Adapalene and Benzoyl Peroxide, the time frame search was limited to December 8, 2008 (Epiduo approval date) to the present.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error or did not involve the product Epiduo.

## **3 DISCUSSION OF DEFICIENCIES IDENTIFIED**

The following summarizes our findings from the AERS search, product design comments and deficiencies identified for the proposed pump, container labels and carton labeling.

---

<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### 3.1 AERS RESULTS

Based on the search strategy and exclusion criteria identified in Section 2, no cases were identified for this product.

### 3.2 PRODUCT DESIGN OF THE PUMP DELIVERY SYSTEM

The introduction of the proposed pump delivery system is reasonable based on the dosage and administration of this product

(b) (4)

(b) (4)

We note that no information is provided regarding the

(b) (4)

The Applicant's submitted a Pump Functionality Testing Report (Document No. 1.BD.05.PMF.0025.R01) with the June 15, 2011 PAS (S-002) amendment, Sequence No. 0020. This report identifies that

(b) (4)

(b) (4)

We note that DRISK provided a similar recommendation in their Patient Labeling Review OSE Review #2010-2052 dated November 12, 2010.

### 3.3 CONTAINER LABELS AND CARTON LABELING

(b) (4)

### 3.4 INSERT LABELING

The Patient Information Section titled "Applying Epiduo Gel" does not include

(b) (4)

(also identified in DRISK OSE Review #2010-2052).

## 4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the addition of a pump closure system for this product line is acceptable. However, we find that the proposed labels and labeling introduce vulnerability that can lead to dosing confusion or medication errors due to lack of

(b) (4) We recommend the following:

### A. Container Label and Carton Labeling

(b) (4)

### B. Insert Labeling

(b) (4)

If you have further questions or need clarifications, please contact, Janet Anderson, OSE Project Manager, at 301-796-0675.

## 5 REFERENCES

### Previous OSE Reviews:

Smith, D. OSE Review #2008-1395 Epiduo Proprietary Name and Labeling Review dated November 26, 2009

Ford, L. OSE Review #2010-2052 Epiduo DRISK Patient Labeling Review dated November 12, 2010

### 1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

**APPENDICES**

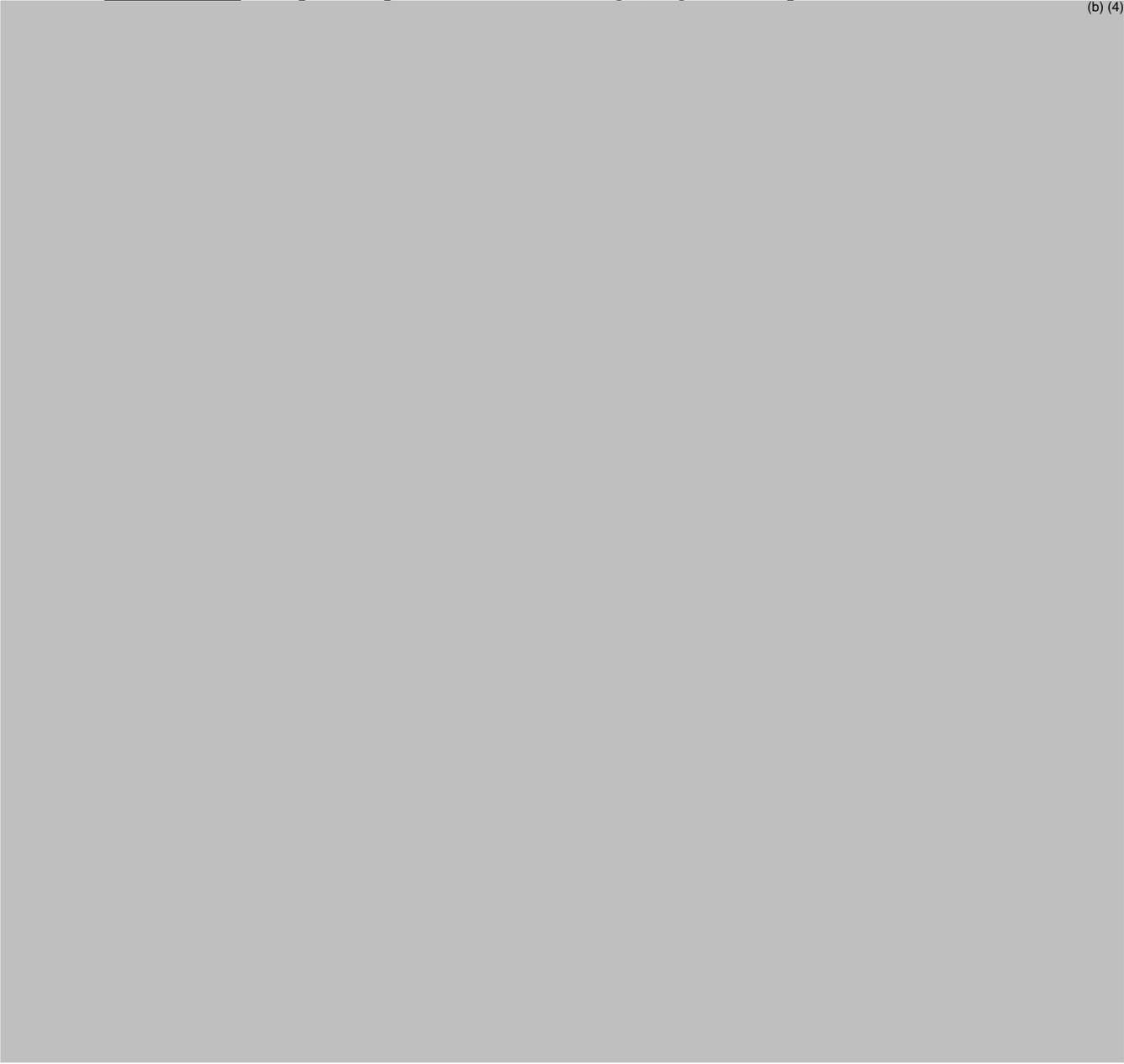
**Appendix A**: Proposed Epiduo Container Labeling (45 gram Pump)



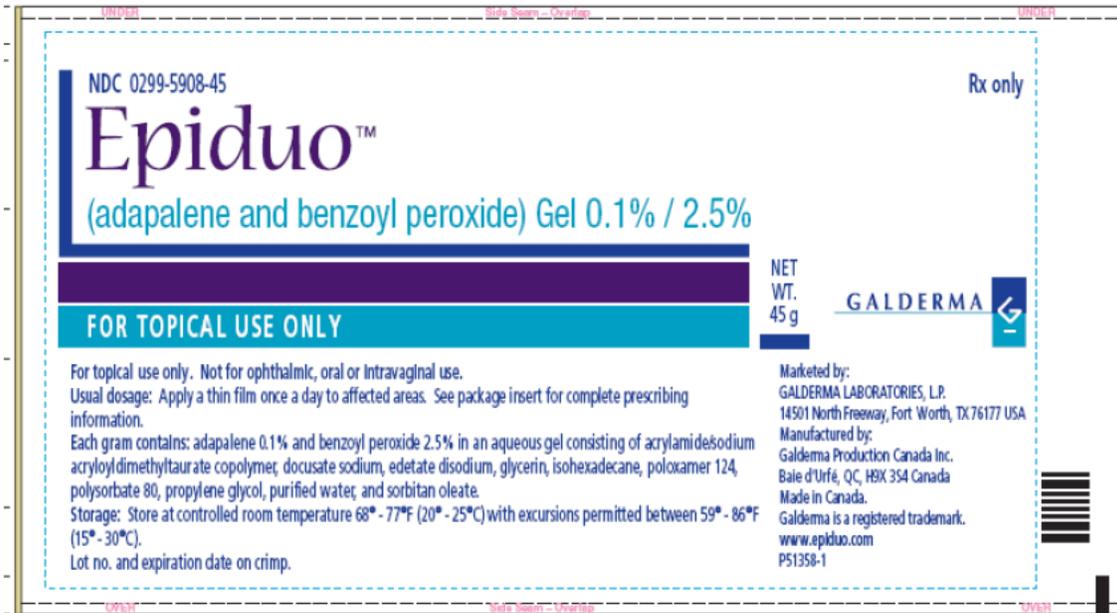
(b) (4)

**Appendix B:** Proposed Epiduo Carton Labeling (45 gram Pump)

(b) (4)



**Appendix C:** Currently marketed Epiduo Container Label (45 gram Tube)



The image shows a rectangular container label for Epiduo. At the top left, it displays 'NDC 0299-5908-45'. The product name 'Epiduo™' is prominently featured in a large, dark blue font, with '(adapalene and benzoyl peroxide) Gel 0.1% / 2.5%' written below it in a smaller, teal font. A dark blue horizontal bar contains the text 'FOR TOPICAL USE ONLY' in white. To the right of the bar, 'NET WT. 45 g' is printed. The Galderma logo, consisting of the word 'GALDERMA' and a stylized 'G' icon, is positioned to the right of the bar. Below the bar, there is a block of text providing usage instructions: 'For topical use only. Not for ophthalmic, oral or intravaginal use. Usual dosage: Apply a thin film once a day to affected areas. See package insert for complete prescribing information. Each gram contains: adapalene 0.1% and benzoyl peroxide 2.5% in an aqueous gel consisting of acrylamide/sodium acryloyl dimethyltaurate copolymer, docusate sodium, edetate disodium, glycerin, isohexadecane, poloxamer 124, polysorbate 80, propylene glycol, purified water, and sorbitan oleate. Storage: Store at controlled room temperature 68° - 77°F (20° - 25°C) with excursions permitted between 59° - 86°F (15° - 30°C). Lot no. and expiration date on crimp.' To the right of this text, it lists 'Marketed by: GALDERMA LABORATORIES, L.P. 14501 North Freeway, Fort Worth, TX 76177 USA' and 'Manufactured by: Galderma Production Canada Inc. Baie d'Urfé, QC, H9X 3S4 Canada Made in Canada. Galderma is a registered trademark. www.epiduo.com P51358-1'. The label also features a barcode on the right side. The entire label is enclosed in a dashed blue border.

(b) (4)

**Appendix D:** Currently marketed Epiduo Carton Labeling (45 gram Tube)

**Epiduo™**  
(adapalene and benzoyl peroxide) Gel 0.1% / 2.5%

**FOR TOPICAL USE ONLY**

**Epiduo™**  
(adapalene and benzoyl peroxide) Gel 0.1% / 2.5%

**NET WT. 45 g**

**GALDERMA**

NDC 0299-5908-45  
Rx only

**GALDERMA**

**Epiduo™**  
(adapalene and benzoyl peroxide) Gel 0.1% / 2.5%

For topical use only. Not for ophthalmic, oral or intravaginal use.  
Usual dosage: Apply a thin film once a day to affected areas. See package insert for complete prescribing information.  
Each gram contains: adapalene 0.1% and benzoyl peroxide 2.5% in an aqueous gel consisting of acrylamide/sodium acryloyldimethylsulfate copolymer, docusate sodium, edetate disodium, glycerin, isohexadecane, poloxamer 124, polysorbate 80, propylene glycol, purified water, and sorbitan oleate.  
Storage: Store at controlled room temperature 68° - 77°F (20° - 25°C) with excursions permitted between 59° - 86°F (15° - 30°C).

Marketed by:  
GALDERMA LABORATORIES, L.P.  
14501 North Freeway, Fort Worth, TX 76177 USA  
www.epiduo.com  
PS1359-1

Manufactured by:  
Galderma Production Canada Inc.  
Baie d'Urfe, QC, H9X 3S4 Canada  
Made in Canada.  
Galderma is a registered trademark.

3 02995 90845 4

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

/s/  
-----

CATHY A MILLER  
10/20/2011

ZACHARY A OLESZCZUK  
10/20/2011

CAROL A HOLQUIST  
10/20/2011

## ***MEMORANDUM***

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### **\*\*PRE-DECISIONAL AGENCY MEMO\*\***

---

**Date:** November 22, 2010

**To:** Dawn Williams, DDDP

**From:** Lynn Panholzer, PharmD, DDMAC  
Sheetal Patel, PharmD, DDMAC

**Re:** NDA# 022320  
Epiduo (adapalene and benzoyl peroxide) Gel 0.1%/2.5%

As requested in your consult dated September 21, 2010, DDMAC has reviewed the draft labeling for Epiduo (adapalene and benzoyl peroxide) Gel 0.1%/2.5%. DDMAC's comments are based on the proposed substantially complete, mark-up, version of the labeling found in the DDDP eRoom titled "sNDA 022320-001 Epiduo 11-15-2010 Labeling Meeting.doc" dated November 17, 2010.

DDMAC's comments are provided directly in the attached marked-up copy of the labeling.

If you have any questions about DDMAC's comments on the PI please contact Lynn Panholzer at 6-0616 or at [Lynn.Panholzer@fda.hhs.gov](mailto:Lynn.Panholzer@fda.hhs.gov). If you have any questions about our comments on the PPI please contact Sheetal Patel at 6-5167 or at [Sheetal.Patel@fda.hhs.gov](mailto:Sheetal.Patel@fda.hhs.gov).

9 pages have been Withheld as draft labeling  
b4 (CCI/TS) immediately following this page

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

/s/  
-----

LYNN M PANHOLZER  
11/22/2010

SHEETAL PATEL  
11/22/2010

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 22-320/S-002**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



NDA 22-320/S-002

**INFORMATION REQUEST**

Galderma Laboratories, L.P.  
Attention: Richard Almond, MBA, RAC  
Manager, Regulatory Affairs  
14501 North Freeway  
Fort Worth, Texas 76177

Dear Mr. Almond:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Epiduo<sup>®</sup> (adapalene and benzoyl peroxide) Gel, 0.1%/2.5%.

We also refer to your submissions dated May 17, 2011, and June 14, 2011.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) sections of your submission and have the following comments and information requests. We request your written response by November 2, 2011, in order to continue our evaluation of your supplemental application.

(b) (4)

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Dawn Williams, Regulatory Project Manager the Office of New Drugs (Dawn.Williams@fda.hhs.gov).

If you have any questions regarding this CMC letter, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Thomas F. Oliver, Ph.D.  
Branch Chief, Branch VI  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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

/s/  
-----

THOMAS F OLIVER  
10/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE/DMEPA</b> <b>Attention: Janet Anderson, RPM</b>		FROM: Dawn Williams, RPM, DDDP Jane Liedtka, Clinical Reviewer, DDDP		
DATE July 28, 2011	IND NO.	NDA NO. 022320/002	TYPE OF DOCUMENT Carton and container labels	DATE OF DOCUMENT June 14, 2011
NAME OF DRUG Epiduo (adapalene and benzoyl peroxide) Gel, 0.1%/2.5%	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti Acne Agent	DESIRED COMPLETION DATE October 20, 2011	
NAME OF FIRM:				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL BIOPHARMACEUTICS <input type="checkbox"/> IN VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: On June 14, 2011, DDDP received a resubmission in response to our February 16, 2011 Complete Response Letter for this pending Prior Approval Supplement. This supplement provides for the addition of a new 45 gm pump. DDDP is requesting that DMEPA review and provide recommendation on the corresponding carton and container labels for this 45 gm pump which are attached to this consult. Thank you!				
SIGNATURE OF REQUESTER Dawn Williams, RPM		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> EMAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND		

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

2 pages have been Withheld as draft labeling b4 (CCI/TS)  
immediately after this page

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

/s/  
-----

DAWN WILLIAMS  
07/28/2011