AUSTRALIAN PRODUCT INFORMATION
EPIDUO ® FORTE GEL

1 NAME OF THE MEDICINE
Adapalene
Benzoyl peroxide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each g of EPIDUO FORTE gel contains: Adapalene 3 mg (0.3%) and Benzoyl Peroxide 25 mg (2.5%).

Chemical Name :
- *Adapalene:* 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid
Molecular Formula: C_{28} H_{28} O_3
Molecular Weight: 412.52

Chemical Name:
- *Benzoyl peroxide:* benzoyl benzenecarboperoxoate
Molecular Formula: $C_{14}H_{10}O_4$
Molecular Weight: 242.2

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM
EPIDUO FORTE is a white to very pale yellow opaque gel.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Cutaneous treatment of *acne vulgaris*, when comedones, numerous papules and pustules are present in patients 12 years of age and older and the condition has not responded to first line treatment. (see Section 5.1 PHARMACODYNAMIC PROPERTIES: clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION
EPIDUO FORTE should be applied once a day in the evening to the entire acne affected areas of the face and the trunk on a clean and dry skin. A thin film of gel should be applied, with the fingertips, avoiding the eyes, lips and mucous membranes (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Patients should be instructed to wash their hands after applying EPIDUO FORTE. Cosmetics may be applied after EPIDUO FORTE has dried.

If irritation occurs, the patient should be directed to apply non-comedogenic moisturisers, 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. If no improvement is observed after 1-4 weeks treatment, the benefit of continued treatment should be reconsidered. Additional systemic treatment or alternative treatments should be considered.

Patients with severe acne may need additional systemic treatment.

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

Elderly
The safety and effectiveness of EPIDUO FORTE in elderly patients aged 65 years and above have not been established.

4.3 CONTRAINDICATIONS
Hypersensitivity to the active substances or to any of the excipients.
Pregnancy
Women planning a pregnancy

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
EPIDUO FORTE is for external use only. EPIDUO FORTE should not be applied to damaged skin, either broken (cuts or abrasions), eczematous or sunburned.

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, including sunlamps, should be avoided during the use of EPIDUO FORTE. Patients with high levels of sun exposure and those with inherent sensitivity to sun should exercise particular caution. Use of sunscreen products and protective apparel (e.g. hat) are recommended when exposure cannot be avoided.

This product contains propylene glycol (EI520) that may cause skin irritation.

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

Depending upon the severity of local cutaneous adverse reactions, reduce the frequency of the application of EPIDUO FORTE, or discontinue use.

As with other topical retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with EPIDUO FORTE.

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).

Use in hepatic impairment
There are no studies for the use of EPIDUO FORTE in these patients but caution should be considered for such patients.

Use in renal impairment
There are no studies for the use of EPIDUO FORTE in these patients but caution should be considered for such patients.

Use in the elderly
Clinical studies of EPIDUO FORTE did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

Pediatric Use
Safety and effectiveness of EPIDUO FORTE in pediatric patients under the age of 12 years have not been established.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS
No formal drug-drug interaction studies have been conducted with EPIDUO FORTE.

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 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 FORTE.

Absorption of adapalene through human skin is low (see Section 5.2 PHARMACOKINETIC PROPERTIES), 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

Effects on Fertility
Fertility testing of EPIDUO FORTE has not been performed in any species. Studies with the individual active components have been performed in rats.

Oral adapalene had no effect on the fertility of rats at doses up to 20 mg/kg/day (≥300 times the maximum recommended human dose, based on C_{max}). Benzoyl peroxide administered orally to male rats at 1 g/kg/day caused testicular atrophy; there was no effect on fertility in male rats at oral doses of 500 mg/kg/day or in female rats at 1 g/kg/day.

Use in Pregnancy (Category D)
Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, topically administered retinoids are generally assumed to result in low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

No adequate or well-controlled studies in pregnant women have been conducted with EPIDUO FORTE, adapalene or benzoyl peroxide. Clinical experience with locally applied adapalene and benzoyl peroxide in pregnancy is limited. There have been isolated reports of birth defects in babies born to women using topical drugs with a similar mechanism of action to adapalene during pregnancy. Because of the potential risk of adverse effects on fetal development, EPIDUO FORTE should not be used by women who are pregnant or who plan to become pregnant during treatment. In the case of unexpected pregnancy, treatment should be discontinued.

Animal embryofetal development studies have not been conducted with adapalene and benzoyl peroxide in combination, but such studies have been performed with the individual active components.

Adapalene was found to be teratogenic in rats and rabbits when administered orally at doses ≥25 mg/kg/day (yielding plasma levels ~300 and 145 times higher in the respective species than the

maximum expected in patients). Craniofacial malformations (cleft palate, exencephaly, encephalocele and microphthalmia) were observed in treated rats; and umbilical hernia, exophthalmos, and kidney and skeletal malformations found in rabbits. Topical dermal administration of adapalene at doses up to 6 mg/kg in rats and rabbits was not teratogenic (yielding at least 32 times the maximum anticipated clinical systemic exposure, based on plasma AUC). Topical doses ≥2 mg/kg/day (rats) and 6 mg/kg/day (rabbits) increased skeletal variations (increased supernumerary ribs) in both species and delayed ossification in rabbits.

Benzoyl peroxide at oral doses of 1 g/kg/day resulted in lower birth weights of rat pups and lower pup body weight gain after birth; no reproductive toxicity was observed in rats at oral doses of 500 mg/kg/day benzoyl peroxide. It is unknown whether benzoyl peroxide can cause fetal harm when used by pregnant women.

Use in Lactation
It is not known whether adapalene, benzoyl peroxide or their metabolites are excreted in human milk. EPIDUO FORTE should be used with caution in breastfeeding women, and to avoid contact exposure of the infant, application of EPIDUO FORTE should only be used on areas away from the chest when used during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
EPIDUO FORTE has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)
Summary of safety profile
Treatment-related adverse effects typically associated with use of EPIDUO FORTE include mild to moderate application site reactions, such as skin irritation characterized by scaling, dryness, erythema, and burning[1]/stinging. These reactions usually occur early in the treatment, and tend to gradually lessen over time.

[1]Cases of application site burn included superficial burn, second degree burn and severe burn reactions.

During clinical trials, 245 participants with acne lesions received EPIDUO FORTE once daily. A total of 217 participants were treated once daily for approximately 12 weeks.

Tabulated list of adverse events reported in ≥1% of patients during treatment with EPIDUO FORTE in 1 Phase 3 vehicle-controlled studies, by System Organ Class, Preferred Terms and frequency (Table 1):

Table 1: Adverse Events Reported by ≥1% of patients during treatment with EPIDUO FORTE in 1 Phase 3 vehicle-controlled study

System Organ Class/Preferred Term [1]	CD0271 (adapalene) 0.3%/ CD1579 (benzoyl peroxide) 2.5% (N=217)	CD0271 (adapalene) 0.1%/CD1579 (benzoyl peroxide) 2.5% (N=217)	Vehicle Gel (N=69)
Infections and infestations	8.8%	7.8%	11.6%
Nasopharyngitis	6.5%	5.1%	1.4%
Upper respiratory tract infection	0.5%	2.3%	5.8%
Influenza	0.9%	0.9%	1.4%
Gastroenteritis	1.4%	0.5%	0
Ear infection	0	0	1.4%
Pharyngitis	0	0	1.4%

System Organ Class/Preferred Term [1]	CD0271 (adapalene) 0.3%/ CD1579 (benzoyl peroxide) 2.5% (N=217)	CD0271 (adapalene) 0.1%/CD1579 (benzoyl peroxide) 2.5% (N=217)	Vehicle Gel (N=69)
Skin and subcutaneous tissue disorders	6.0%	1.8%	2.9%
Skin irritation	4.1%	0.5%	0
Dermatitis allergic	0.5%	1.4%	0
Eczema	1.4%	0	0
Rash	0.5%	0	1.4%
Urticaria	0.5%	0	1.4%
Nervous system disorders	1.4%	0.9%	2.9%
Headache	1.4%	0.9%	1.4%
Dizziness	0	0	1.4%
Respiratory, thoracic and mediastinal disorders	0.5%	0.5%	2.9%
Cough	0.5%	0.5%	1.4%
Rhinitis seasonal	0	0	1.4%
General disorders and administration site conditions	0	0.5%	1.4%
Fatigue	0	0.5%	1.4%
Pyrexia	0	0	1.4%
Ear and labyrinth disorders	0	0	1.4%
Motion sickness	0	0	1.4%
Metabolism and nutrition disorders	0	0	1.4%
Hypokalemia	0	0	1.4%

Adverse reactions (considered as related) reported by ≥1% to <10% of patients during treatment with EPIDUO FORTE in a Phase 3 vehicle-controlled study:
common (≥1/100 to <1/10)

- Skin irritation
- Skin burning sensation
- Atopic dermatitis

Adverse reactions (considered as related) reported by <1% of patients during treatment with EPIDUO FORTE in 1 Phase 3 vehicle-controlled studies:
Eye disorders
uncommon (≥ 1/1,000 to < 1/100)

- Erythema of eyelid

Nervous system disorders
uncommon (≥ 1/1,000 to < 1/100)

- Paresthesia (tingling at application site)

Skin and subcutaneous tissue disorders
uncommon (≥ 1/1,000 to < 1/100)

- Pruritus

- Rash
- Dry skin
- Application Site Burn (No Known Frequency)

Skin irritation was more commonly seen with EPIDUO FORTE than with EPIDUO. The skin irritation described after application of EPIDUO FORTE, is generally mild or moderate, with signs and symptoms including erythema, dryness, scaling, burning and pain of skin (stinging pain), peaking during the first weeks and then subsiding spontaneously.

In addition to some of the above, other adverse drug effects were reported with EPIDUO (Adapalene 0.1%/Benzoyl peroxide 2.5%), the previously approved fixed combination of adapalene and benzoyl peroxide.

Other adverse drug reactions reported in clinical trials with Epiduo gel: irritative contact dermatitis (common) and sunburn (uncommon).

Post-Marketing surveillance data

The following events have been reported since the global launch of EPIDUO. These events have been chosen for inclusion due to either their seriousness, causal connection to EPIDUO or frequency of reporting. Post-market adverse events are reported spontaneously from a population of unknown size, thus estimates of frequency cannot be made.
Eye disorders: Eyelid oedema, conjunctivitis.
Respiratory, thoracic and mediastinal disorders: Throat tightness, dyspnoea[2].
Skin and subcutaneous tissue disorders: Pain of skin (e.g. stinging pain), allergic contact dermatitis, swelling of face, blister (vesicles), sunburn, pruritus, skin discolouration, rash, eczema, urticaria, anaphylactic reaction[2].

[2]Anaphylactic reactions include generalized skin eruptions or skin reactions associated with respiratory disorders mainly represented by oedemas, throat tightness, dyspnoea and urticaria.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSAGE

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. For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

If the medications are applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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 alters the pathology of *acne vulgaris:* it is a potent modulator of cellular differentiation and keratinisation and has anti-inflammatory properties. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors. Current evidence indicates that topical adapalene normalises the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Adapalene inhibits the chemotactic responses of human polymorphonuclear leucocytes *in vitro*; 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 indicates that the cell mediated inflammatory component of acne is reduced by adapalene.

- *Benzoyl peroxide (BPO)*: Benzoyl peroxide has been shown to have antimicrobial activity; particularly against *Propionibacterium acnes*, which is abnormally present in the acne-affected pilosebaceous unit. It exerts its bactericidal effect by generating free radicals that oxidise proteins and other essential cellular components in the bacterium wall. Additionally benzoyl peroxide has demonstrated exfoliative and keratolytic activities acting against comedones at all stages of their development. Benzoyl peroxide is also sebostatic, counteracting the excessive sebum production associated with acne.

Clinical trials

Clinical efficacy and safety

The safety and efficacy of EPIDUO FORTE applied once daily for the treatment of *acne vulgaris* were assessed in a 12-week, multicenter, randomised, double-blind, controlled clinical study, comparing EPIDUO FORTE to the gel vehicle in 503 acne patients. In this study, 217 patients were treated with EPIDUO FORTE, 217 patients with adapalene 0.1% / benzoyl peroxide 2.5% gel and 69 patients with the Vehicle gel. At baseline, 50% of subjects were graded as “moderate” (IGA Grade 3) and 50% were graded as “severe” (IGA Grade 4) on the IGA scale. Subjects had an average of 98 (range 51-226) total lesions of which the mean number of inflammatory lesions was 38 (range: 20-99) and the mean number of non-inflammatory lesions was 60 (range 30-149). Patients with Acne Conglobata, Acne Fulminans, secondary (chloracne, drug-induced acne), nodulo-cystic acne or acne requiring systemic treatment have not been studied with EPIDUO FORTE.

Table 2: Investigator's Global Assessment scale

Investigator's Global Assessment		
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognisable; less than half the face is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the face is involved. Many comedones, papules and pustules. One small nodule may be present.
4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules may or may not be present.

The efficacy criteria were:
- Success rate, defined as the percent of subjects who were rated 'Clear' or 'Almost Clear' at Week 12 with at least a two-grade improvement based on the Investigator's Global Assessment (IGA). An IGA score of 'Clear' corresponded to clear skin with no inflammatory or non-inflammatory lesions. An IGA score of 'Almost Clear' corresponded to a few scattered comedones and a few small papules.

- Mean absolute change from baseline at Week 12 in both inflammatory and non-inflammatory lesion counts.

At Baseline, 50% of enrolled patients had acne severity assessed as "moderate" (IGA=3) and 50% had scores of "severe" (IGA=4). In the overall study population, up to two nodules were allowed. For lesion counts, subjects had an average of 98 (range: 51-226), of which the mean number of inflammatory lesions was 38 (range: 20-99) and the mean number of non-inflammatory lesions was 60 (range: 30-149). The age of the patients ranged from 12 to 57 years (mean age: 19.6 years), with 273 (54.3%) patients 12 to 17 years of age. A similar number of males (47.7%) and females (52.3%) were enrolled. The patients treated the face and other acne affected areas on the trunk as needed once daily in the evening. Statistical analyses were performed to compare and interpret study results in a stepwise manner:
− EPIDUO FORTE versus Vehicle gel in the overall population of patients with moderate and severe acne (IGA=3 and IGA=4).
− EPIDUO FORTE versus Vehicle gel in the subgroup of patients with severe acne (IGA=4).

The efficacy results are shown for EPIDUO FORTE in Table 3 for the combined moderate and severe acne populations.

Superiority of EPIDUO FORTE over vehicle gel was demonstrated in the overall study population of patients with moderate to severe acne (IGA=3 and IGA=4) at Week 12 for Success Rate (33.7% vs. 11.0%, $p<0.001$) and for reductions in inflammatory (27.8 vs. 13.2, $p<0.001$) and non-inflammatory lesion counts (40.5 vs. 19.7, $p<0.001$). See Table 3.

Table 3: Clinical efficacy in the overall population: patients with moderate and severe acne vulgaris at Week 12 (combined IGA = 3 and 4, MI, ITT population)

Efficacy Parameters	**EPIDUO FORTE (N=217)**	**Adapalene 0.1% / benzoyl peroxide 2.5% Gel (N = 217)**	**Vehicle Gel (N=69)**
Success Rate (minimum 2-grade improvement and IGA "clear" or "almost clear")	33.7% *	27.3%	11.0%

Change in Inflammatory Lesions, Mean absolute (percent) reduction	27.8 * (68.7%)	26.5 (69.3%)	13.2 (39.2%)
Change in Non-inflammatory Lesions, Mean absolute (percent) reduction	40.5 * (68.3%)	40.0 (68.0%)	19.7 (37.4%)

MI = Multiple Imputation; ITT = Intent-to-treat
****p < 0.001 vs vehicle***

Results of primary efficacy analyses in the severe acne population are shown in Table 4.

Superiority of EPIDUO FORTE over vehicle gel was demonstrated in the population of patients with severe acne (IGA=4) at Week 12 for Success Rate (31.9% vs. 11.8%, p=0.029) and for reductions in inflammatory (37.3 vs. 14.3, p<0.001) and non-inflammatory lesion counts (46.3 vs. 17.8, p<0.001). See Table 4.

Table 4: Clinical efficacy in patients with severe acne vulgaris (IGA = 4, MI, ITT population)

Efficacy Parameters	**EPIDUO FORTE (N=106)**	**Adapalene 0.1% / benzoyl peroxide 2.5% Gel (N = 112)**	**Vehicle Gel (N=34)**
Success Rate (minimum 2-grade improvement and IGA "clear" or "almost clear")	31.9%¤	20.5%	11.8%
Change in Inflammatory Lesions, Mean absolute (percent) reduction	37.3* (74.4%)	30.2 (68%)	14.3 (33.0%)
Change in Non-inflammatory Lesions, Mean absolute (percent) reduction	46.3* (72.1%)	43.9 (68.4%)	17.8 (30.8%)

MI= Multiple Imputation; ITT= Intent-to-treat
¤ p = 0.029 vs vehicle
**p<0.001 vs vehicle*

Adapalene 0.1% / benzoyl peroxide 2.5% gel was included in this trial as a reference therapy, however this study was not designed or powered to statistically compare the efficacy of EPIDUO FORTE to the lower strength reference therapy, nor to compare the reference therapy to the vehicle control. In subjects graded as "moderate" (IGA Grade 3) EPIDUO FORTE had similar levels of effectiveness to the adapalene 0.1%/benzoylperoxide 2.5%.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

A pharmacokinetic study was conducted with EPIDUO FORTE in 26 adult and adolescent subjects (12 to 33 years of age) with severe *acne vulgaris*. The subjects were treated with once-daily applications on all potentially affected areas during a 4-week period with, on average, 2.3 grams/day (range: 1.6-3.1 grams/day) of EPIDUO FORTE applied as a thin layer to the face, shoulders, upper chest and upper back. After 4 weeks of treatment, 16 subjects (62%) had quantifiable adapalene plasma concentrations above the limit of quantification (LOQ of 0.1 ng/mL), with a mean Cmax of 0.16 ± 0.08 ng/mL and a mean AUC0-24h of 2.49±1.21 ng.h/mL. The most exposed subject had adapalene Cmax and AUC0-24h values of 0.35 ng/mL and 6.41 ng.h/mL, respectively.
Adapalene systemic exposure tends to increase proportionally to the applied dose, as observed in another study, where the most exposed subject treated with Epiduo Gel presented a Cmax of 0.13 ng/mL and an AUC0-24h value of 1.99 ng.h/mL.

Pharmacokinetic studies conducted with both EPIDUO and EPIDUO FORTE have evidenced that the systemic circulating levels of adapalene are not affected by benzoyl peroxide. The percutaneous penetration of benzoyl peroxide is low; when applied on the skin, it is completely converted into benzoic acid which is rapidly eliminated.

Distribution
The total binding of adapalene in the blood was greater than 99%, with adapalene bound primarily to lipoproteins and human serum albumin. In human blood with a haematocrit of 45%, the erythrocyte fraction of blood contained only 26% of the total adapalene indicating that adapalene was distributed to erythrocytes at a lesser extent.

The distribution for benzoyl peroxide could not be determined since it is converted into benzoic acid, which is an endogenous substance.

Metabolism
Following 24-hour incubation with human hepatocytes, more than 90% of adapalene was metabolised. Metabolism of adapalene chiefly involves hydroxylation and subsequent conjugation with glucuronic acid (predominantly) and sulfates.

The metabolism of benzoyl peroxide metabolism evaluated *in vitro* in human skin confirmed benzoyl peroxide is metabolised into benzoic acid before passing into the circulation.

Excretion
Excretion of adapalene appears to be primarily via the biliary route. After topical administration inmonkeys, benzoyl peroxide was mainly and rapidly excreted in urine (45% of applied dose), nearly exclusively in the form of benzoic acid.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Genotoxicity testing of EPIDUO FORTE has not been conducted.

Adapalene did not demonstrate mutagenic or clastogenic activity in *in vitro* tests with bacterial and mammalian cells and showed no clastogenic activity in mammalian cells *in vitro* or in an *in vivo* test in mice.

Benzoyl peroxide was not mutagenic in bacteria or clastogenic in Chinese Hamster Lung cells *in vitro*, but did induce DNA damage *in vitro* in the unscheduled DNA synthesis test and the *E. coli* SOS chromotest, probably by a reactive oxygen species (ROS) mechanism. Protective mechanisms against ROS are known to exist *in vivo*. Benzoyl peroxide was not genotoxic *in vivo* in a dominant lethal mutation study in mice, a cytogenetic assay in rats or a host-mediated assay in rats.

Carcinogenicity
Studies have not been conducted to investigate the carcinogenic potential of the combination product EPIDUO FORTE.

Lifetime (2-year) carcinogenicity studies with adapalene have been conducted in mice at topical doses of up to 6 mg/kg/day, and in rats at oral doses of up to 1.5 mg/kg/day. These doses yielded plasma levels of adapalene up to 450 times (mice) and 70 times (rats) the maximum plasma concentration of adapalene expected in patients treated with EPIDUO FORTE at the maximum recommended human dose of 2 grams of gel per day. In the rat study, an increased incidence of benign and malignant pheochromocytomas was observed in the adrenal medulla of male rats at 1.5 mg/kg/day. No treatment-related increase in tumour incidence was observed in male rats at 0.5 mg/kg/day (yielding 50 times the maximum anticipated clinical exposure) or in female rats or mice. EPIDUO FORTE is unlikely to induce

phaeochromocytomas in patients.

Animal studies on compounds with a similar mode of action to adapalene have indicated that these may enhance the development of skin cancers caused by UV light. Adapalene is essentially stable to oxygen and light and is chemically non-reactive. While short-term studies have shown no phototoxic or photoallergic potential of adapalene, small numbers of reactions consistent with phototoxicity were reported in clinical studies, and the safety of using adapalene during long or repeated exposures to sunlight or UV radiation has not been established in animals or humans. Exposure to excessive sunlight or UV irradiation (including sunlamps) should be avoided during treatment with adapalene.

Benzoyl peroxide has been shown to be a tumour promoter and progression agent in a number of animal studies. Studies in mice have shown that benzoyl peroxide does not increase the growth of tumours initiated by UV light. The clinical significance of this is unknown. Alone, benzoyl peroxide was not carcinogenic by the dermal route in 2-year studies conducted in rodents involving treatment with up to 15–25% strengths. Mice received up to 15 or 25 mg/animal/day, male rats up to 138 mg/kg/day and female rats up to 205 mg/kg/day benzoyl peroxide. In terms of body surface area, the highest doses tested in rats are 25–37 times the dose of benzoyl peroxide provided by EPIDUO FORTE at the maximum recommended human dose of 2 grams of gel per day.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Acrylamide/sodium acryloyldimethyltaurate copolymer
Disodium edetate
Docusate sodium
Glycerol
Isohexadecane
Poloxamer 124
Polysorbate 80
Propylene glycol (E1520)
Sorbitan oleate
Purified water

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not refrigerate.
Shelf-life after first opening: 3 months.

6.5 NATURE AND CONTENTS OF CONTAINER

2g and 5g high density polyethylene (HDPE) tubes, closed with a polypropylene (PP) screw-cap.
15g, 30g and 45g PP/HDPE bottles with pump and PP/HDPE/VLDPE airless pump system, closed with a PP cap.

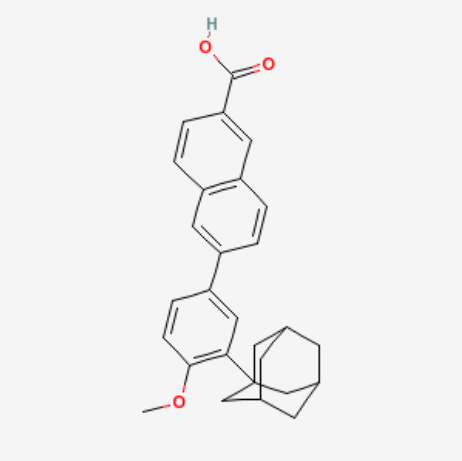
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

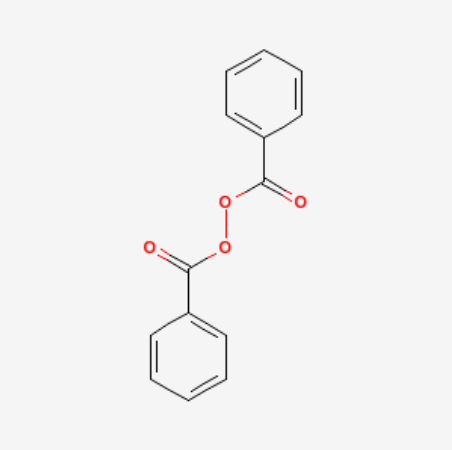
In Australia any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
Adapalene



Benzoyl Peroxide



CAS number
Adapalene**:** 106685-40-9
Benzoyl peroxide**:** 94-36-0

7 MEDICINE SCHEDULE (POISONS STANDARD)
PRESCRIPTION MEDICINE (S4)

8 SPONSOR
Galderma Australia Pty Ltd
Suite 4, 13B Narabang Way
Belrose NSW 2085

Telephone: 1800 800 765

9 DATE OF FIRST APPROVAL
03 March 2017

10 DATE OF REVISION
15 February 2021

Table 5: Summary table of changes

Section changed	Summary of new information
Multiple sections	Reformatting of the PI to comply with the new TGA requirements
4.3 CONTRAINDICATIONS and 4.6 FERTILITY, PREGNANCY AND LACTATION [Use in Pregnancy (Category D)]	Update to section 4.3 CONTRAINDICATIONS to add "Pregnancy" and "Women planning a pregnancy". Update to section 4.6 FERTILITY, PREGNANCY AND LACTATION [Use in Pregnancy (Category D)] to add warning regarding use of orally administrated and topical retinoids and risk of systemic exposure.
6.5 Nature and contents of container	45g, 60g and 70g pack sizes have been deleted and an alternate container closure system has been added
4.8 Adverse Effects	Application site burn has been included in Adverse Effects
6.5 Nature and contents of container	Addition of 45g pack size