Differin®
adapalene
GEL

PRODUCT INFORMATION

COMPOSITION

Differin Gel contains 0.1% w/w adapalene (BAN, INN, USAN), as the active ingredient in a gel base containing carbomer, propylene glycol, poloxamer 182, disodium edetate, methyl parahydroxybenzoate, phenoxyethanol, sodium hydroxide to adjust the pH to 5 and purified water to complete the formulation.

PHARMACOLOGICAL PROPERTIES

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 tretinoin to specific retinoic acid nuclear receptors but, unlike tretinoin, 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. This 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).

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-1. 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 by O-demethylation, hydroxylation and conjugation, and excretion is primarily by the billary route.

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 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-1.d-1 and in rats at oral doses of 0.15, 0.5 and 1.5 mg.kg-1.d-1. 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-1.d-1. These changes are considered to have no relevance to the cutaneous use of adapalene.

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.

CONTRA-INDICATIONS

Pregnancy (see section Pregnancy and Lactation).
Women planning a pregnancy.
Hypersensitivity to any ingredient of the product.

UNDESIRABLE EFFECTS

Differin may cause the following adverse drug reactions:

Body System (MedDRA)	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, application site burn**, skin hypopigmentation, skin hyperpigmentation
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.

WARNINGS AND PRECAUTIONS

General: If a reaction suggesting sensitivity or severe irritation occurs, use of the medication should be discontinued. If the degree of local irritation warrants, patients 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 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), sunburn or eczematous skin, nor should it be used in patients with severe acne.

Exposure to excessive sunlight or UV irradiation should be avoided.

PREGNANCY AND LACTATION

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 into 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.

Pregnancy: Differin is contraindicated (see section Contraindications) in pregnancy, or in women planning a pregnancy. If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.
Lactation: It is not known whether this drug is excreted in animal or human milk. Because many drugs are excreted in human milk, caution should be exercised when Differin Gel is administrated to nursing mothers. In this event, the product should not be used on the chest.

INTERACTIONS

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, 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, astringents or irritant products may produce additive irritant effects. However, cutaneous antiacne treatments, 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.

DOSAGE AND ADMINISTRATION

Differin Gel should be applied to the acne affected areas once a day before retiring and after washing. A thin film of the product should be applied avoiding the eyes and lips (see Warnings and Precautions). Ensure that the affected areas are dry before application.
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.
The safety and effectiveness of Differin Gel has not been studied in neonates and young children.

INSTRUCTIONS FOR USE:

Squeeze the tube gently at its base to place a quantity of product on the fingertips sufficient to cover the affected areas. Replace the cap tightly after use.

OVERDOSAGE

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.
The acute oral dose of Differin Gel required to produce toxic effects in mice is greater than 10 g/kg. Nevertheless, unless the amount accidentally ingested is small, an appropriate method of gastric emptying should be considered.

EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

Based upon the pharmacodynamic profile and clinical experience, performance related to driving and using machines should not be affected.

SHELF-LIFE

This medicine should not be used after the expiry date (Exp. Date) shown on the pack.

STORAGE

Store at room temperature (not exceeding 25°C).
Avoid freezing during transport and storage.
Keep out of reach of children.

CONTAINER

Differin Gel is packaged in 15g and 30g white low density polyethylene tubes fitted with white polypropylene screw caps.

Manufactured by:
Laboratoires Galderma
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