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Adapalene Differin®

ANTI – ACNE

PRODUCT DESCRIPTION

Adapalene (Differin) 0.1% (1mg/g) Gel: smooth white homogenous gel
Adapalene (Differin) 0.3% (3mg/g) Topical Gel: white to pale yellow gel
Adapalene (Differin) 0.1% (1mg/g) Cream: white, shiny cream

FORMULATION

Adapalene (Differin) 0.1% (1mg/g) Gel:
One gram contains:
Adapalene Ph. Eur. ..... 1 mg
Excipients: Carbomer 940, Propylene Glycol, Poloxamer 182, Disodium edetate, Methyl para-hydroxybenzoate, Phenoxyethanol, Sodium hydroxide solution (qs pH = 5.0) and Purified water.
Excipients with known effect:
methyl parahydroxybenzoate (E218)
propylene glycol: One gram of gel contains 40mg of Propylene glycol (E1520)

Adapalene (Differin) 0.3% (3mg/g) Topical Gel:
One gram contains:
Adapalene Ph. Eur. ..... 3 mg
Excipients: Carbomer 934P, PEG-20 methyl glucose sesquistearate, Glycerol, Natural squalane, Methyl parahydroxybenzoate, Propyl parahydroxybenzoate, Disodium edetate, Methyl glucose sesquistearate, Phenoxyethanol, Cyclomethicone, Sodium hydroxide solution (qs pH = 6.3 to 6.7) and Purified water.
Excipients with known effect: methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216)

Adapalene (Differin) 0.1% (1mg/g) Cream:
One gram contains:
Adapalene Ph. Eur. ..... 1 mg
Excipients: Carbomer 934P, PEG-20 methyl glucose sesquistearate, Glycerol, Natural squalane, Methyl parahydroxybenzoate, Propyl parahydroxybenzoate, Disodium edetate, Methyl glucose sesquistearate, Phenoxyethanol, Cyclomethicone, Sodium hydroxide solution (qs pH = 6.3 to 6.7) and Purified water.
Excipients with known effect: methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).

PHARMACODYNAMICS AND PHARMACOKINETICS

Pharmacodynamic Properties

Adapalene is a chemically stable, naphthoic acid derivative with retinoid-like activity. Biochemical and pharmacological profile studies have demonstrated that adapalene acts in the pathology of Acne vulgaris: it is a potent modulator of cellular differentiation and keratinisation and it has anti-inflammatory properties. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors. Current evidence suggests that topical adapalene normalizes 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 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 suggests that the cell mediated inflammatory component of acne is reduced by adapalene.
The clinical significance of these findings for the mitigation of facial photoaging is unknown.

Pharmacokinetic Properties

A pharmacokinetic trial was conducted in 50 adults with acne vulgaris who were treated with once-daily applications during a 4-week period with 2 grams/day of Adapalene (Differin) 0.1 % GEL or Adapalene (Differin) 0.3 % GEL applied as a thin layer to the face, shoulders, upper chest and upper back.

- Over the 4-week treatment with Adapalene (Differin) 0.1 % GEL, only 4 to 7 subjects out of 25 had quantifiable adapalene plasma concentrations above the limit of quantification of 0.1 ng/mL at steady state, with a mean Cmax of 0.04 ± 0.08 ng/mL and a mean AUC0-24h of 0.50 ± 0.99 ng.h/mL The most exposed subject had adapalene Cmax and AUC0-24h of 0.31 ng/mL and 3.47 ng.h/mL, respectively.
- Over the 4-week treatment with Adapalene (Differin) 0.3 % GEL, 20 to 22 subjects out of 25 had quantifiable adapalene plasma concentrations above the limit of quantification of 0.1 ng/mL at steady state, with a mean Cmax of 0.18 ± 0.09 ng/mL and a mean AUC0-24h of 2.84 ± 1.75 ng.h/mL. The most exposed subject had adapalene Cmax and AUC0-24h of 0.40 ng/mL and 5.99 ng.h/mL, respectively.

Similar results were observed in adult and adolescent subjects (12 years of age and older) with acne vulgaris who were treated with once-daily applications during a 4-week period with, on average, 1.95 grams/day (range 1.2 – 2.9 grams/day) of Differin 0.1 % gel or with on average, 2.3 grams/day (range 1.4 – 3.2 grams/day) of Differin 0.3 % gel applied as a thin layer to the face, shoulders, upper chest and upper back.

- Over the 4-week treatment with Adapalene (Differin) 0.1 % GEL in 24 adult and adolescent subjects (12 years of age and older) with moderate to severe acne vulgaris, all the subjects had quantifiable adapalene plasma concentrations above the limit of quantification of 0.02 ng/mL at steady state, with a mean Cmax of 0.05 ± 0.03 ng/mL and a mean AUC0-24h of 0.87 ± 0.43 ng.h/mL. The most exposed subject had adapalene Cmax and AUC0-24h of 0.17 ng/mL and 2.90 ng.h/mL, respectively.
- Over the 4-week treatment with Adapalene (Differin) 0.3 % GEL in 30 adult and adolescent subjects (12 years of age and older) with severe acne vulgaris, 14 to 16 subjects had quantifiable adapalene plasma concentrations above the limit of quantification of 0.1 ng/mL at steady state, with a mean Cmax of 0.15 ± 0.08 ng/mL and a mean AUC0-24h of 2.47 ± 1.31 ng.h/mL. The most exposed subject had adapalene Cmax and AUC0-24h of 0.46 ng/mL and 7.40 ng.h/mL, respectively.

Excretion of adapalene appears to be primarily by the biliary route.

INDICATIONS

Adapalene (Differin) 0.1% (1mg/g) Gel, 0.3% (3mg/g) Topical Gel, and 0.1% (1mg/g) Cream:
Adapalene (Differin) products are indicated for the cutaneous treatment of acne vulgaris. Acne of the face, chest or back is appropriate for treatment.

Adapalene (Differin) 0.3% (3mg/g) Topical Gel:
Indicated also for the treatment of facial skin photoaging which is a consequence of exposure to the sun. It helps to minimize the signs of photodamage skin which may include fine wrinkles and some types of hyperpigmentation such as blemishes, related to sun exposures, and when use together with appropriate skin care and sunlight avoidance programs.

DOSAGE AND ROUTE OF ADMINISTRATION

Adapalene (Differin) products should be applied to the face acne affected areas once a day at bedtime and after washing. Ensure that the affected areas are dry before application. A thin film of the product should be applied avoiding the eyes, lips and mucous membranes and the angles of the nose. (See SPECIAL WARNINGS AND PRECAUTIONS).
Clinical improvement for acne vulgaris is expected to be evident in four to eight weeks of treatment. Further improvement may be assessed after three months of treatment with Adapalene (Differin).
Clinical improvement for facial photoaging, periorbital wrinkles, ephelides/melanosis and forehead wrinkles is expected in 12 weeks. Further improvement may be assessed after 24 weeks of treatment with Adapalene (Differin) 0.3%.
Cutaneous safety of Adapalene (Differin) products has been demonstrated over a 12- months period.
If patients use cosmetics, these should be non-comedogenic and non-astringent.
The safety and effectiveness of Adapalene (Differin) products have not been studied in children below 12 years of age.
The safety and effectiveness of Adapalene (Differin) 0.3% has not been established in patients under the age of 35 years of age with facial photoaging.
Safety and effectiveness in geriatric patients age 65 and above have not been established.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.
Pregnancy and women planning a pregnancy.

SPECIAL WARNINGS AND PRECAUTIONS

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, should be instructed to either use a moisturizer, to discontinue use temporarily until symptoms subside or to discontinue use altogether. Once daily application may be resumed if it is judged that the patient is able to tolerate the treatment.
Adapalene (Differin) products 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.
Adapalene (Differin) products should not be used in patients with severe acne involving large areas of the body. As with other retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with adapalene.
As Adapalene (Differin) products have the potential to induce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect and products with high concentrations of alcohol, astringents, spices, or lime) should be considered with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with Adapalene (Differin) products. If these preparations have been used, it is advisable not to start therapy with Adapalene (Differin) products until the effects of such preparations have subsided
Exposure to sunlight and artificial UV irradiation, including sunlamps, should be minimized during use of adapalene. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with Adapalene (Differin) products.
Allergic/hypersensitivity reactions have been reported during postmarketing use of adapalene. A patient should stop using Adapalene (Differin) products and consult a doctor if allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) occur during treatment.

Adapalene (Differin) 0.1% and 0.3% Gel contain:

- methyl parahydroxybenzoate (E218). It may cause allergic reactions which can possibly be delayed.

Adapalene (Differin) 0.1% Cream contains:

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

Effects on ability to drive and use machines

Adapalene (Differin) products have no influence on the ability to drive and use machines

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 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.

Pregnancy

Animal studies by the oral route have shown reproductive toxicity at high systemic exposure.
Clinical experience with locally applied Differin products in pregnancy is limited but the few available data do not indicate harmful effects on pregnancy or on the health of the foetus exposed in early pregnancy. Differin products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Due to the limited available data and because a very weak cutaneous passage of adapalene is possible, Adapalene (Differin) should not be used during pregnancy. In case of unexpected pregnancy, treatment should be discontinued.
Physicians should ensure that female patients are not pregnant or trying to conceive before prescribing Adapalene (Differin) products.

Lactation

It is not known whether Adapalene (Differin) products are excreted in animal or human milk after cutaneous application of Adapalene (Differin) products. In animal studies, infant rats suckled by mother with circulating levels of adapalene at least 300 times those demonstrated in clinical use developed normally. Because many drugs are excreted in human milk, caution should be exercised when Adapalene (Differin) products are administered to a nursing woman.
Adapalene (Differin) can be used during breastfeeding. To avoid contact exposure of the infant, application of Adapalene (Differin) to the chest should be avoided when used during breast-feeding.

INTERACTIONS

Absorption of adapalene through human skin is low (see Pharmacokinetic properties), and therefore interaction with systemic medications is unlikely.
There are no formal drug-drug interaction studies conducted with other medications which might be used cutaneously and concurrently with Adapalene (Differin) products.
Cutaneous antiacne treatments such as 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 with Adapalene (Differin) products used at night as there is no mutual degradation or cumulative irritation. However, other retinoids or drugs with a similar mode of action should not be used concurrently with Adapalene (Differin) products.
Adapalene (Differin) products are 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 (Differin) products, the safety of using Adapalene (Differin) products 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.
Adapalene (Differin) products have a potential for mild local irritation, and therefore it is possible that concomitant use of peeling agents, abrasive cleansers, strong drying agents, astringents or irritant products (aromatic and alcoholic agents) may produce additive irritant effects.

ADVERSE DRUG REACTIONS

Adapalene (Differin) products 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.

OVERDOSE AND TREATMENT

Adapalene (Differin) products are not to be taken orally and are for cutaneous use only.
The oral route toxicity for Adapalene (Differin) products in mice is greater than 10 mL/kg. Unless the amount accidentally ingested is small, an appropriate method of gastric emptying should be considered.

STORAGE CONDITIONS

Adapalene (Differin) 0.1% Gel:
Store at temperatures not exceeding 25°C. Avoid freezing during transport and storage. Keep out of reach of children.
Adapalene (Differin) 0.3% Topical Gel:
Store at temperatures not exceeding 30°C. Keep from freezing. Keep container tightly closed. Keep in a safe place. Keep out of reach of children.
Adapalene (Differin) 0.1% Cream:
Store at temperatures not exceeding 30°C. Avoid freezing during transport and storage. Keep out of reach of children.

AVAILABILITY

Adapalene (Differin) 0.1% (1mg/g) Gel White LDPE Tube with White Polypropylene Screw Cap x 15g and 30g (Box of 1's)
Adapalene (Differin) 0.3% (3mg/g) Topical Gel White LDPE Tube with White Polypropylene Screw Cap x 15g and 30g (Box of 1's)
Adapalene (Differin) 0.1% (1mg/g) Cream White collapsible aluminum tube with white polypropylene screw cap x 30g (Box of 1's)

MANUFACTURER

Adapalene (Differin) 0.1% Cream and 0.1% Gel:
Laboratoires Galderma, Zi Montdesir, Alby-sur-Cheran, 74540, France

(Differin) 0.3% Topical Gel:
Galderma Brasil Ltda., Rodovia SP 10 I, Km. 9 s/n Condominio Techtown-Chacara Assay - Hortolandia- Sao Paulo, Brazil

MARKETING AUTHORIZATION HOLDER

Galderma Philippines, Inc.
35th Floor, Joy-Nostalg Center, No. 17 ADB Avenue, Ortigas Center, Pasig, Metro Manila

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph and to Galderma Local Safety Officer at philippines.pharmacovigilance@galderma.com.
Seek medical attention immediately at the first sign of ADR.

Adapalene (Differin) 0.1% (1mg/g) Gel: DR-XY22369
Adapalene (Differin) 0.3% (3mg/g) Topical Gel: DR-XY43033
Adapalene (Differin) 0.1% (1mg/g) Cream: DR-XY27030

DATE OF RENEWAL OF THE AUTHORIZATION

Adapalene (Differin) 0.1% (1mg/g) Gel: 07 December 2021
Adapalene (Differin) 0.3% (3mg/g) Topical Gel: 13 December 2018
Adapalene (Differin) 0.1% (1mg/g) Cream: 30 July 2020

DATE OF REVISION OF PACKAGE INSERT: 12 May 2023

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GALDERMA

FRONT

DIFFERIN 0.1% 15G COMMON INSERT (GPIAW-24007)

BACK

APPROVED
By Samuel Evan Pacamparra at 2:43 pm, Feb 23, 2024