SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Differin 0.1% w/w Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Adapalene 0.1% w/w.
1g cream contains 1mg adapalene.

Excipients with known effect:
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Cream
White shiny cream

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Differin Cream is proposed for the cutaneous treatment of mild to moderate acne vulgaris where comedones, papules and pustules predominate. Differin Cream is best suited for use on dry and fair skin. Acne of the face, chest or back is appropriate for treatment.

4.2 Posology and method of administration

Differin Cream should be applied to the acne affected areas once a day before retiring and after washing. A thin film of cream should be applied, with the fingertips, 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 Cream.

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 Cream 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, patients should be directed to use the medication less frequently, to discontinue use temporarily until symptoms subside or to discontinue use altogether. Differin Cream 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), sunburnt or eczematous skin, nor should it be used in patients with severe acne, or acne involving large areas of the body.

Exposure to sunlight and artificial UV irradiation, including sunlamps, should be minimised during use of adapalene. Patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided.

Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) 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 Cream; 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 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 Cream.

Differin Cream 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 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 Cream is used at night as there is no mutual degradation or cumulative irritation.

4.6 Fertility, 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:
Differin is contraindicated (see section 4.3) in pregnancy, or in women planning a 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 but the few 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 during pregnancy. If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, 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 Cream has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Differin 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, application site burn**, skinhypopigmentation, 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 burns” 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 professionals are asked to report any suspected adverse reactions via www.medicinesauthority.gov.mt/adrportal

.9 Overdose

Differin Cream 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 Cream 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.

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. Mechanically, 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 keratinisation 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).

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 [^{14}C]-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 biliary 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 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
Macrogol-20 methyl glucose sesquistearate
Glycerol (E422)
Natural squalane
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Disodium edetate
Methyl glucose sesquistearate
Phenoxyethanol
Cyclomethicone
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.
Keep out of the sight and reach of children.

6.5 Nature and contents of container

Collapsible Aluminium tube coated internally with an epoxy-phenolic resin and fitted with a white Polypropylene screw cap. Pack sizes 5g (Sample Pack), 30g, 45g and 50g.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

A thin film of the cream should be applied, avoiding eyes, lips and mucous membranes.

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

7. MARKETING AUTHORISATION HOLDER

Galderma International
Tour Europlaza – La Defense 4
20, Avenue Andre` Prothin
92927 La Defense Cedex
France

8. MARKETING AUTHORISATION NUMBER

MA117/00201

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12th March 2007/15th January 2012

10. DATE OF REVISION OF THE TEXT

11/2019