

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

EPIDUO FORTE

Adapalene 3 mg/g (0.3 %) and benzoyl peroxide 25 mg/g (2.5 %) gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 1 gram of EPIDUO FORTE gel contains:

adapalene 3 mg (0.3 %)

benzoyl peroxide 25 mg (2.5 %).

Excipient with known effect: propylene glycol: (E1520) 40 mg/g (4.0 %).

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

EPIDUO FORTE is indicated for the cutaneous treatment of *Acne vulgaris*, when comedones, papules and pustules are present in adults, adolescents, and children aged 12 years and above. (See sections 4.2 and 5.1).

4.2 Posology and method of administration

Posology

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

EPIDUO FORTE should be applied once a day in the evening on a clean and dry skin to the entire acne affected areas of the face and the trunk.

The duration of treatment should be determined by the doctor based on the overall clinical condition and on the therapeutic response to the treatment. Early signs of clinical improvement usually appear after 1 to 4 weeks of treatment. If no improvement is observed after 4 - 8 weeks of treatment, the benefit of continued treatment should be reconsidered.

A lower strength of EPIDUO FORTE is available (Epiduo 0.1 % / 2.5 % gel) and this concentration should be considered in patients with moderate acne vulgaris (see section 5.1). Doctors may choose between the two concentrations based on the presenting patient's clinical condition and severity.

Special populations

Elderly (≥ 65 years of age)

The safety and efficacy of EPIDUO FORTE in elderly patients have not been established.

Renal and hepatic impairment

EPIDUO FORTE has not been studied in patients with renal and hepatic impairment.

Paediatric population

The safety and efficacy of EPIDUO FORTE have not been studied in children below 12 years of age.

Method of administration

For external cutaneous use only.

Apply a thin layer of EPIDUO FORTE 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), avoiding the eyes and lips (see section 4.4).

Patients should be instructed to wash their hands after applying the EPIDUO FORTE.

Cosmetics may be applied after EPIDUO FORTE has dried.

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

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

4.3 Contra-indications:

- Hypersensitivity to the active substances or 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 FORTE should not be applied to damaged skin, either broken (cuts or abrasions), sunburn or eczematous skin.

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

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

Excessive exposure to sunlight or UV radiation should be avoided.

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

The efficacy and safety of EPIDUO FORTE in patients with severe nodular or deep nodulocystic acne have not been studied. As patients with severe nodular /nodulocystic acne are at increased risk of permanent scarring secondary to acne lesions, the use of EPIDUO FORTE in these patients is not recommended due to the risk of insufficient therapeutic response.

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

Paediatric population

The safety and effectiveness of EPIDUO FORTE has not been studied in children below 12 years of age, therefore, it should not be used in these patients.

4.5 Interactions with other medicines and other forms of interaction

No interaction studies have been conducted with EPIDUO FORTE.

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

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 FORTE.

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, medicated or abrasive soaps and cleansers are used, as they may produce additive irritant effects with EPIDUO FORTE.

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 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:

Pregnancy

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

Safety in pregnancy has not been established.

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

If the patient becomes pregnant while taking this drug, treatment should be discontinued.

Lactation

Safety during breastfeeding has not been established.

No study on animal or human milk transfer was conducted after cutaneous application of EPIDUO FORTE.

EPIDUO FORTE 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 FORTE.

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

However, no effects of adapalene or benzoyl peroxide on fertility were found in rats in reproductive studies (see section 5.3).

4.7 Effects on ability to drive and the use of machines

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

4.8 Undesirable effects

Summary of safety profile

Approximately 10 % of patients can be expected to experience adverse skin reactions. Treatment related adverse reactions typically associated with the use of EPIDUO FORTE include mild to moderate application site reactions, such as skin irritation mainly characterized by scaling, dryness, erythema, burning and pain of skin (stinging pain).

In such cases, the recommendation is to use a moisturiser, temporarily reduce the application frequency to every other day, or temporarily discontinue its use until once daily schedule can be resumed.

These reactions usually occur early in the treatment, and tend to gradually lessen over time.

Tabulated summary of adverse reactions

The adverse reactions are classified by System Organ Class and frequency, using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $1 < 100$), rare ($\geq 1/10,000$ to $<1/1,000$), very rare ($<1/10,000$), not known (cannot be estimated from the available data) and were reported with EPIDUO FORTE in vehicle-controlled Phase 3 clinical study (see Table 1).

Applicant: Galderma Laboratories South Africa (Pty) Ltd
 Product name: Epiduo Forte
 Dosage form: Gel
 Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
 Registration number: 50/13.12/9031

Table 1: Adverse reactions

System Organ Class	Frequency	Adverse reactions
Immune system	Not known*	Anaphylactic reaction
Nervous system disorders	Uncommon	Paresthesia (tingling at application site)
Eye disorders	Uncommon	Erythema of eyelid
	Not known*	Eyelid oedema
Respiratory, thoracic and mediastinal disorders	Not known*	Throat tightness, dyspnoea
Skin and subcutaneous tissue disorders	Common	Atopic dermatitis, eczema, skin burning sensation, skin irritation, erythema, skin exfoliation (scaling)
	Uncommon	Dry skin, pruritus, rash
	Not known*	Allergic contact dermatitis, swelling face, pain of skin (stinging pain) and blisters (vesicles), skin discolouration (hyperpigmentation or hypopigmentation), urticaria, application site burn**

* Post-marketing surveillance data reported since the global launch of EPIDUO FORTE, from a population of unknown size

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

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of EPIDUO FORTE is important. It allows continued monitoring of the benefit/risk balance of EPIDUO FORTE. Healthcare 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>

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

4.9 Overdose

Symptoms: Refer to section 4.8.

EPIDUO FORTE is for once-daily cutaneous use only. Excessive application of EPIDUO FORTE may result in severe irritation. In this event, discontinue use and wait until the skin has recovered.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 13.12 Acne preparations.

Mechanism of action and pharmacodynamic effects

EPIDUO FORTE 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 normalizes 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. In vitro studies have shown inhibition of the AP-1 factors and the inhibition of the expression of toll like receptors 2. 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 *Cutibacterium acnes*, which is abnormally present in the acne-affected pilosebaceous unit. The mechanism of action of benzoyl peroxide has been explained by its highly lipophilic activity, enabling its penetration through the epidermis into bacterial and keratinocyte cell membranes of the

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

pilosebaceous unit. Benzoyl peroxide is recognized as a very effective broad spectrum antibacterial agent in the treatment of acne vulgaris. It has been demonstrated to exert bactericidal effect by generating free radicals that oxidize proteins and other essential cellular components in the bacterial wall. The minimum inhibitory concentration of benzoyl peroxide is bactericidal and has demonstrated effectiveness on antibiotic sensitive and antibiotic resistant *C.acnes* strains. Additionally, benzoyl peroxide has demonstrated exfoliative and keratolytic activities.

Clinical efficacy and safety

The safety and efficacy of adapalene 0.3 % / 2.5 % benzoyl peroxide applied once daily for the treatment of acne vulgaris were assessed in a 12 week, multicenter, randomised, double blind, controlled clinical study, comparing adapalene 0.3 % / 2.5 % benzoyl peroxide to the gel vehicle in 503 acne patients. EPIDUO FORTE was effective in the treatment of moderate and severe acne (IGA=3 and IGA=4) and caused at least a 2-grade improvement in the Success Rate ($p<0.001$) and significantly reduced the number of inflammatory lesions ($p<0.001$) at Week 12. Patients with severe acne (IGA=4) had at least a 3-grade improvement in the Success Rate ($p=0.029$).

The effect of adapalene / benzoyl peroxide 0.3% / 2.5% gel on acne scarring was also investigated in the OSCAR study. This was a multi-centre, randomised, investigator-blinded, vehicle-controlled trial using intra-individual comparison (right half-face vs. left half-face) investigating male and female subjects aged 16 to 35 years ($n=67$) with moderate to severe facial acne vulgaris, with an average mean number of acne lesions of 40 acne lesions (18 inflammatory lesions, 22 non-inflammatory lesions) on each side. The primary endpoint analysis showed that drug therapy reduced the total number of acne scars (mean treatment difference -3.7 ± 4.4 , $p<0.0001$).

Epiduo 0.3% / 2.5% gel primarily reduced scars of 2-4 mm size (mean treatment difference -3.1 ± 4.1), while the reduction in scars of >4 mm was smaller (mean treatment difference -0.6 ± 1.5).

5.2 Pharmacokinetic properties

Absorption

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

A pharmacokinetic study was conducted in patients with severe acne vulgaris (12 to 33 years of age) who were treated with once-daily applications on the face, shoulders, upper chest and back areas for 4 weeks with, on average, 2.3 grams/daily (range: 1.6 - 3.1 grams/day) applications of Epiduo Forte gel. Following repeated topical application, adapalene systemic concentration reached steady state at day 15 with no tendency for accumulation. At the end of treatment period, 62% of patients had quantifiable adapalene plasma concentrations above the limit of quantification (LOQ of 0.1 ng/mL), with a mean C_{max} 0.16 ± 0.08 ng/mL and a mean AUC_{0-24h} 2.49 ± 1.21 ng.h/mL. The most exposed patient had adapalene C_{max} and AUC_{0-24h} values 0.35 ng/mL and 6.41 ng.h/mL, respectively.

The percutaneous penetration of benzoyl peroxide is low; when applied topically, it is completely converted into benzoic acid in the skin with approximately 5% of the benzoic acid being systemically absorbed and eliminated in the urine.

Distribution

Adapalene bounds primarily to lipoproteins and human serum albumin. Benzoyl peroxide is converted into benzoic acid and not possible to be determined.

Metabolism

The major products of adapalene metabolism are glucuronides. Benzoyl peroxide is rapidly metabolized into benzoic acid in the skin before passing into the circulation.

Excretion

Adapalene is excreted primarily by the biliary route. Benzoyl peroxide is excreted in urine in the form of benzoic acid.

Pharmacokinetics studies conducted with adapalene 0.3 % / benzoyl peroxide 2.5 % gel indicate that the transdermal absorption of adapalene is not affected by benzoyl peroxide.

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

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

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 adapalene 0.3 % / benzoyl peroxide 2.5 % gels include local tolerance studies and dermal repeat-dose toxicity studies in rat, dog and/or 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 to 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.

Environmental Risk Assessment (ERA):

Environmental risk assessment studies have shown that adapalene has the potential to be very persistent, and toxic to the environment (see section 6.6).

Environmental risk assessment studies have shown that adapalene may pose a risk for aquatic compartment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Disodium edetate

Docusate sodium

Glycerol (glycerin)

Poloxamer

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

Propylene glycol (E1520)

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

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

After first opening: 3 months

Any unused product should be discarded (see section 6.6).

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Epiduo 0.3% / 2.5% gel is supplied in a multidose container with airless pump.

15 g, 30 g, 45 g and 60 g multidose container with airless pump and snap on cap, made of polypropylene and high density polyethylene or polypropylene, high-density polyethylene and very low density polyethylene.

Each multidose container is packed in a carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

EPIDUO FORTE may pose a risk to the environment (see section 5.3).

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

Applicant: Galderma Laboratories South Africa (Pty) Ltd
Product name: Epiduo Forte
Dosage form: Gel
Strength: 0,3 % (3 mg) adapalene and 2,5 % (25 mg) benzoyl peroxide per 1 g gel
Registration number: 50/13.12/9031

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Galderma Laboratories South Africa (Pty) Ltd

Nicol Main Office Park,

Block C, First Floor,

FutureSpace,

2 Bruton Road,

Bryanston

2191

8. REGISTRATION NUMBER/S:

50/13.12/9031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF TEXT:

13 September 2022

10. DATE OF REVISION OF THE TEXT