AUSTRALIAN PRODUCT INFORMATION – EPIDUO® (ADAPALENE AND BENZOYL PEROXIDE) GEL

1. NAME OF THE MEDICINE

Adapalene

Benzoyl peroxide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g of EPIDUO contains Adapalene 1mg (0.1%) and Benzoyl Peroxide 25 mg (2.5%).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Epiduo is a white to very pale-yellow opaque gel.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Cutaneous treatment of *acne vulgaris* on the face, chest and back when comedones, papules and pustules are present, and the condition has not responded to first line treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

EPIDUO should be applied to the entire acne affected areas once a day on a clean and dry skin. A thin film of gel should be applied, with the fingertips, avoiding the eyes, lips, and mucous membranes (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients should be instructed to wash their hands after applying EPIDUO. Cosmetics may be applied after EPIDUO has dried.

If irritation occurs, the patient should be directed to apply non-comedogenic moisturisers, to use the medication less frequently (e.g., every other day), to suspend use temporarily, or to discontinue use altogether.

The duration of treatment should be determined by the Doctor on the basis of the clinical condition. Early signs of clinical improvement usually appear after 1 to 4 weeks of treatment.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients.

Pregnancy.

Women planning a pregnancy.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified Precautions
EPIDUO is for external use only. EPIDUO should not be applied to damaged skin, either broken (cuts or abrasions), sunburnt or eczematous skin.

EPIDUO should not come into contact with the eyes, mouth, nostrils, or mucous membranes. If product enters the eye, wash immediately with warm water.

This product contains propylene glycol (E1520) that may cause skin irritation.

If a reaction suggesting sensitivity to any component of the formula occurs, the use of EPIDUO should be discontinued.

Excessive exposure to sunlight or UV radiation (e.g., sunlamps) should be avoided.

EPIDUO should not come into contact with any coloured material including hair and dyed fabrics as this may result in bleaching and discolouration.

Depending upon the severity of local cutaneous adverse reactions, patients should be instructed to use a moisturiser, reduce the frequency of the application of EPIDUO, or discontinue use.

As with other topical retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with EPIDUO.

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).

Use in the elderly
No data available.

Paediatric use
The safety and effectiveness of EPIDUO have not been studied in children below 12 years of age.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been conducted with EPIDUO.

From previous experience with adapalene and benzoyl peroxide, there are no known interactions with other medicinal products which might be used cutaneously and concurrently with EPIDUO. However, other retinoids or benzoyl peroxide or drugs with a similar mode of action should not be used concurrently. Caution should be exercised if cosmetics with desquamative, irritant or drying effects are used, as they may produce additive irritant effects with EPIDUO.

Absorption of adapalene through human skin is low (see Section 5.2 PHARMACOKINETIC PROPERTIES), and therefore interaction with systemic medicinal products is unlikely.

The percutaneous penetration of benzoyl peroxide in the skin is low and the drug substance is completely metabolised into benzoic acid which is rapidly eliminated. Therefore, the potential interaction of benzoic acid with systemic medicinal products is unlikely to occur.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Fertility testing of EPIDUO Gel has not been performed in any species.

Oral adapalene had no effect on the fertility of rats at doses up to 20 mg/kg/day (>500 times the maximum recommended human dose, based on C_{max}).

Benzoyl peroxide administered orally to male rats at 1 g/kg/day resulted in testicular atrophy; there was no effect on fertility in male rats at oral doses of 500 mg/kg/day or in female rats at 1 g/kg/day.

Use in pregnancy - Pregnancy Category D
Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result in low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g., damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

Animal embryofoetal developmental studies have not been conducted with EPIDUO Gel.

No adequate or well-controlled studies in pregnant women have been conducted with topical benzoyl peroxide. Benzoyl peroxide at oral doses of 1 g/kg/day resulted in lower birthweights of rat pups and lower pup body weight gain after birth; no reproductive toxicity was observed in rats at oral doses of 500 mg/kg/day benzoyl peroxide. It is unknown whether benzoyl peroxide can cause foetal harm when used by pregnant women.

Adapalene administered orally at high doses (≥ 25 mg/kg/day) to pregnant rats and rabbits was found to induce foetal abnormalities. In addition, the incidences of various skeletal variations were increased at lower oral doses in rats. Topical administration at doses up to 6 mg/kg, resulting in an exposure level ~230 times (based on C_{max}) that anticipated clinically, was not associated with teratogenicity. Nevertheless, increased incidences of various naturally occurring skeletal variations were still observed following topical administration to rats at 2mg/kg (C_{max} exposure ~60 times that anticipated clinically) and to rabbits at 6 mg/kg (C_{max} exposure ~76 times that anticipated clinically); topical no effect levels were 0.6 and 2mg/kg respectively (C_{max} exposure ~19 and 48 times that anticipated clinically).

There have been isolated reports of birth defects in babies born to women using topical drugs with a similar mechanism of action to adapalene during pregnancy. However, there are no adequate or well controlled studies in pregnant women. Because of the potential risk of adverse effects on foetal development, adapalene should not be used by women who are pregnant or who plan to become pregnant during treatment. In the case of unexpected pregnancy, treatment should be discontinued.

Use in lactation.
It is not known whether adapalene is distributed into human milk. After IV or oral administration, adapalene was excreted in rat milk. Oral treatment of rat dams with up to 15

mg/kg/day adapalene (300 times that anticipated clinically, based on C_{max}) after organogenesis and during lactation was not associated with adverse effects on functional development of rat pups. It is unknown whether benzoyl peroxide or its metabolite benzoic acid is distributed into breast milk. Benzoyl peroxide has not been reported to cause problems in breastfed babies. EPIDUO should be used with caution in breastfeeding women, and to avoid contact exposure of the infant, application of EPIDUO should only be used on areas away from the chest when used during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

EPIDUO has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

EPIDUO may cause the following adverse reactions, ranked in the table below by frequency and within each frequency grouping by decreasing medical seriousness.

If skin irritation appears after application of EPIDUO, the intensity is generally mild or moderate, with local tolerability signs and symptoms [erythema, dryness, scaling, burning[1] and pain of skin (including stinging)] peaking during the first two weeks and then subsiding spontaneously.

[1] Cases of application site burn included superficial burns, second degree burns and severe burn reactions.

Tabulated summary of adverse reactions

The adverse reactions are classified by System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to 1<100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data) and were reported with Epiduo in clinical studies.

Table 1: Adverse Events Reported in Clinical Studies and Post-Marketing Surveillance.

Body System (MedDRA)	***Frequency***	***Adverse Drug Reaction***
Eye disorders	Not known*	Eyelid oedema
Respiratory, thoracic and mediastinal disorders	Not known*	Throat tightness, dyspnoea[2]
Skin and subcutaneous tissue disorders	Common	Irritative contact dermatitis, skin burning sensation, dry skin, skin irritation, erythema, skin exfoliation (scaling)
	Uncommon	Pruritus, sunburn
	Not known*	Anaphylactic reaction[2], urticaria, allergic contact dermatitis, swelling face, skin discoloration, pain of skin (e.g., stinging pain), blisters (vesicles), Application site burn.

* Post marketing surveillance data

[2] Anaphylactic reactions include generalised skin eruptions or skin reactions associated with respiratory disorders mainly represented by oedemas, throat tightness, dyspnoea and urticaria.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

EPIDUO is for once-daily cutaneous use only.

In case of accidental ingestion, appropriate symptomatic measures should be taken.

If the medications are applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur.

The acute oral toxicity of adapalene topical gel, 0.1% in mice and rats is greater than 10 mL/kg (10 mg/kg). Inadvertent oral ingestion of adapalene may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A, including teratogenesis in women of childbearing years. Therefore, pregnancy testing should be carried out in women of childbearing potential who have ingested the product.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: D10A Anti-Acne Preparations for Topical Use

ATC code: D10AD53

Mechanism of action
EPIDUO combines two active substances, which act through different, but complementary mechanisms of action.

Adapalene: Adapalene is a chemically stable, naphthoic acid derivative with retinoid-like activity. Biochemical and pharmacological profile studies have demonstrated that adapalene alters the pathology of acne vulgaris: it is a potent modulator of cellular differentiation and keratinisation and has anti- inflammatory properties. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors. Current evidence indicates that topical adapalene normalises the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Adapalene inhibits the chemotactic responses of human polymorphonuclear leucocytes in vitro; it also inhibits the metabolism of arachidonic acid to inflammatory mediators. In vitro studies have shown inhibition of the AP-1 factors and the inhibition of the expression of toll like receptors 2. This profile indicates that the cell mediated inflammatory component of acne is reduced by adapalene.

Benzoyl peroxide (BPO): Benzoyl peroxide has been shown to have antimicrobial activity; particularly against P. acnes, which is abnormally present in the acne-affected pilosebaceous unit. Additionally, benzoyl peroxide has demonstrated exfoliative and keratolytic activities acting against comedones at all stages of their development. Benzoyl peroxide is also sebostatic, counteracting the excessive sebum production associated with acne.

Clinical trials

Clinical efficacy was established in a multi-centre, double-blind, active- and vehicle- controlled 12-week trial with 517 acne patients, who were randomised to the 4 parallel arms of the study. The patients with acne vulgaris enrolled in this study were approximately 60% male and 40% female subjects, mean age of study subjects: 16.5 years; range 12 – 56, presenting 20 to 50 inflammatory lesions with no nodules and cysts and 30 to 100 noninflammatory lesions at baseline. Success rate results among the treatment groups began to diverge early in favour of EPIDUO and continued to separate throughout the course of the study. After 12 weeks of treatment the efficacy of EPIDUO was statistically significantly better than that of its individual components and its vehicle in total, inflammatory and noninflammatory lesion counts (all p<.001). Significant differences in speed of onset of action for EPIDUO were demonstrated as early as week 1 (EPIDUO 19.7%; adapalene 13% [p=.001]; BPO 11.3% [p=.01]; vehicle 7.8% [p=.002]). Early onset of action was also observed in inflammatory lesion count reductions at week 1 (EPIDUO 25.7%; adapalene 14.7% [p<.001]; BPO 20% [p=.001]; vehicle 13.6% [p<.001]). The net beneficial effect (active minus vehicle) obtained from EPIDUO was greater than the sum of the net benefits obtained from the individual components, thus indicating a potentiation of the therapeutic activities of these substances when used in a fixed-dose combination (Table 2).

Table 2: Clinical Efficacy of EPIDUO

ITT population: Week 12 (LOCF)	**EPIDUO Adapalene/Benzoyl Peroxide N=149**	**Adapalene 0.1% N=148**	**Benzoyl Peroxide 2.5% N=149**	**Gel Vehicle N=71**
Success Rate (clear or almost clear)	27.5%[a]	15.5%	15.4%	9.9%
Percent Change (median)				
Inflammatory Lesion Count	-63%[b]	-46%	-44%	-38%
Noninflammatory Lesion Count	-51%[b]	-33%	-36%	-38%
Total Lesion Count	-51%[b]	-35%	-36%	-31%
Change from baseline counts				
Inflammatory Lesion Count	-17[b]	-13	-13	-11
Noninflammatory Lesion Count	-22[b]	-17	-16	-14
Total Lesion Count	-40[b]	-29	-27	-26

[a] p=0.002

[b] p<0.001, Adapalene/Benzoyl Peroxide Gel compared to Gel Vehicle.

Statistical significance was also reached for Adapalene/Benzoyl Peroxide compared to its individual active substances:

- Success Rate in clearing acne lesions: Adapalene/Benzoyl Peroxide is significantly superior to Adapalene (p=.008) and to Benzoyl Peroxide (p=.003)
- Percent Change and Change in acne lesion counts: Adapalene/Benzoyl Peroxide is significantly superior to Adapalene (p<.001) and to Benzoyl Peroxide (p<.001)

The long-term (up to 12 months) safety and efficacy of EPIDUO was evaluated in a multi-centre, open label study in 452 acne patients. Patients were aged 12 years or older and had 20 to 50 inflammatory lesions, 30 to 100 non-inflammatory lesions, and no nodules or cysts. Patients were evaluated at baseline, weeks 1 and 2, and months 1, 2, 4, 6, 8, 10 and 12. Clinically significant inflammatory and non-inflammatory lesion count reductions were observed with EPIDUO as early as week 1 and were sustained for up to 1 year. For the 327 patients who remained in the study until their month 12 visit, the percent reductions in total, inflammatory

and non-inflammatory lesion counts were 70.8%, 76% and 70% respectively. Local cutaneous tolerability of the study treatment was good throughout the study. Adverse events were mild to moderate, mainly mild dermal irritation, occurred early in the treatment and were transient. The results of the study demonstrated that EPIDUO is well-tolerated, safe**,** and effective in the long-term management of *acne vulgaris*.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic (PK) profile of adapalene in EPIDUO is similar to the PK profile of Adapalene 0.1% gel alone.

In a 30-day clinical PK study conducted in patients with acne who were tested with either the fixed- combination gel or with an adapalene 0.1% matched formula under maximised conditions (with application of 2 g gel per day), adapalene was not quantifiable in the majority of plasma samples (limit of quantification 0.1 ng/mL). Low levels of adapalene (C_{max} between 0.1 and 0.2 ng/mL) were measured in two blood samples taken from the subjects treated with EPIDUO and in three samples from the subjects treated with Adapalene 0.1% Gel. The highest adapalene $AUC_{0\text{-}24h}$ determined in the fixed-combination group was 1.99 ng.h/mL.

These results are comparable to those obtained in previous clinical PK studies on various Adapalene 0.1% formulations, where systemic exposure to adapalene was consistently low.

The percutaneous penetration of benzoyl peroxide is low; when applied on the skin, it is completely converted into benzoic acid which is rapidly eliminated. Benzoic acid also has a wide margin of safety and is an approved food additive.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Genotoxicity testing of EPIDUO Gel has not been conducted.

Adapalene did not demonstrate mutagenic or clastogenic activity in *in vitro* tests with bacterial and mammalian cells and showed no clastogenic activity in mammalian cells *in vitro* or in an *in vivo* test in mice.

Benzoyl peroxide was not mutagenic in bacteria or clastogenic in Chinese Hamster Lung cells *in vitro* but did induce DNA damage in vitro in the unscheduled DNA synthesis test and the *E coli* SOS chromotest, probably by a reactive oxygen species (ROS) mechanism. Protective mechanisms against ROS are known to exist *in vivo*. Benzoyl peroxide was not genotoxic *in vivo* in a dominant lethal mutation study in mice, a cytogenetic assay in rats or a host-mediated assay in rats.

Carcinogenicity
Studies have not been conducted to investigate the carcinogenic potential of the combination product EPIDUO.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses up to 6 mg/kg/day, and in rats at oral doses up to 1.5 mg/kg/day. These doses are up to 760 times (mice) and 120 times (rats) the exposure at the maximum recommended human dose of 2 grams EPIDUO Gel, based on plasma concentration data. In the rat oral dosing study, there was an increased incidence of phaeochromocytomas in the adrenal medullas of male rats at 1.5 mg/kg/day but not at lower doses (≤0.5 mg/kg/day; about 85 times the clinical exposure based

on C_{max}). This finding was not observed in female rats or in mice. EPIDUO at the recommended clinical dose is unlikely to induce phaeochromocytomas in *acne vulgaris* patients.

Animal studies on compounds with a similar mode of action to adapalene have indicated that these may enhance the development of skin cancers caused by UV light. Adapalene is essentially stable to oxygen and light and is chemically non-reactive. While short-term studies have shown no phototoxic or photoallergic potential of adapalene, small numbers of reactions consistent with phototoxicity were reported in clinical studies, and the safety of using adapalene during long or repeated exposures to sunlight or UV radiation has not been established in animals or humans. Exposure to excessive sunlight or UV irradiation (including sunlamps) should be avoided during treatment with adapalene.

Benzoyl peroxide has been shown to be a tumour promoter and progression agent in a number of animal studies. Studies in mice have shown that benzoyl peroxide does not increase the growth of tumours initiated by UV light. The clinical significance of this is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Acrylamide/sodium acryloyldimethyltaurate copolymer
Disodium edetate
Docusate sodium
Glycerol
Isohexadecane
Poloxamer
Polysorbate 80
Propylene glycol (E1520)
Sorbitan oleate
Purified water

Refer to Section 2 - Qualitative and quantitative composition.

6.3 INCOMPATIBILITIES

Not applicable.

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.4 SHELF LIFE

Shelf Life is 2 Years.

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

2 g, 5g, 30 g, 45 g and 60 g HDPE tubes, closed with a PP screw-cap.

5 g, 30 g, 45 g and 60 g PP bottles with pump, closed with a PP cap.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

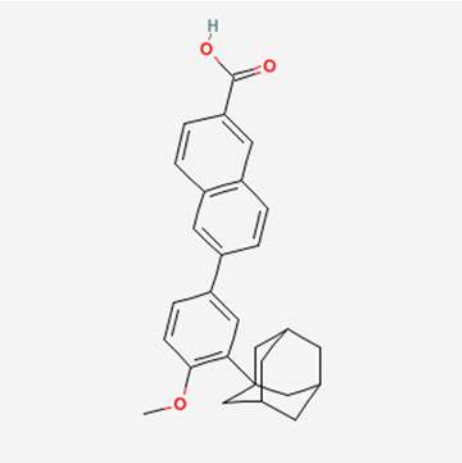
No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

ADAPALENE

Chemical structure:



Chemical Name: 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid

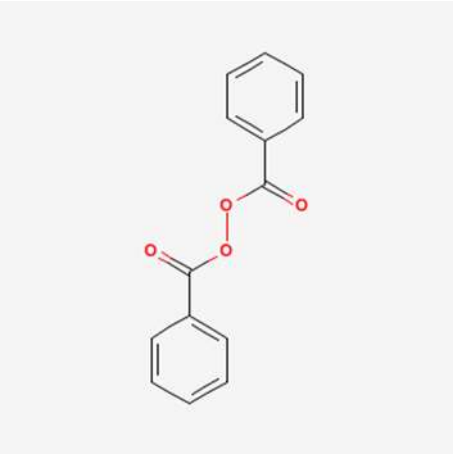
Molecular Formula: $C_{28}H_{28}O_3$

Molecular Weight: 412.52

CAS Number: 106685-40-9

BENZOYL PEROXIDE

Chemical structure:



Chemical Name: benzoyl benzenecarboperoxoate

Molecular Formula: $C_{14}H_{10}O_4$

Molecular Weight: 242.2

CAS Number: 94-36-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

PRESCRIPTION MEDICINE (S4)

8. SPONSOR

Galderma Australia Pty Ltd
Level 18, 1 Denison Street
North Sydney NSW 2060

Telephone: 1800 800 765

9. DATE OF FIRST APPROVAL

22 January 2009

10. DATE OF REVISION

13 July 2023.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	Minor editorial changes to fully comply with the TGA PI format and to enhance readability.
8	Change in Sponsor address due to office move.