PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S3**

1. NAME OF THE MEDICINE

Cream

DIFFERIN® CREAM

Gel

DIFFERIN® GEL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

DIFFERIN® CREAM contains: 1 mg/g [0,1 % (*m/m*)] adapalene in a hydrophilic cream.

DIFFERIN® GEL contains: 1 mg/g [0,1 % (*m/m*)] adapalene in a hydrophilic gel.

Differin Cream excipients: carbomer 934P, cyclomethicone, disodium edetate, glycerol (E422), macrogol-20 methyl glucose sesquistearate, methyl glucose sesquistearate, natural squalane, purified water and sodium hydroxide.

Differin Cream preservatives: Methylparaben 0,2 % (*m/m*), propylparaben 0,1 % (*m/m*) and phenoxyethanol 0,5 % (*m/m*).

Differin Gel excipients: carbomer 940, propylene glycol, poloxamer 182, disodium edetate, sodium hydroxide and purified water.

Differin Gel preservatives: Methylparaben 0,1 % (*m/m*) and phenoxyethanol 0,25 %.(*m/m*)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Differin Cream: A smooth, white, shiny cream.

Differin Gel: A smooth, white gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Differin Cream and Differin Gel is indicated for the treatment of *acne vulgaris* of the face, chest and back where comedones, papules and pustules predominate.

4.2 Posology and method of administration

Posology

Differin Cream and Differin Gel should be applied to the acne affected areas once a day before retiring and after washing.

A thin film of the cream or gel should be applied avoiding the eyes, lips and mucous membranes see section 4.4.

Clinical improvement is expected to be clearly evident after four to eight weeks of treatment with further improvement expected with continued use. 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 tolerate the treatment.

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

Differin Cream and Differin Gel should not be used in patients with severe acne.

Method of administration

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

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

Paediatric population

The safety and effectiveness of Differin Cream and Differin Gel have not been studied in children below 12 years of age, therefore, it should not be used in these patients.

4.3 Contra-indications:

Hypersensitivity to the active or any of the excipients listed in section 6.1.

Pregnancy (see section 4.6)

Women planning a pregnancy

4.4 Special warnings and precautions for use

Differin Gel contains:

- Methyl parahydroxybenzoate (E218) that can cause allergic reactions (can arise after the treatment is completed)
- Propylene glycol that can be irritating to the skin.

Differin Cream contains:

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

If a reaction suggesting sensitivity or severe irritation occurs, use of Differin Cream and Differin Gel should be discontinued.

If the degree of local irritation warrants, patients should be directed to use the medication less frequently, to discontinue use temporarily or to discontinue use altogether.

Differin Cream and Differin Gel should not come into contact with the eyes, mouth, angles of the nose or mucous membranes. If Differin Cream and Differin Gel come into contact with the eye, wash immediately with warm water.

Differin Cream and Differin Gel should not be applied to broken skin (cuts and abrasions) or to eczematous skin, nor should it be used in patients with severe acne involving large areas of the body, especially in women of childbearing age who are not on effective contraception.

Differin Cream and Differin Gel should not be used in patients with severe acne.

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 therefore be avoided.

Paediatric population

The safety and effectiveness of Differin Cream and Differin Gel have not been studied in children below 12 years of age, therefore, it should not be used in these patients.

4.5 Interaction~~s~~ with other medicines and other forms of interaction

There are no known interactions with other medications which might be used cutaneously and concurrently with Differin Cream and Differin Gel, however, other retinoids or medicines 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 therefore be avoided.

Absorption of adapalene through human skin is low, and therefore interaction with systemic medication is unlikely. There is no evidence that the efficacy of oral medicines such as contraceptives and antibiotics is influenced by the cutaneous use of Differin Cream and Differin Gel.

Differin Cream and Differin Gel has a potential for 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 creams up to 10 %, may be used in the morning when Differin Cream and Differin Gel 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 Cream and Gel are contraindicated (see section 4.3) in pregnancy, or in women planning a pregnancy.

In case of unexpected pregnancy, treatment should be discontinued.

Animal studies by the oral route have shown teratogenicity.

Lactation

No study on animal or human milk transfer was conducted after cutaneous application of Differin Cream and Differin Gel.

Safety in lactation has not been demonstrated.

Differin Cream and Differin Gel should not be used during breastfeeding.

4.7 Effects on ability to drive and the use of machines

Differin Cream and Differin Gel have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The side-effects tend to be more pronounced during the first two weeks of treatment.

The major undesirable effect which may occur is irritation of the skin which is reversible when treatment is reduced in frequency or discontinued.

Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) ~~that~~ can cause allergic reactions (can arise after the treatment is completed)

Propylene glycol can be irritating to the skin.

Differin Cream and 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)	Contact dermatitis, skin discomfort, sunburn, pruritus, skin exfoliation, acne flare
	Unknown*	Dermatitis allergic (allergic contact dermatitis), skin pain, 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.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Refer to section 4.8.

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

If the medication is applied excessively, no more rapid results will be obtained and marked redness, peeling or discomfort may occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 13.12 Acne preparations.

Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinisation and inflammatory processes all of which represent important features in the pathology of *acne vulgaris*.

Adapalene binds to specific retinoid 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

cutaneous 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. This profile suggests that the cell-mediated inflammatory component of acne is modified by adapalene.

Studies in human patients provide clinical evidence that cutaneous adapalene is effective in reducing the inflammatory components of acne (i.e. papules and pustules).

5.2 Pharmacokinetic properties

Absorption

Absorption of adapalene through human skin is low.

Elimination

Metabolism in animals is mainly by O-demethylation, hydroxylation and conjugation, and excretion is primarily by the biliary route.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Differin Cream excipients: carbomer 934P, cyclomethicone, disodium edetate, glycerol (E422), macrogol-20 methyl glucose sesquistearate, methyl glucose sesquistearate, natural squalane, purified water and sodium hydroxide.

Differin Cream preservatives: Methylparaben 0,2 % (*m/m*), propylparaben 0,1 % (*m/m*) and phenoxyethanol 0,5 % (*m/m*).

Differin Gel excipients: carbomer 940, propylene glycol, poloxamer 182, disodium edetate, sodium hydroxide and purified water.

Differin Gel preservatives: Methylparaben 0,1 % (*m/m*) and phenoxyethanol 0,25 %.(*m/m*)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Do not refrigerate. Keep tube well closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Differin Cream: Collapsible aluminium tube internally coated with an epoxy-phenolic resin and fitted with a white polypropylene screw cap, containing 30 g or 60 g cream.

Differin Gel: Plastic tube fitted with a white polypropylene cap, containing 30 g gel.

Single tubes are packed in folded carton boxes.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Galderma Laboratories South Africa (Pty) Ltd

Nicol Main Office Park,

Block C First Floor,

Futurespace,

2 Bruton Road,

Bryanston,

2191

8. REGISTRATION NUMBERS:

Differin Cream: 32/13.12/0476

Differin Gel: 29/13.12/0606

9. DATE OF FIRST AUTHORISATION

Date on the registration certificate of the medicine:

Differin Cream (32/13.12/0476): 29 March 2012

Differin Gel (29/13.12/0606): 23 January 2013

10. DATE OF REVISION OF THE TEXT

4 September 2020