SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sunactic

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains 30 mg diclofenac sodium (3% w/w)
Excipient(s) with known effect 1 g of gel contains 10 mg of benzyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the topical treatment of actinic keratosis

4.2 Posology and method of administration

Use in Adults*:* Sunactic is applied locally to the affected area twice daily and smoothed into the skin gently. The amount needed depends on the size of the affected area. Normally 0.5 grams (the size of a pea) of the gel is used on a 5 cm x 5 cm lesion site. The usual duration of therapy is from 60 to 90 days.

Maximum efficacy has been observed with treatment duration towards the upper end of this range. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy.

A maximum of 8 grams daily should not be exceeded. Long term efficacy has not been established.

Use in the Elderly*:* The usual adult dose may be used.

Use in Children**:** Dosage recommendations and indications for the use of Sunactic have not been established for use in children.

4.3 Contraindications

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

Because of cross-reactions, the gel should not be used by patients who have experienced hypersensitivity reactions such as symptoms of asthma, allergic rhinitis or urticaria, to acetylsalicylic acid or other non-steroidal anti-inflammatory agents.

The use of Sunactic is contraindicated during the third trimester of pregnancy (see Section 4.6).

4.4 Special warnings and precautions for use

The likelihood of systemic side effects occurring following the topical application of Sunactic is very small compared to the frequency of side effects with oral diclofenac, owing to low systemic absorption with Sunactic. However, the possibility of systemic adverse events from application of topical diclofenac cannot be excluded if the preparation is used on large areas of skin and over a prolonged period (see product information on systemic forms of diclofenac). This product should be used with caution in patients with a history of and/or active gastrointestinal ulceration or bleeding, or reduced heart, liver or renal function, since isolated cases of systemic adverse reactions consisting of renal affection, has been reported with topically administered antiphlogistics.

It is known that nonsteroidal anti-inflammatory drugs (NSAIDs) can interfere with platelet function. Although the likelihood of systemic side effects is very low, caution should be used in patients with intracranial hemorrhage and bleeding diathesis.

Direct sunlight, including solarium, should be avoided during treatment. If sensitivity skin reactions occur, discontinue use.

Sunactic should not be applied to skin wounds, infections or exfoliative dermatitis. It should not be allowed to come into contact with the eyes or mucous membranes and should not be ingested.

Discontinue the treatment if a generalised skin rash develops after applying the product.

Topical diclofenac can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.

This medicine contains 10 mg benzyl alcohol in each g. Benzyl alcohol may cause allergic reactions and mild local irritation.

4.5 Interaction with other medicinal products and other forms of interaction

Since systemic absorption of diclofenac from a topical application is very low such interactions are very unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The systemic concentration of diclofenac is lower after topical administration, compared to oral formulations. With reference to experience from treatment with NSAIDs with systemic uptake, the following is recommended:

• Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1.5 %. The risk is believed to increase with the dose and duration of therapy.

• Animal studies have shown reproductive toxicity. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and postimplantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low (< 30% of the body surface) and duration of treatment as short as possible (not longer than 3 weeks).

If NSAID treatment is necessary between about 20 weeks and 28 weeks gestation, limit Sunactic use to the lowest effective dose and shortest duration possible.

During the second and third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

• Functional renal injury in the foetus. From the 12th week: oligohydramnios (usually reversible after the end of treatment), or anamnios (particularly with prolonged exposure). After birth: kidney failure may persist (particularly with late or prolonged exposure).

• Pulmonary and cardiac toxicity in the foetus (pulmonary hypertension with premature closure of the ductus arteriosus). This risk exists from the beginning of the 6th month and increases if administration is close to full term.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the mother and the neonate, to:

• Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.

• Inhibition of uterine contractions resulting in delayed or prolonged labour.

• Increased risk of oedema formation in the mother.

Consequently, Sunactic is contraindicated during the third trimester of pregnancy (see section 4.3)

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs, including Sunactic, in pregnant women at about 28 weeks gestation and later. NSAIDs, including Sunactic, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including Sunactic, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

Consider ultrasound monitoring of amniotic fluid if Sunactic treatment extends beyond 5 days. Discontinue Sunactic if oligohydramnios occurs and follow up according to clinical practice.

Breastfeeding:

Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at the recommended therapeutic doses of Sunactic no effects on the suckling child are anticipated. Because of a lack of controlled studies in lactating women, the product should only be used during lactation under advice from a healthcare professional.

Under this circumstance, Sunactic should not be applied on the breasts of nursing mothers, nor elsewhere on large areas of skin or for a prolonged period of time (see section 4.4).

4.7 Effects on ability to drive and use machines

Cutaneous application of topical diclofenac has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Most frequently reported reactions include skin reactions such as contact dermatitis, erythema and rash or application site reactions such as inflammation, irritation, pain and blistering. In studies there appeared to be no age specific increase or pattern of reactions.

Adverse reactions are listed in Table 1 according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class and in decreasing frequency defined as follows:: very common: (>1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); Not known: frequency cannot be estimated from the available data.

Table 1: Treatment-related adverse reactions reported by body system and frequency

Infections and Infestations	
Very rare (<1/10,000)	Rash pustular
Immune System Disorders	
Very rare (<1/10,000)	Topical application of large amounts may result in systemic effects including all types of hypersensitivity (including urticaria, angioneurotic oedema)
Nervous System disorders	
Common (≥1/100, <1/10)	Hyperesthesia, hypertonia, localised paraesthesia
Eye Disorders	
Common (≥1/100, <1/10)	Conjunctivitis

Uncommon (≥1/1,000, <1/100)	Eye pain, lacrimation disorder
Vascular Disorders	
Uncommon (≥1/1,000, <1/100)	Haemorrhage
Respiratory, Thoracic and Mediastinal Disorders	
Very rare (<1/10,000)	Asthma
Gastrointestinal Disorders	
Uncommon (≥1/1,000, <1/100)	Abdominal pain, diarrhoea, nausea
Very rare (<1/10,000)	Gastrointestinal haemorrhage
Skin and Subcutaneous Tissue Disorders	
Common (≥1/100, <1/10)	Dermatitis (including contact dermatitis), eczema, dry skin, erythema, oedema, pruritus, rash, scaly rash, skin hypertrophy, skin ulcer, vesiculobullous rash
Uncommon (≥1/1,000, <1/100)	Alopecia, face oedema, maculopapular rash, seborrhoea
Rare (≥1/10,000, <1/1,000)	Dermatitis bullous
Very rare (<1/10,000)	Photosensitivity reaction
Renal and Urinary System Disorders	
Very rare (<1/10,000)	Renal failure
General Disorders and Administration Site Conditions	
Common (≥1/100, <1/10)	Application site reactions (including inflammation, irritation, pain and tingling or blistering at the treatment site)

Temporary hair discolouration at the application site has been reported. This is usually reversed on stopping treatment.

Patch testing of previously treated patients indicate a 2.18% probability of allergic contact dermatitis sensitisation (type IV) to diclofenac with as yet unknown clinical relevance. Cross-reactivity to other NSAIDs is not likely. Serum testing more than 100 patients indicated no presence of type I anti-diclofenac antibodies.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
Additionally, you can also report to www.perrigo-pharma.co.il.

4.9 Overdose

Due to the low systemic absorption of Sunactic, overdosage is extremely unlikely as a result of topical use. However, the skin should be rinsed with water. There have been no clinical cases of ingestion of Sunactic inducing overdosage.

In the event of accidental ingestion (100 g Sunactic gel contain the equivalent of 3000 mg diclofenac sodium) resulting in significant systemic side effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatories should be used.

Supporting and symptomatic treatment should be given for complications such as renal failure, convulsions, gastrointestinal irritation and respiratory depression. Gastric decontamination and the use of activated charcoal should be considered, especially within a short time of ingestion.

Specific therapies such as forced diuresis and dialysis will probably not be therapeutic in eliminating NSAIDs due to their high rate of protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-Code: D11AX18

Other Dermatologicals

Mechanisms of action: Diclofenac is a non-steroidal anti-inflammatory drug.

The mechanism of action of diclofenac in AK may be related to the inhibition of the cyclooxygenase pathway leading to reduced prostaglandin E2 (PGE2) synthesis. In addition, immunohistochemistry (IHC) from skin biopsies ac revealed that the clinical effects of diclofenac in AK are primarily due to anti-inflammatory, anti-angiogenic and possibly anti-proliferative effects and apoptosis-inducing mechanisms.
Pharmacodynamic Effects: Sunactic has been shown to clear AK lesions with maximum therapeutic effect seen 30 days after cessation of drug therapy.

Clinical efficacy and safety: Data from 3 company-sponsored, randomised, double-blind clinical trials in which diclofenac sodium was used as a comparator arm (Studies 0908, 1004 and 0702) provide further evidence on the efficacy of diclofenac sodium in the treatment of AK lesions (including hyperkeratotic lesions) across a number of endpoints. Specifically, the diclofenac sodium arm showed histological clearance rates between 47.6% and 54.1% while these were between 33,9% and 42.7% for vehicle. Complete clinical clearance of AK lesions was achieved in 37.9% and 23.4% of patients at 30 (n=11/29) and 60 days post-treatment (n= 76/380).

In a three arm study comparing 0.5% 5-FU, diclofenac sodium and vehicle, both active arms were superior to vehicle in histological and complete cure rates, whereas 0.5% 5-FU was not inferior to diclofenac sodium and showed higher histological clearance compared to it (70.1% vs 54.1%).

Moderate-to-significant improvements were reported using investigator and patient Global Improvement Index following diclofenac sodium treatment.

Observational 1-year follow-up data indicate that following treatment with diclofenac sodium, complete clearance was achieved by 28.8% and 36.8% at 6 and 12 months post treatment respectively (18.9% and 25.0% with placebo at similar time points).

The efficacy of diclofenac sodium has been investigated in 32 patients (24 on diclofenac sodium, 8 on placebo) who had previously undergone organ transplantation, and now had a currently stable graft. diclofenac sodium was superior to vehicle in both complete clearance of AK lesions (41% vs 0%) and lesion count reduction (53% vs 17%).

5.2 Pharmacokinetic properties

Absorption: Mean absorption through the skin varies between <1-12% with large inter-individual variability. Absorption is dependent on the amount of the topical dose applied and the site of application.

Distribution: Diclofenac binds highly to serum albumin.

Biotransformation: Biotransformation of diclofenac involves partly conjugation of the intact molecule, but mainly single and multiple hydroxylations resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, however to a much lesser extent than diclofenac. Metabolism of diclofenac following percutaneous and oral administration is similar.

Elimination: Diclofenac and its metabolites are excreted mainly in the urine. Systemic clearance of diclofenac from plasma is 263 ± 56 ml/min (mean value ±standard deviation) following oral administration. Terminal plasma half-life is short (1-2 hours). For the metabolites also have short terminal half-lives of 1-3 hours.

Pharmacokinetics in special patient populations: After topical application, the absorption of diclofenac in normal and compromised epidermis are comparable although there is a large inter-individual variation. Systemic absorption of diclofenac is approximately 12% of the administered dose for compromised skin and 9% for intact skin.

5.3 Preclinical safety data

Published animal studies have shown that when given orally, the principal adverse effect is on the gastrointestinal tract. Diclofenac inhibited ovulation in the rabbit and impaired implantation, as well as early embryonic development in the rat. The embryo/foeto-toxic potential of diclofenac was evaluated in three animal species (rat, mouse and rabbit). Foetal death and growth retardation occurred at maternal toxic doses, however, on the basis of the available data, diclofenac is not considered to be teratogenic. The gestation period and the duration of parturition were extended by diclofenac. Doses lower than maternal toxic ones did not affect the postnatal development. Results from extensive genotoxicity and carcinogenicity testing suggest that it is unlikely that diclofenac would pose a significant carcinogenic hazard to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified Water, Glycerin, Polyethylene Glycol Monomethyl Ether, Diethylene Glycol Monoethyl Ether, Hydroxyethyl Cellulose, Benzyl Alcohol

6.2 Incompatibilities

Not applicable.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials. Shelf life after first opening: 3 months

6.4 Special precautions for storage

Store below 25°C.

Protect from heat. Avoid freezing.

6.5. Nature and contents of container

The product is supplied in an aluminum tube with a screw cap, in 50 g size.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER AND MARKETING AUTHORIZATION HOLDER

Perrigo Israel Pharmaceuticals, Ltd., P.O.B 16 Yeruham Israel

8.REGISTRATION NUMBER

150-56-33561

Rrevised on *07/2021* according to MOH guidelines