AUSTRALIAN PRODUCT INFORMATION
DIFFERIN® (ADAPALENE) TOPICAL GEL

1 NAME OF THE MEDICINE

Adapalene

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect

Methyl hydroxybenzoate

For the full list of excipients see section **6.1 List of excipients**

3 PHARMACEUTICAL FORM

Topical gel

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

A thin film of DIFFERIN Topical Gel 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 gel has been demonstrated in 85 patients for up to 26 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 gel after three months of use.

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 gel 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 gel 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 Gel 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.

Differin Gel contains Methyl hydroxybenzoate (E218) that can cause allergic reactions (can arise after the treatment is completed) and propylene glycol that can be irritating to the skin.

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 avoided.

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

Use in the elderly

No data available.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There are no known interactions with other medications which might be used topically and concurrently with DIFFERIN® topical gel; 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 Pharmacokinetic properties**) and therefore interaction with systemic medication is unlikely.

DIFFERIN® topical gel 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

Effects on fertility

No data available.

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 2 mg/kg (AUC exposure about 13 times that anticipated clinically); topical no effect levels were 0.6 and 2 mg/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. 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.

Cautionary use of Differin during breast feeding should 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

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

A feeling of warmth, burning, pruritis, 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 gel to date. The allergic potential of adapalene has not been established.

The most frequent side effects reported at some point in time during three to six month clinical trials were erythema which ranged from 6% to 27% in different studies; dryness (6% to 37%); scaling (4% to 63%); pruritis (4% to 11%); and burning after application (7% to 33%). 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 proportion of patients withdrawing from the trials because of these topical effects was 1.6%. Reactions consistent with phototoxicity have been reported in the clinical studies.

Other infrequent cutaneous adverse events reported which may be related to the application of adapalene included contact dermatitis/eczema, skin discomfort, skin exfoliation, vesiculobullous eruptions, sunburn, herpes labialis, acne flare and eyelid oedema.

Post Marketing Data

Differin Cream 0.1% and Differin 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 world wide sales with the gel formulation.

Body As A Whole

Rare (> 0.01% and < 0.1%):	Allergic reaction
	Lack of drug effect

Immune System Disorders

Uncommon (> 0.1% and < 1%): Anaphylactic reaction and Angioedema.

Skin and Subcutaneous Tissue Disorders

Very common (> 10%):	Irritation
	Redness
	Dry skin
	Burning sensation at the site of application
Common (> 1% and < 10%):	Erythema
Uncommon (> 0.1% and < 1%):	Contact eczema, contact dermatitis**,** transient worsening of acne, exfoliative dermatitis - predominantly associated with mechanical abrasion such as waxing.
	Pain of skin, skin swelling, eyelid irritation, eyelid erythema, eyelid pruritus, eyelid swollen, skin discomfort, sunburn, pruritis, skin exfoliation, acne, application site burn, skin hypopigmentation and skin hyper pigmentation.
Unknown*:	Dermatitis allergic (allergic contact dermatitis)

*Post marketing surveillance data

These events often spontaneously resolve upon adaptation to therapy regimen.

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 and contact Galderma.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

No data available.

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 ng/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 7 consecutive days, the resultant circulating plasma levels were below the limit of detection (0.15 ng.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, 4 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 4 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 3 months, found that there was no evidence of circulating adapalene in the plasma (limit of detection 0.15 ng.mL^{-1}). On day 90, adapalene levels in the adipose tissue were not quantifiable in 5 of the 6 volunteers (limit of detection 1 ng.g^{-1}). In the 6th volunteer the mean concentration at 3 sites was 1.1, 1.3 and 5.5 ng.g^{-1}. These concentrations were no longer evident when re-evaluated at the same sites in this subject 1 month after the cessation of treatment.

5.3 PRECLINICAL SAFETY DATA

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 Gel in acne vulgaris is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Carbomer 940
- propylene glycol
- poloxamer
- disodium edetate
- methyl hydroxybenzoate
- phenoxyethanol
- sodium hydroxide
- 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.

The product should not be used beyond the date indicated on the label on the carton.

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.

6.5 NATURE AND CONTENTS OF CONTAINER

5g white, low density polyethylene tube with white polypropylene cap.

30g white, low density polyethylene tube with white polypropylene cap.

50g white, low density polyethylene tube with white polypropylene cap.

Marketing Authorisation Number: Aust. R 53918

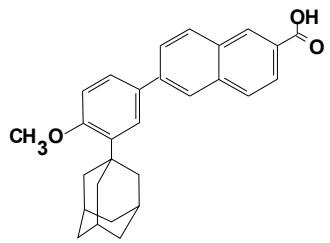
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Common Name: Adapalene

Chemical Name: 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid.

Molecular Formula: C_{28} H_{28} O_3

Molecular Weight: 412.52

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Galderma Australia
Suite 4, 13B Narabang Way
Belrose NSW 2085
Call 1800 800 765 (Australia)

Distributed in New Zealand by:

Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
Call 0800 174 104 (New Zealand)

9 DATE OF FIRST APPROVAL

29 November 1995

10 DATE OF REVISION

12 March 2020

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information; minor editorial changes
4.8 Adverse Reactions	Application site burn, skin hypopigmentation and skin hyperpigmentation with frequency unknown have been included under Skin and subcutaneous tissue disorders. Immune System Disorders category has been included.