Applicant/PHRC:	GALDERMA LABORATORIES SOUTH AFRICA (PTY) LTD
Product proprietary name:	EPIDUO 0.1 %/ 2.5 %
Dosage form and strength:	Gel 1 mg (0,1 %) of adapalene and 25 mg (2,5 %) of benzoyl peroxide per 1 gram

PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

Epiduo® 0,1 % / 2,5 %®

Gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of Epiduo 0,1 % / 2,5 % contains:

Adapalene 1 mg (0,1 %)

Benzoyl peroxide 25 mg (2,5 %)

Excipients with known with known effect: Propylene glycol (E1520; 4 %.)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel

A white to very pale yellow opaque gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cutaneous treatment of *Acne vulgaris* when comedones, papules and pustules are present in adults, adolescents and children aged 9 years and over (See section 5.1).

4.2 Posology and method of administration

Posology

Epiduo should be applied to the entire acne affected areas once a day in the evening on a clean and dry skin. A thin film of gel should be applied, with the fingertips, avoiding the eyes, lips and nostrils (See section 4.4).

If irritation occurs, the patient should be directed to apply non-comedogenic moisturisers, to use Epiduo ~~l~~ess 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.

Special populations

Paediatric population

The safety and effectiveness of Epiduo have not been studied in children below 9 years of age.

Method of administration

For external cutaneous use only.

4.3 Contraindications

- Hypersensitivity to the active ingredients or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6)
- Women planning a pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

Epiduo should not be applied to damaged skin, either broken (cuts or abrasions), eczematous or sunburned.

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

Epiduo 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 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.

Epiduo is FOR EXTERNAL USE ONLY.

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, and pain of skin (including stinging)) peaking during the first week and then subsiding spontaneously.

Epiduo contains 40 mg propylene glycol (E1520) per gram, which is equivalent to 40 mg/g (4.0 %). Propylene glycol (E1520) may cause skin irritation.

4.5 Interaction with other medicines and other forms of interaction

Formal interaction studies have not been performed.

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 medicines 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), and therefore interaction with systemic medicinal products is unlikely.

The percutaneous penetration of benzoyl peroxide in the skin is low and the medicinal 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

Safety in pregnancy and lactation has not been established.

Pregnancy:

Epiduo is contraindicated (see section 4.3) in pregnancy, or in women planning a pregnancy.

Animal studies by the oral route have shown reproductive toxicity at high systemic exposure (see section 5.3).

Due to the limited available data and because a very weak cutaneous passage of adapalene is possible, Epiduo should not be used during pregnancy.

In case of unexpected pregnancy, treatment should be discontinued.

Breastfeeding*:*

No study on animal or human milk transfer was conducted after topical application of Epiduo Gel.

Epiduo should not be used during breastfeeding, especially in case of acne treatment requiring product application on the chest.

Fertility

No human fertility studies were conducted with Epiduo gel.

4.7 Effects on ability to drive and use machines

Epiduo does not affect the ability to drive and use machinery.

4.8 Undesirable effects

a) Summary of the Safety Profile

During clinical trials, a total of 4538 subjects were exposed to Epiduo. A total of 3958 subject with acne vulgaris, aged 9 years and older, were treated with Epiduo once daily for 12 weeks to 12 months. The most commonly reported adverse events are irritative contact dermatitis, dry skin, skin burning, erythema and skin exfoliation. Different degrees of skin irritation appear after application of Epiduo, the intensity is generally mild or moderate, with local tolerability signs and symptoms (erythema, dryness, scaling, burning and pain of skin (stinging pain) peaking during the first week and then subsiding spontaneously.

b) Table 1: Tabulated list of Adverse Events

Epiduo may cause the following adverse reactions at the site of application:

System organ class (MedDRA)	**Frequency**	**Adverse Drug Reaction**
Skin and subcutaneous tissue disorders	Common (≥ 1/100 to < 1/10)	Dry skin, irritative contact dermatitis, skin burning sensation, skin irritation, erythema, skin exfoliation (scaling)
	Uncommon (≥ 1/1000 to ≤ 1/100)	Pruritus and sunburn

***c)*Table 2: Tabulated list of Adverse Events from Post Marketing Studies**

Epiduo may cause the following adverse reactions at the site of application as obtained from post marketing surveillance data:

System organ class (MedDRA)	**Frequency**	**Adverse Drug Reaction**
Immune system	Not known (cannot be estimated from the available data)	Anaphylactic reaction
Eye disorders	Not known (cannot be estimated from the available data)	Eyelid oedema
Respiratory, thoracic and mediastinal disorders	Not known (cannot be estimated from the available data)	Throat tightness, dyspnoea
Skin and subcutaneous tissue disorders	Not known (cannot be estimated from the available data)	Allergic contact dermatitis, swelling face, pain of skin (stinging pain), blisters (vesicles), skin discolouration (hyperpigmentation and hypopigmentation), urticaria, application site burn*

* Most of the cases of “application site burn” were superficial burns but cases with second degree burn or severe burn reactions have been reported.

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 and pain of skin (stinging pain) peaking during the first week and then subsiding spontaneously.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Epiduo is for once-daily topical use only.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 13.12 Other

Mechanism of action and Pharmocodynamic effects:

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 acts in the pathology of *Acne vulgaris:* it is a potent modulator of cellular differentiation and keratinisation and it has anti-inflammatory properties. Mechanistically, adapalene binds to specific retinoic acid nuclear

receptors. Current evidence suggests that topical adapalene normalises the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Adapalene inhibits the chemotactic (directional) and chemokinetic (random) responses of human polymorphonuclear leucocytes in *in vitro* assay models; it also inhibits the metabolism of arachidonic acid to inflammatory mediators. This profile suggests that the cell mediated inflammatory component of acne is reduced by adapalene.

Benzoyl peroxide: 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. Benzoyl peroxide is also sebostatic, counteracting the excessive sebum production associated with acne.

Clinical efficacy of Epiduo in children

The safety and efficacy of Epiduo applied once daily for the treatment of acne vulgaris were assessed in both children 9-11 years old and in children 12 years and older.

The study concludes that the efficacy and safety profiles of Epiduo Gel in the treatment of facial acne in this specific younger age group are consistent with results of other pivotal studies in subjects with acne vulgaris aged 12 years and older showing significant efficacy with an acceptable tolerability.

5.2 Pharmacokinetic properties

In a 30-day clinical pharmacokinetic study, conducted in patients with acne who were tested with either the fixed-combination gel or with an adapalene 0,1 % matched formula under maximized 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 the combination of adapalene 0,1 % and benzoyl peroxide 2,5 % gel and in three samples from the subjects treated with adapalene 0,1 % gel. The highest adapalene AUC_{0-24h} determined in the fixed combination group was 1,99 ng.h/mL.

The percutaneous penetration of benzoyl peroxide is low; when applied on the skin, it is completely converted into benzoic acid which is rapidly eliminated.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, phototoxicity or carcinogenicity.
Reproductive toxicology studies with adapalene have been performed by the oral and dermal routes of administration in the rat and rabbit. A teratogenic effect has been demonstrated at high systemic exposures (oral doses from 25 mg/kg/day). At lower exposures (dermal dose of 6 mg/kg/day), changes in the numbers of ribs or vertebrae were seen.
Animal studies performed with Epiduo include local tolerance studies and dermal repeat-dose toxicity studies in rat, dog and minipig up to 13 weeks and demonstrated local irritation and a potential for sensitisation, as expected for a combination containing benzoyl peroxide. Systemic exposure to adapalene following repeat dermal application of the fixed combination in animals is very low, consistent with clinical pharmacokinetic data. Benzoyl peroxide is rapidly and completely converted to benzoic acid in the skin and after absorption is eliminated in the urine, with limited systemic exposure.
Reproductive toxicity of adapalene was tested by the oral route in rats for fertility.
There were no adverse effects upon reproductive performance and fertility, F1 litter survival, growth and development to weaning, and subsequent reproductive performance following treatment with adapalene oral at doses up to 20 mg/kg/day.
A reproductive and developmental toxicity study conducted in rats exposed groups to oral doses of benzoyl peroxide of up 1000 mg/kg/day (5 mL/kg) showed that Benzoyl peroxide did not induce teratogenicity or effects on reproductive function at doses up to 500 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Docusate sodium

Glycerol

Poloxamer

Propylene glycol (E1520)

Simulgel 600PHA (copolymer of acrylamide and sodium acryloyldimethyltaurate, isohexadecane, polysorbate 80, sorbitan oleate)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Epiduo in-use stability is at least 6 months after first opening.

6.4 Special precautions for storage

Store at or below 25 ºC.

Once opened Epiduo should be used within 6 months and any unused product should be discarded.

6.5 Nature and contents of the container

Epiduo Gel is presented in white multidose containers with an airless pump and snap on cap, made of polypropylene, low density polyethylene and high density polyethylene containing 30 g of gel.

Each multidose container is packed in a carton box.

6.6 Special precautions for disposal

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Galderma Laboratories South Africa (Pty) Ltd

Wedgefield Office Park Phase 2

1st Floor Block D

17 Muswell Road South

Bryanston

South Africa

8. REGISTRATION NUMBER

44/13.12/0109

9. DATE OF FIRST AUTHORISATION

26 October 2012

10. DATE OF REVISION OF THE TEXT

19 November 2021