

New Zealand Datasheet

1 PRODUCT NAME

DIFFERIN™

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Adapalene 1 mg/g topical cream

3 PHARMACEUTICAL FORM

DIFFERIN topical cream is a smooth white cream containing 1 mg/g adapalene.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DIFFERIN topical cream 0.1% is indicated for the topical treatment of comedo, papular and pustular acne (acne vulgaris) of the face, chest or back.

4.2 Dosage and method of administration

A thin film of DIFFERIN topical cream should be applied to the affected areas once a day before bedtime and after washing avoiding the eyes lips and mucous membranes. The affected areas should be dry before application.

Clinical improvement is expected to be evident in four to eight weeks of treatment, with further improvement to be expected with continued use. Cutaneous safety of DIFFERIN topical cream has been demonstrated in 311 patients for up to 12 weeks of treatment. Since it is customary to alternate therapies in the treatment of acne vulgaris, it is recommended that the physician assess continued treatment of the patient with DIFFERIN topical cream after three months of use.

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

4.3 Contraindications

Not to be used in patients who are hypersensitive to the active substance or any of the excipients.

Pregnancy.

Women planning a pregnancy.

4.4 Special warnings and precautions for use

FOR EXTERNAL USE ONLY

DIFFERIN topical cream should not come into contact with the eyes, lips, mouth and mucous membranes, angles of the nose or broken skin (cuts and abrasions), sunburn or eczematous skin, nor should it be used in patients with severe acne involving large areas of the body. If product enters the eye, wash immediately with warm water. Because of a potential for increased irritation DIFFERIN topical cream should not be used by patients with eczema, seborrhoeic dermatitis or severe acne involving large areas of the body.

If a reaction suggesting severe irritation occurs, discontinue use of the medication. If the irritation is not severe, use the medication less frequently, discontinue use temporarily until symptoms subside, or discontinue use altogether.

If patients use cosmetics, these should be non-comedogenic and non-astringent. Only oil-free moisturisers should be used to relieve dry facial skin.

Because DIFFERIN topical cream may cause some irritation, it is possible that simultaneous use of abrasive cleansers, astringents or strong drying agents or irritant products may cause additive irritant effects.

Animal studies on compounds with a similar mode of action to adapalene have suggested 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. Whilst short term studies have shown no phototoxic to photoallergic potential of adapalene, small numbers of reactions consistent with phototoxicity were reported in clinical studies, 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 sunlight or UV irradiation (including sunlamps) should be avoided during treatment with adapalene. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided.

Efficacy and safety in the treatment of severe pustular or deep cystic acne (acne conglobulata) have not been studied.

DIFFERIN Cream contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) that can cause allergic reactions (can arise after the treatment is completed).

Use in children

Safety and efficacy in children below the age of 12 years have not been studied.

Genotoxicity

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* and an *in vitro* test in mice.

Carcinogenicity

Lifetime studies with adapalene have been completed in mice at topical doses of 0.6, 2 and 6 mg/kg and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg. Phaeochromocytomas were observed in the adrenal medulla of male rats dosed at 1.5 mg/kg but not at the lower doses. This finding was not observed in female rats or in mice. The relevance of the finding in male rats to the use of DIFFERIN topical cream in acne vulgaris is not known.

4.5 Interaction with other medicines and other forms of interaction

There are no known interactions with other medications which might be used topically and concurrently with DIFFERIN topical cream; however other retinoids or drugs with a similar mode of action should not be used concurrently with adapalene. Exposure of adapalene to other topical anti-acne drugs such as erythromycin, clindamycin phosphate or benzoyl peroxide does not produce any mutual degradation.

Absorption of adapalene through human skin is low (see section 5.2) and therefore interaction with systemic medication is unlikely.

DIFFERIN topical cream has potential for local irritation and it is possible that concomitant use of peeling agents, astringents or irritant products may produce additive irritant effects.

4.6 Fertility, Pregnancy and lactation

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.

In pregnant rats and rabbits, adapalene administered orally at relatively high doses (≥ 25 mg/kg leading to exposures ≥ 25 times that anticipated clinically based on AUC) was found to induce foetal abnormalities. In addition, the incidences of various skeletal variations were increased at lower oral doses in rats. Topical administration at doses up to 6 mg/kg, resulting in an exposure level about 45 times greater (based on AUC) than that anticipated clinically, was not associated with teratogenicity. Nevertheless, increased incidences of various naturally occurring skeletal variations were still observed following topical administration to rats at 2mg/kg (AUC exposure about 13 times that anticipated clinically); topical no effect levels were 0.6 and 2mg/kg respectively (AUC about 5 times that anticipated clinically).

Because of the risk of teratogenicity shown in animals, and since there are no adequately controlled studies in pregnant women, adapalene should not be used by women who are pregnant or who plan to become pregnant during treatment. DIFFERIN should not be used during pregnancy. In case of unexpected pregnancy, treatment should be discontinued.

Use in lactation

It is not known whether adapalene is excreted in human milk. Therefore, the preparation should be used with caution in nursing mothers, and only on areas away from the chest. DIFFERIN can be used during breastfeeding. To avoid contact exposure of the infant, application of DIFFERIN to the chest should be avoided when used during breast-feeding.

4.7 Effects on ability to drive and use machines

DIFFERIN Cream has no influence on the ability to drive and use machines.

4.8 Undesirable effects

A feeling of warmth, burning, pruritus, dryness, scaling or slight stinging may occur following application. Local adverse events may persist despite cessation of therapy. No systemic reactions have been attributed to the application of the cream to date. The allergic potential of adapalene has not been established.

Side Effects

The incidences of cutaneous side effects reported by patients treated with Adapalene (1mg/g) cream during clinical trials were as follows:

Common (> 1% and < 10%):	Redness
	Dry skin
	Burning sensation at the site of application
	Scaling
	Skin irritation
	Erythema
	Sunburn
Uncommon (> 0.1% and < 1%):	Contact dermatitis/eczema
	Skin discomfort
	Skin exfoliation

Acne flare
 Facial and eyelid oedema
 Vesiculobullous eruptions
 Herpes labialis
 Conjunctivitis
 Pruritus

Most reactions occurred within one month of the initiation of therapy and were generally observed to resolve with continued use of the product or temporary adjustment of the treatment schedule. The incidence of patients withdrawing from the trials because of these topical effects was 7/311 (2.2%).

Table: Adverse events (> 1%) reported by patients treated with Adapalene (1mg/g) cream, Adapalene vehicle and Tretinoin cream during controlled clinical trials. These are not necessarily drug related.

	Adapalene cream (n= 311) Incidence (%)	Adapalene Vehicle (n= 175) Incidence (%)	Tretinoin cream (n= 141) Incidence (%)
<i>Body as a whole</i>			
Flu syndrome	4.8%	3.4%	2.1%
Headache	7.4%	9.1%	-
Accidental injury	3%	-	-
Pain back	-	1%	-
Surg./Med. Procedure	-	1.5%	-
Unevaluable reaction	-	-	1.4%
<i>Digestive</i>			
Tooth Anomaly	-	1%	-
Tooth Disorder	1.2%	1%	-
<i>Respiratory System</i>			
Pharyngitis	-	2.8%	1.4%
Rhinitis	4.5%	6.0%	-
Sinusitis	-	1.7%	-
<i>Skin & Appendage</i>			
Skin Dry			2.1%
Skin Irritation	1.6%		2.9%
Sunburn	2.2%	3.4%	-
<i>Special Senses</i>			
Conjunctivitis		1.0%	
<i>Urogenital System</i>			
Dysmenorrhea	1.5%	4.0%	

Post Marketing Data

DIFFERIN topical cream 0.1% and DIFFERIN topical gel 0.1% are two formulations with the same active ingredient, adapalene. The gel formulation was first marketed in France in September 1995. The post marketing data detailed below refer to reports collected from the worldwide sales with the gel formulation.

Body as a Whole

Rare ($\geq 0.01\%$ and $\leq 0.1\%$): Allergic reaction
 Lack of drug effect

Immune System Disorders

Uncommon ($> 0.1\%$ and $< 1\%$): Anaphylactic reaction

Angioedema.

Skin and Subcutaneous Tissue Disorders

Common ($\geq 1\%$ and $< 10\%$):

Irritation
Redness
Dry skin
Burning sensation at the site of application
Erythema

Uncommon ($\geq 0.1\%$ and $\leq 1\%$):

Contact eczema
Contact dermatitis
Transient worsening of acne
Exfoliative dermatitis - predominantly associated with mechanical abrasion such as waxing
Skin discomfort,
Sunburn,
Pruritus,
Skin exfoliation,
Acne
Scaling
Application site burn
Skin hypopigmentation
Skin hyperpigmentation.

Unknown*:

Dermatitis allergic (allergic contact dermatitis).
Pain of skin
Skin swelling

Eye disorders:

Eyelid irritation
Eyelid erythema
Eyelid pruritus
Eyelid swollen

*Post marketing surveillance data

These events often spontaneously resolve upon adaptation to therapy regimen.

4.9 Overdose

DIFFERIN topical cream is intended for topical use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur.

DIFFERIN topical cream is not to be taken orally. The oral route toxicity for DIFFERIN Topical cream in mice is greater than 10 mL/kg. Unless the amount accidentally ingested is small, an appropriate method of gastric emptying should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: D10A Anti-Acne Preparations for Topical Use - ATC code: D10AD03

Adapalene is a chemically stable compound with retinoid-like pharmacological activity. Biochemical and pharmacological profile studies have demonstrated that adapalene is a

potent modulator of cellular differentiation, keratinisation and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but unlike tretinoin, does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown current evidence suggests that topical adapalene normalises 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 by lipoxidation, to inflammatory mediators.

Clinical Trials

The efficacy of DIFFERIN topical cream has been assessed in two randomised, double blind, parallel comparison clinical trials. In the first trial, 350 subjects with acne vulgaris associated with at least 20 facial non-inflammatory comedones and 10 inflammatory lesions were enrolled for treatment with DIFFERIN topical cream or the cream vehicle administered once daily. For DIFFERIN topical cream and vehicle groups respectively after twelve weeks treatment, the mean % reductions from baseline in total lesions were 32% vs 15% ($p < 0.05$), in non-inflammatory lesion counts were 37% vs 15% ($p < 0.05$) and investigator's global assessment scores were 1.13 vs 1.26 ($p < 0.05$). The difference between the treatment groups in % reduction in inflammatory lesions (15% vs 5%) was not statistically significant.

In the second trial, 277 subjects with acne vulgaris were enrolled for treatment with DIFFERIN topical cream or tretinoin cream 0.05% administered once daily. For DIFFERIN topical and tretinoin treatment groups respectively after twelve weeks treatment, the mean % reductions from baseline in total lesions were 60% vs 67% ($p < 0.05$), in non inflammatory lesions were 64% vs 72% ($p < 0.05$), in inflammatory lesions were 43% vs 56% ($p < 0.05$) and in the investigator's global assessment scores were 51% vs 57% ($p < 0.05$).

5.2 Pharmacokinetic properties

In clinical trials adapalene was seldom detected in plasma, and then only in trace amounts following chronic topical application with an analytical limit of quantification of 0.25 nanograms/mL. After administration of (^{14}C)-adapalene to rats, rabbits and dogs, radioactivity was distributed in several tissues, the highest levels being found in liver, spleen, adrenals and ovaries. Metabolism in animals is maintained by O-demethylation, hydroxylation and conjugation, and excretion is primarily by the biliary route.

In a human study performed using the gel formulation in which male volunteers followed a course of exaggerated topical application, 30g (a full tube) was applied all over the body each day for seven consecutive days, the resultant circulating plasma levels were below the limit of detection (0.15 nanogram mL^{-1}). There were low quantities of the parent substance in the faeces. In another study healthy volunteers used radiolabelled adapalene 0.1% topical gel, four of the subjects received 14 daily topical applications of non-radiolabelled adapalene 0.1% topical gel prior to the single application of radiolabelled adapalene 0.1% topical gel. The other four subjects received a single topical application of the radiolabelled product. Levels of radioactivity in all plasma, urine, faeces and skin strip samples analysed were below the limits of reliable quantification, indicating that either very little or no radioactivity was absorbed through the skin.

A further study carried out to investigate the distribution of adapalene in the adipose tissue of women after repeated daily application of adapalene gel for three months, found that there was no evidence of circulating adapalene in the plasma (limit of detection 0.15 nanogram mL^{-1}). On day 90, adapalene levels in the adipose tissue were not quantifiable in five of the six volunteers (limit of detection 1 nanogram g^{-1}). In the sixth volunteer the mean concentration at three sites was 1.1, 1.3 and 5.5 nanogram g^{-1} . These concentrations were

no longer evident when re-evaluated at the same sites in this subject one month after the cessation of treatment.

5.3 Preclinical safety data

In animal studies, adapalene was well tolerated on cutaneous application for periods of up to six months in rabbits and for up to two years in mice. The major symptom of toxicity found in all animal species by the oral route were related to a hypervitaminosis A syndrome, and included bone dissolution, elevated alkaline phosphatase and a slight anaemia. Large oral doses of adapalene produced no adverse neurological, cardiovascular or respiratory effects in animals. Adapalene is not mutagenic. Lifetime studies with adapalene have been completed in mice at cutaneous doses of 0.6, 2 and 6 mg/kg/day and in rats at oral doses of 0.15, 0.5 and 1.5 mg/kg/day. The only significant finding was a statistically significant increase of benign phaeochromocytomas of the adrenal medulla among male rats receiving adapalene at 1.5 mg/kg/day. These changes are unlikely to be of relevance to the cutaneous use of adapalene.

Adapalene produces teratogenic effects by the oral route in rats and rabbits. At cutaneous doses up to 200-fold the therapeutic dose, producing circulating plasma levels of adapalene at least 35 to 120 times higher than plasma levels demonstrated in therapeutic use, adapalene increased the incidence of additional ribs in rats and rabbits, without increasing the incidence of major malformations.

It is not known whether adapalene is secreted in animal or human milk. In animal studies, infant rats suckled by mother with circulating levels of adapalene at least 300 times those demonstrated in clinical use developed normally.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 934P, PEG-20 methyl glucose sesquistearate, glycerol, squalane, methyl hydroxybenzoate, propyl hydroxybenzoate, disodium edetate, methyl glucose sesquistearate, phenoxyethanol, cyclomethicone, sodium hydroxide, purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C and out of reach of children. Avoid exposure to excessive heat. Replace cap tightly after use.

Replace cap tightly after use.

6.5 Nature and contents of container

Collapsible aluminium tube of 5 g, 30 g or 50 g, coated internally with an epoxy-phenolic resin and fitted with a white polypropylene screw cap.

6.6 Special precautions for disposal

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

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

Sponsor and distributor in New Zealand
Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand
Ph (09) 918 5100
Fax (09) 918 5101

For:

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

9 DATE OF FIRST APPROVAL

17 December 1998

10 DATE OF REVISION OF THE TEXT

12 December 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Additional adverse effects added for Anaphylactic reaction, Angioedema, Scaling, Application site burn, Skin hypopigmentation, Skin hyperpigmentation