New Zealand Datasheet

1 PRODUCT NAME
Epiduo topical gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Adapalene 0.1% / benzoyl peroxide 2.5% gel

3 PHARMACEUTICAL FORM
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%)

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cutaneous treatment of *Acne vulgaris* when comedones, papules and pustules are present.

4.2 Dosage and method of 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.

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

4.4 Special warnings and precautions for use
Epiduo Gel 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) 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.

4.5 Interaction with other medicines and other forms of interaction

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.

4.6 Fertility, Pregnancy and lactation

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 on 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.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Epiduo may cause the following adverse reactions, ranked below by decreasing frequency category and, within each frequency category, by decreasing medical seriousness. All the adverse reactions reported occurred at the site of application:

Common (≥ 1/100 to <1/10): dry skin, irritative contact dermatitis, skin burning sensation, skin irritation, erythema and skin exfoliation (scaling).

Uncommon (≥ 1/1000 to ≤1/100): pruritus and sunburn.

Unknown (Post marketing surveillance data): throat tightness, blisters (vesicles), allergic contact dermatitis, swelling face, eyelid oedema, pain of skin (stinging pain) application site burns.

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 weeks 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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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

For information on management of overdose, contact the Poison Information Centre on 0800 746766 (New Zealand)

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
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)

5.2 Pharmacokinetic properties

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 $_{0\text{-}24h}$ 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.

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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage
Store below 25°C.
Epiduo in-use stability is at least 6 months after first opening.

6.5 Nature and contents of container
2 g, 5 g, 15 g, 30 g, 45 g, 60 g and 90g HDPE tubes closed with a white polypropylene screw-cap.

15 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
Not applicable.

7 MEDICINE SCHEDULE
Prescription Medicine except in medicines containing 1 milligram or less per milliliter or gram and when supplied by a pharmacist in a pack containing not more than 30 grams for the treatment of comedo, papular and pustular acne (acne vulgaris) of the face, chest or back.

8 SPONSOR
Healthcare Logistics
58 Richard Pearce Drive
Airport Oaks
AUCKLAND
Telephone (09) 9185100

9 DATE OF FIRST APPROVAL
7 April 2011

10 DATE OF REVISION OF THE TEXT
26 March 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Additional adverse effect for application site burn