

## New Zealand Datasheet

### Name of Medicine

Epiduo 0.1% / 2.5% gel

### Presentation

Epiduo is a white to very pale yellow opaque gel containing in each 1 g of gel, adapalene 1 mg (0.1%) and benzoyl peroxide 25 mg (2.5%)

### Uses

#### Actions

Pharmacotherapeutic group: D10A Anti-Acne Preparations for Topical Use  
ATC code: D10AD53

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. 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 production associated with acne.

Clinical efficacy of Epiduo:

The safety and efficacy of Epiduo applied once daily for the treatment of acne vulgaris were assessed in two 12-week, multicenter, controlled clinical studies of similar design, comparing Epiduo to its individual active components, adapalene and benzoyl peroxide, and to the gel vehicle in acne patients. A total of 2185 patients were enrolled in Study 1 and Study 2. The distribution of patients in the two studies was approximately 49% male

and 51% female, 12 years of age or older (mean age: 18.3 years; range 12 – 50), presenting 20 to 50 inflammatory lesions and 30 to 100 noninflammatory lesions at baseline. The patients treated the face and other acne affected areas as needed once daily in the evening.

The efficacy criteria were:

- (1) Success rate, percentage of patients rated ‘Clear’ and ‘Almost Clear’ at Week 12 based on the Investigator’s Global Assessment (IGA);
- (2) Change and Percent Change from baseline at Week 12 in
  - Inflammatory lesion counts
  - Non-inflammatory lesion counts
  - Total lesion count

The efficacy results are presented for each study in Table 1 and combined results in Table 2. Epiduo was shown to be more effective compared to its monads and gel vehicle in both studies. Overall, 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. An early treatment effect of Epiduo was consistently observed in Study 1 and Study 2 for Inflammatory Lesions at Week 1 of treatment. Noninflammatory lesions (open and closed comedones) noticeably responded between the first and fourth week of treatment. The benefit on nodules in acne has not been established.

Table 1 Clinical efficacy in two comparative trials

Study 1				
Study 1 Week 12 LOCF; ITT	Adapalene+BPO N=149	Adapalene N=148	BPO N=149	Vehicle N=71
Success (Clear, Almost Clear)	41 (27.5%)	23 (15.5%) p=0.008	23 (15.4%) p=0.003	7 (9.9%) p=0.002
Median Reduction (% Reduction) in Inflammatory Lesion Count	17 (62.8 %)	13 (45.7 %) p<0.001	13 (43.6 %) p<0.001	11 (37.8 %) p<0.001
Noninflammatory Lesion Count	22 (51.2 %)	17 (33.3 %) p<0.001	16 (36.4 %) p<0.001	14 (37.5 %) p<0.001
Total lesion Count	40 (51.0 %)	29 (35.4 %) p<0.001	27 (35.6 %) p<0.001	26 (31.0 %) p<0.001
Study 2				
Study 2 Week 12 LOCF; ITT	Adapalene+BPO N=415	Adapalene N=420	BPO N=415	Vehicle N=418
Success (Clear, Almost Clear)	125 (30.1%)	83 (19.8%) p<0.001	92 (22.2%) p=0.006	47 (11.3%) p<0.001
Median Reduction (% Reduction) in				

Inflammatory Lesion Count	16 (62.1 %)	14 (50.0 %) p<0.001	16 (55.6 %) p=0.068	10 (34.3 %) p<0.001
Noninflammatory Lesion Count	24 (53.8 %)	22 (49.1 %) p=0.048	20 (44.1 %) p<0.001	14 (29.5 %) p<0.001
Total Lesion Count	45 (56.3 %)	39 (46.9 %) p=0.002	38 (48.1 %) p<0.001	24 (28.0 %) p<0.001

*Table 2 Clinical efficacy in combined comparative trials*

	Adapalene+BPO N=564	Adapalene N=568	BPO N=564	Gel Vehicle N=489
Success (Clear, Almost Clear)	166 (29.4%)	106 (18.7%)	115 (20.4%)	54 (11.1%)
Median Reduction (% Reduction) in				
Inflammatory Lesion Count	16.0 (62.1)	14.0 (50.0)	15.0(54.0)	10.0 (35.0)
Noninflammatory Lesion Count	23.5 (52.8)	21.0 (45.0)	19.0 (42.5)	14.0 (30.7)
Total Lesion Count	41.0 (54.8)	34.0 (44.0)	33.0 (44.9)	23.0 (29.1)

### Pharmacokinetics

The pharmacokinetic (PK) properties of Epiduo are 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<sub>0-24h</sub> 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.

### Indications

Cutaneous treatment of *Acne vulgaris* when comedones, papules and pustules are present.

## **Dosage and Administration**

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 and lips (see Warnings and Precautions).

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

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

## **Contraindications**

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

## **Warnings and Precautions**

Epiduo Gel should not be applied to damaged skin, either broken (cuts or abrasions) 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) which 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 discoloration.

## **Use in 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, Epiduo should not be used during pregnancy. In case of unexpected pregnancy, treatment should be discontinued.

### **Use in Lactation**

No study on animal or human milk transfer was conducted after cutaneous application of Epiduo (adapalene / benzoyl peroxide) Gel. No effects on the suckling child are anticipated since the systemic exposure of the breast-feeding woman to Epiduo is negligible. Epiduo can be used during breast-feeding. To avoid contact exposure of the infant, application of Epiduo to the chest should be avoided when used during breast-feeding.

### **Effects on Ability to Drive and Use Machines**

Not relevant.

### **Undesirable effects**

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

Common ( $\geq 1/100$  to  $<1/10$ ): dry skin, irritative contact dermatitis, burning and skin irritation.

Uncommon ( $\geq 1/1000$  to  $\leq 1/100$ ): pruritus and sunburn.

Unknown (Post marketing surveillance data): allergic contact dermatitis

If skin irritation appears after application of Epiduo, the intensity is generally mild or moderate, with local tolerability signs and symptoms (erythema, dryness, scaling and burning) peaking during the first weeks and then subsiding spontaneously.

### **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 Pharmacokinetics), 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.

## **Overdose**

Epiduo is for once-daily cutaneous use only. In case of accidental ingestion, appropriate symptomatic measures should be taken.

## **Pharmaceutical Precautions**

Store below 25°C.

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

## **Medicine Classification**

Prescription Medicine.

## **Package Quantities**

2 g, 5 g, 15 g, 30 g, 45 g, 60 g and 90 g white plastic tubes having a laminate or HDPE body structure with a high density polyethylene head, closed with a white polypropylene screw-cap.

Not all pack sizes may be marketed.

## **Further Information**

### **List of Excipients**

Disodium edetate

Docusate sodium

Glycerin

Poloxamer

Propylene glycol (E1520)

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

Purified water

### **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 route of administration in the rat and rabbit. A teratogenic effect has been demonstrated at high systemic exposures (oral doses from 25 mg/kg/day).

Animal studies performed with Epiduo include local tolerance studies and dermal repeat-dose toxicity studies in rat, dog and minipig up to 13 weeks demonstrating 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 which after absorption is eliminated in the urine, with limited systemic exposure.

**Incompatibilities**

Not applicable.

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