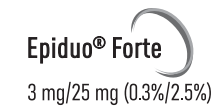


Adapalene + Benzoyl Peroxide



3 mg/25 mg (0.3%/2.5%) per gram Topical Gel
ANTI-ACNE



PRODUCT DESCRIPTION

Adapalene + Benzoyl Peroxide (Epiduo Forte) Gel is a white to very pale yellow opaque gel containing 0.3% w/w (3 mg/g) of adapalene and 2.5% w/w (25 mg/g) of benzoyl peroxide, as the drug substances, dispersed in an aqueous gel dosage form, for the topical treatment of acne vulgaris.

FORMULATION: Each gram contains:

Adapalene, Ph. Eur. 3 mg (0.3% w/w)
Benzoyl Peroxide, Ph. Eur. 25 mg (2.5% w/w)

Excipients: Simulgel 600 PHA, Docusate sodium, Edetate disodium, Glycerin, Poloxamer 124, Propylene glycol, Purified water

GENERAL PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of action and Pharmacodynamic 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 normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Studies in acne patients provide clinical evidence that topical adapalene is effective in reducing the noninflammatory acne lesions (open and closed comedones). 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 *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 excretion associated with acne.

As both active substances (adapalene and benzoyl peroxide) are well-characterized pharmacologically, and as no interactions are likely to occur, no specific nonclinical pharmacology studies were performed with Epiduo. Safety pharmacological studies for both individual active substances (adapalene and benzoyl peroxide) suggest no overall impairment of the major physiological body systems (including central nervous system, cardiovascular and respiratory functions).

PHARMACOKINETICS

A pharmacokinetic study was conducted in 26 adult and adolescent subjects (12 to 33 years of age) with severe acne vulgaris who were treated with once-daily applications during a 4-week period with, on average, 2.3 grams/day (range 1.6-3.1 grams/day) of Epiduo Forte gel or Adapalene 0.3% gel applied as a thin layer to the face, shoulders, upper chest and upper back. After a 4-week treatment, 16 subjects (62%) had quantifiable adapalene plasma concentrations above the limit of quantification of 0.1 ng/mL, with a mean C_{max} of 0.16 ± 0.08 ng/mL and a mean AUC_{0-24hr} of 2.49 ± 1.21 ng.h/mL. The most exposed subject had adapalene C_{max} and AUC_{0-24hr} of 0.35 ng/mL and 6.41 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.

INDICATIONS:

Adapalene + Benzoyl Peroxide (Epiduo Forte) is indicated for the cutaneous treatment of moderate to severe Acne vulgaris in patients 12 years of age and older.

DOSAGE AND ADMINISTRATION

Adapalene + Benzoyl Peroxide (Epiduo Forte) Topical Gel should be applied as a thin film to the entire acne affected areas of the face, chest and back once daily in the evening, on a clean and dry skin.

A small amount of Adapalene + Benzoyl Peroxide (Epiduo Forte) should be applied to provide a thin film, avoiding eyes, lips and mucous membranes. These medications should not be applied to cuts, abrasions, eczematous, or sunburned skin.

If irritation occurs, the patient should be directed to apply non-comedogenic moisturizers.

Discontinue treatment if a severe local inflammatory response is experienced. Reinstigate therapy when the reaction has subsided, initially applying the preparation less frequently (e.g. every other day). Once-daily application may be resumed if it is judged that the patient is able to tolerate the treatment.

Missed Dose

If a single dose is missed, dosing should continue as per usual the following day, and the usual amount should be applied.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.
Pregnancy.
Damaged skin, either broken (cuts or abrasions), eczematous or sunburned.

WARNINGS AND PRECAUTIONS

Adapalene + Benzoyl Peroxide (Epiduo / Epiduo Forte) Gel should not be applied to damaged skin, either broken (cuts or abrasions), eczematous or sunburned.

Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte) 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 Adapalene + Benzoyl Peroxide (Epiduo Forte) should be discontinued.

Depending upon the severity of local cutaneous adverse reactions, patients should be instructed to use a moisturizer, reduce the frequency of the application of Adapalene + Benzoyl Peroxide (Epiduo Forte) gel, or discontinue use.

As with other topical retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with Adapalene + Benzoyl Peroxide (Epiduo / Epiduo Forte) 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).

Excessive exposure to sunlight or UV radiation (sunlamps) should be avoided. Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte) should not come into contact with any coloured material including hair and dyed fabrics as this may result in bleaching and discoloration.

Use in Renally Impaired

Pharmacokinetic studies have not been conducted in subjects with a medical condition which might interfere with the absorption, distribution, metabolism, or excretion of Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte), in particular, a history of hepatic or renal disease.

Use in Hepatically Impaired

Pharmacokinetic studies have not been conducted in subjects with a medical condition which might interfere with the absorption, distribution, metabolism, or excretion of Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte), in particular, a history of hepatic or renal disease.

Use in Geriatrics

The safety and efficacy of Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte) in geriatric patients aged 65 years and above have not been established.

Use in Pediatrics

Safety and effectiveness of Adapalene + Benzoyl Peroxide (Epiduo Forte) gel in pediatric patients under the age of 12 have not been established.

Carcinogenesis/mutagenesis

Preclinical data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenicity.

PREGNANCY AND LACTATION

PREGNANCY. Animal studies by the oral route have shown reproductive toxicity at high systemic exposure. Clinical experience with locally applied adapalene and benzoyl peroxide in pregnancy is limited but the few available data do not indicate harmful effects in patients exposed in early pregnancy. Due to the limited available data and because a very weak cutaneous passage of adapalene is possible, Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte) should not be used during pregnancy. In case of unexpected pregnancy, treatment should be discontinued.

LACTATION.

No study on animal or human milk transfer was conducted after cutaneous application of Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte). No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to adapalene and benzoyl peroxide are negligible. Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte) can be used during breast-feeding. To avoid contact exposure of the infant, application of Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte) to the chest should be avoided when used during breastfeeding.

FERTILITY

No fertility studies were conducted with Adapalene + Benzoyl Peroxide (Epiduo Forte).

In rat oral studies, 20 mg adapalene/kg/day did not affect the reproductive performance and fertility of F0 males and females, or the growth, development and reproductive function of F1 offspring.

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.

INTERACTIONS

No interaction studies have 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 Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte). 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 Adapalene + Benzoyl Peroxide (Epiduo/Epiduo Forte).

Absorption of adapalene through human skin is low, 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.

Concomitant topical acne therapy is not recommended because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

ADVERSE DRUG REACTIONS

Adverse Reactions-clinical studies
Treatment-related adverse events or adverse reactions typically associated with use of Adapalene + Benzoyl Peroxide (Epiduo Forte) include mild to moderate application site reactions, such as skin irritation characterized by scaling, dryness, erythema, and burning/stinging. These reactions usually occur early in the treatment and tend to gradually lessen and subside spontaneously over time.

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 in vehicle-controlled Phase 3 study with Epiduo Forte.

System Organ Class (SOC)	Frequency	Adverse Reactions
Eye disorders	Uncommon	Erythema of eyelid
Nervous system disorders	Uncommon	Paresthesia (tingling at application site)
Skin and subcutaneous tissue disorders	Uncommon	Skin irritation, eczema, skin burning sensation, atopic dermatitis
	Uncommon	Pruritus, rash, dry skin
	Uncommon	Application site burn

OVERDOSE AND TREATMENT

Adapalene + Benzoyl Peroxide (Epiduo / Epiduo Forte) is for once-daily cutaneous use only.
In case of accidental ingestion, appropriate symptomatic measures should be taken.
Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.
Acute overdosage with the topical use is unlikely. 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.

STORAGE CONDITION:

Store at temperatures not exceeding 25°C
Protect from light.
Keep out of reach of children.
Keep away from heat.

AVAILABILITY:

Airless pump system:
15g, 30g, and 45g in White airless pump system composed mainly of a PP/HDPE bottle and a PP pump/overcap (Box of 1's)

Tube:
2g and 5g in High Density Polyethylene (HDPE) Tube with polypropylene (PP) caps (Box of 1's)

SPECIAL HANDLING INSTRUCTIONS

Adapalene + Benzoyl Peroxide (Epiduo Forte) should be used within a period of 3 months after first opening. Any unused portion should be discarded 3 months after opening or at product expiry date (whichever comes first).

Marketing Authorization Holder:

Galderma Philippines, Inc.
35th Floor, Joy-Nostalgie Center
No. 17 ADB Avenue, Ortigas Center,
Pasig City, Philippines

Manufactured by:

G PRODUCTION INC
19400 Rte Transcanadienne
BAIE D'URFE, QUEBEC,
CANADA H9X 3S4

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA at www.fda.gov and to Galderma Local Safety Officer at philippines.pharmacovigilance@galderma.com

Airless Pump System: DR-XY46058
Tube: DR-XY46059

Date of Approval of the Authorization:

DR-XY46058: 04 October 2017
DR-XY46059: 04 October 2017

Date of Revision of Package Insert: 13 May 2022

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