Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Differin 0.1% w/w Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Adapalene 0.1% w/w
Excipients with known effect:
One gram of gel contains 40mg of Propylene glycol (E1520)
Methyl Parahydroxybenzoate (E218).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel.

A smooth white gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Differin Gel is proposed for the cutaneous treatment of acne vulgaris where comedones, papules and pustules predominate. Acne of the face, chest or back is appropriate for treatment.

4.2 Posology and method of administration

Differin Gel should be applied to the acne affected areas once a day before retiring and after washing. A thin film of the gel should be applied avoiding the eyes and lips (see 4.4 Special warnings and special precautions for use, below). Ensure that the affected areas are dry before application.

Since it is customary to alternate therapies in the treatment of acne, it is recommended that the physician assess the continued improvement of the patient after three months of treatment with Differin Gel.

With patients for whom it is necessary to reduce the frequency of application or to temporarily discontinue treatment, frequency of application may be restored or therapy resumed once it is judged that the patient can again tolerate the treatment.

If patients use cosmetics, these should be non-comedogenic and non-astringent.

Paediatric population: The safety and effectiveness of Differin Gel have not been studied in children below 12 years of age.

4.3 Contraindications

Pregnancy (see section 4.6).
Women planning a pregnancy.
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

If a reaction suggesting sensitivity or severe irritation occurs, use of the medication should be discontinued. If the degree of local irritation warrants, the patient should be directed to use the medication less frequently, to discontinue use temporarily until symptoms subside, or to discontinue use altogether. Differin Gel should not come into contact with the eyes, mouth, angles of the nose (outer, lower folds) or mucous membranes. If product enters the eye, wash immediately with warm water.

The product should not be applied to either broken (cuts and abrasions), sunburned or eczematous skin, nor should it be used in patients with severe acne involving large areas of the body.
Exposure to sunlight should be minimised during use of Differin Gel.
For use in women of child bearing potential, pregnancy and lactation see section 4.6.
This medicine contains 40mg propylene glycol (E1520) in each gram which is equivalent to 4% w/w. It may cause skin irritation.
This medicine also contains methyl parahydroxybenzoate (E218). It may cause allergic reactions which can possibly be delayed.

4.5 Interaction with other medicinal products and other forms of interaction

There are no known interactions with other medications which might be used cutaneously and concurrently with Differin Gel, however, other retinoids or drugs with a similar mode of action should not be used concurrently with adapalene.

Adapalene is essentially stable to oxygen and light and is chemically non-reactive. Whilst extensive studies in animals and man have shown neither phototoxic nor photoallergic potential for adapalene, the safety of using adapalene during repeated exposure to sunlight or UV irradiation has not been established in either animals or man. Exposure to excessive sunlight or UV irradiation should be avoided.

Absorption of adapalene through human skin is low (see 5.2 Pharmacokinetic properties), and therefore interaction with systemic medications is unlikely. There is no evidence that the efficacy of oral drugs such as contraceptives and antibiotics is influenced by the cutaneous use of Differin Gel.

Differin Gel has a potential for mild local irritation, and therefore it is possible that concomitant use of peeling agents, abrasive cleaners, strong drying agents, astringents or irritant products (aromatic and alcoholic agents) may produce additive irritant effects.

However, cutaneous antiacne treatment, (e.g. erythromycin up to 4%) or clindamycin phosphate (1% as the base) solutions or benzoyl peroxide water based gels up to 10% may be used in the morning when Differin Gel is used at night as there is no mutual degradation or cumulative irritation.

4.6 Fertility, pregnancy and lactation

Pregnancy :
Animal studies by the oral route have shown reproductive toxicity at high systemic exposure (see section 5.3). Clinical experience with locally applied adapalene in pregnancy is limited and the safe use of Differin in pregnancy has not been established, but the limited available data do not indicate harmful effects on pregnancy or on the health of the foetus exposed in early pregnancy. Due to the limited available data and because a very weak cutaneous passage of adapalene is possible Differin should not be used in pregnancy or in those intending to conceive. Physicians should ensure that female patients are not pregnant or trying to conceive before prescribing Differin. In case of unexpected pregnancy, treatment should be discontinued.

Breast-feeding:
No study on animal or human milk transfer was conducted after cutaneous application of Differin. No effects on the suckling child are anticipated since the systemic exposure of the breast-feeding woman to Differin is negligible. 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 Gel has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Differin Gel may cause the following adverse drug reactions:

Body System (MeDRA)	Frequency	Adverse Drug Reaction
Skin and subcutaneous tissue disorders	Common (≥1/100 to <1/10)	Dry skin, skin irritation, skin burning sensation, erythema
	Uncommon (≥1/1000 to <1/100)	Dermatitis contact, skin discomfort, sunburn, pruritus, skin exfoliation, acne

	Unknown*	Dermatitis allergic (allergic contact dermatitis), pain of skin, skin swelling
Eye disorders	Unknown*	eyelid irritation, eyelid erythema, eyelid pruritus, eyelid swelling
Immune system disorders	Unknown*	Anaphylactic reaction, angioedema

*Post marketing surveillance data
** Most of the cases of "application site burn" were superficial burns but cases with second degree burn reactions have been reported.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professional are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel + 353 1 6764971; Fax: + 353 1 6762517. Website: www.hpra.ie, Email: medsafety@hpra.ie

4.9 Overdose

Differin Gel is not to be taken orally and is for cutaneous 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.

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 retinoid-like compound which in in-vivo and in -vitro models of inflammation, has been demonstrated to possess anti -inflammatory properties: Adapalene is essentially stable to oxygen and light and is chemically non-reactive. Mechanistically, adapalene binds like tretinion to specific retinoic acid nuclear receptors but, unlike tretinion, not to cytosolic receptor binding proteins.

Adapalene applied cutaneously is comedolytic in the rhino mouse model and also has effects on the abnormal processes of epidermal keratinization and differentiation, both of which are present in the pathogenesis of acne vulgaris. The mode of action of adapalene is suggested to be a normalisation of differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

Adapalene is superior to reference retinoids in standard anti-inflammatory assays, both in-vivo and in-vitro. Mechanistically, it inhibits chemotactic and chemokinetic responses of human polymorphonuclear leucocytes and also the metabolism by lipoxidation of arachidonic acid to pro-inflammatory mediators.

The profile suggests that the cell mediated inflammatory component of acne may be modified by adapalene. Studies in human patients provide clinical evidence that cutaneous adapalene is effective in reducing the inflammatory components of acne (papules and pustules).

5.2 Pharmacokinetic properties

Absorption of adapalene through human skin is low: in clinical trials measurable plasma adapalene levels were not found following chronic cutaneous application to large areas of acneic skin with an analytical sensitivity of 0.15 ng/ml.

After administration of [14C] adapalene in rats (IV, IP, oral and cutaneous), rabbits (IV, oral and cutaneous) and dogs (IV and oral), radioactivity was distributed in several tissues, the highest levels being found in liver, spleen, adrenals and ovaries. Metabolism in animals has been tentatively identified as being mainly O-demethylation, hydroxylation and conjugation, and excretion is primarily by the billary route.

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 symptoms of toxicity found in all animal species by the oral route were related to an hypervitaminosis A syndrome, and included bone dissolution, elevated alkaline phosphatase and slight anaemia.

Large oral doses of adapalene produced no adverse neurological, cardiovascular or respiratory effects in animals.

Adapalene is not mutagenic. As expected for a retinoid-like substance 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer
Propylene glycol (E1520)
Poloxamer 182
Disodium edetate
Methyl parahydroxybenzoate (E218)
Phenoxyethanol
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.

6.5 Nature and contents of container

White LDPE tube with white PP screw cap.
Pack sizes: 30g, 45g, 50g and 60g
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Galderma International
La Défense 4 Tour Europlaza
20 Avenue André Prothin
Paris La Défense Cedex
92927
France

8 MARKETING AUTHORISATION NUMBER

PA22743/005/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th November 1994
Date of last renewal: 1st March 2008

9 DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

10 DATE OF REVISION OF THE TEXT

April 2024