

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-320

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 only

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

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)

EPIDUO Gel is not for oral, ophthalmic, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Each gram of EPIDUO Gel contains 1 mg (0.1%) adapalene and 25 mg (2.5%) benzoyl peroxide in an aqueous based gel. (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, and stinging/burning may occur with use of EPIDUO Gel. (5.2)

ADVERSE REACTIONS

Observed local adverse reactions in patients treated with EPIDUO Gel were erythema, scaling, dryness, stinging, and burning. Other most commonly reported adverse events ($\geq 1\%$ in patients treated with EPIDUO Gel) were dry skin, contact dermatitis, application site burning, application site irritation, 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

DRUG INTERACTIONS

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)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2008

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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

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.

EPIDUO Gel is not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Each gram of EPIDUO Gel contains 1 mg (0.1%) adapalene and 25 mg (2.5%) benzoyl peroxide in an 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. Depending upon the severity of these side effects, 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 Studies (N=553) Treatment Emergent Signs and Symptoms

	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.

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 ($\text{mg}/\text{m}^2/\text{day}$) 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 0.6-6.0 mg adapalene/kg/day [25-59 times (mg/m^2) 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

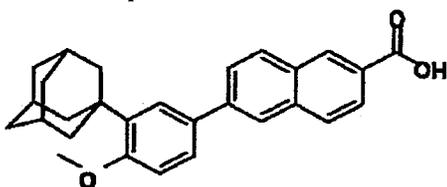
aged 65 and over to determine whether they respond differently from younger subjects

11 DESCRIPTION

EPIDUO Gel is a combination product for topical use containing adapalene (a synthetic retinoid) and benzoyl peroxide.

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

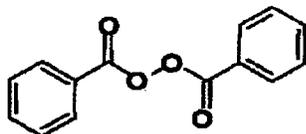
Adapalene:



Molecular formula: $C_{28}H_{28}O_3$ 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: $C_{14}H_{10}O_4$ Molecular weight: 242.23

EPIDUO Gel contains the following inactive ingredients: acrylamide/sodium acryloyldimethyltaurate copolymer, docusate sodium, edetate disodium, glycerin, isohehexadecane, 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 bacteriocidal 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 cm² of acne involved skin, (face, chest, and upper back). Two subjects (20%) had quantifiable adapalene plasma concentrations above the limit of quantification (LOQ=0.1ng/mL). The highest adapalene C_{max} and AUC_{0-24h} was 0.21 ng/mL and 1.99 ng·h/mL, respectively. Excretion of adapalene appears to be primarily by the biliary route.

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/m²/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/m²/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, 20mg adapalene/kg/day (120mg/m²/day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F0 males and females, or growth, development and reproductive function of F1 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

Study 1				
	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%)
Study 2				
	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	125 (30.1%)	83 (19.8%)	92 (22.2%)	47 (11.3%)

Clear				
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 supplied as follows:

45 gram tube NDC 0299-5908-45

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

- 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.

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

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(Part Number)

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/s/

Susan Walker
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