SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diclofenac sodium 3% gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of gel contains 30 mg diclofenac sodium.

Excipient with known effect:

Each gram of gel contains 15 mg benzyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel
Clear, transparent, colourless to yellowish

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of actinic keratoses (AKs).

4.2 Posology and method of administration

Posology

Adults:
Diclofenac sodium gel should be applied to the affected skin areas twice daily and smoothed into the skin gently. The amount used depends on the size of the area to be treated.

Usually 0.5 g of gel (about the size of a pea) is applied to a 5x5 cm lesion site. The maximum daily amount of 8 grams of product allows simultaneous treatment of up to 200 cm^2 skin surface area. The usual duration of treatment is 60 to 90 days. Maximum effect has been observed with treatment durations at the upper end of this time range.

Complete healing of the lesion(s) or optimal therapeutic effect may not be seen for up to 30 days after completion of therapy.

Elderly people:
The normal dosage can be used.

Paediatric population:
AK is a condition not generally seen within the paediatric population and was not studied. Therefore, dosage recommendations and indications for the use of Diclofenac sodium have not been established for use in children and adolescent.

Method of administration
Cutaneous use.

Afterwards, the hands should be wiped on a paper towel and then washed, unless they are the area to be treated. The paper towel should be disposed of in the residual waste. This helps to significantly reduce diclofenac release into the waste water system (water pollutant).

4.3 Contraindications

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

Because of the potential for cross-reactions, the gel should not be used in patients who have experienced hypersensitivity reactions such as symptoms as asthma, allergic rhinitis or urticaria to 2-acetoxybenzoic acid (acetylsalicylic acid) or any other non-steroidal anti-inflammatory medicinal products (NSAIDs).

The use of Diclofenac sodium gel is contraindicated in the third trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Due to the low systemic absorption of Diclofenac sodium gel, the likelihood of systemic adverse reactions following the external use of Diclofenac sodium gel is small compared to the frequency of adverse reactions with oral diclofenac. 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 of time (see medicinal product information for systemic formulations of diclofenac).

This medicinal product should be used with caution in patients with a history of and/or active gastrointestinal ulceration and/or bleeding, or reduced heart, liver or kidney function because there have been isolated reports of systemic adverse reactions (such as kidney disorders) associated with externally used anti-inflammatory medicinal products.

Non-steroidal anti-inflammatory medicinal products are known to have anti-platelet activity. Therefore, although the likelihood of systemic adverse reactions is small,

caution should be used in patients with intracranial haemorrhage and bleeding diathesis.

Exposure to direct sunlight and solarium use should be avoided during treatment. If hypersensitivity reactions of the skin occur, treatment must be stopped.

Topical diclofenac should be applied only to intact skin, and not to skin wounds, open injuries, infected skin areas or exfoliative dermatitis. The gel must not 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 medicinal product.

Topical diclofenac can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.
This medicinal product contains 15 mg benzyl alcohol in each gram of gel. 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 formulation is very low, such interactions are very unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The systemic concentration of diclofenac is lower after topical application compared to oral formulations.

With reference to experience from treatment with non-steroidal anti-inflammatory medicinal products (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 post-implantation 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.

There are no clinical data from the use of Diclofenac sodium gel during pregnancy. Even if systemic exposure is lower compared with oral administration, it is not known

if the systemic Diclofenac sodium gel exposure reached after topical administration can be harmful to an embryo/fetus.

During the first and second trimesters of pregnancy, diclofenac should not be used unless clearly necessary. If diclofenac is used by a woman attempting to conceive or during the first or 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).

During the second and third trimester of pregnancy, systemic use of prostaglandin synthetase inhibitors including diclofenac may expose the foetus to the following risks:

- renal dysfunction in the foetus. From the 12th week: oligohydramnios (usually reversible after the end of treatment) or anamnios (particularly with prolonged exposure). After birth: renal insufficiency may persist (particularly with late or prolonged exposure);
- cardiopulmonary 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 the end of pregnancy.

At the end (during the third trimester) of pregnancy, all prostaglandin synthesis inhibitors may expose the mother and the neonate to the following risks:

- 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, diclofenac is contraindicated during the last trimester of pregnancy (see section 4.3).

Breast-feeding:

Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at the recommended therapeutic dosage of Diclofenac sodium gel no effects on the suckling child are anticipated.

Because of a lack of controlled studies in lactating women, the medicinal product should only be used during lactation under advice from a healthcare professional. Under these circumstances, Diclofenac sodium gel 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 use of topical diclofenac has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Common adverse reactions:
The most frequently reported adverse reactions are local skin reactions such as contact dermatitis, erythema and rash or application site reactions such as inflammation, skin irritation, pain and blistering.

In clinical studies to date there has appeared to be no age-related increase or age-specific 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 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

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

Organ system	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**
Infections and infestations				Pustular rash
Immune system disorders				All types of hypersensitivity reactions (including urticaria, angio-oedema)
Nervous system disorders	Hyperaesthesia, hypertonia, localised paraesthesia			
Eye disorders	Conjunctivitis	Eye pain, lacrimation disorder		
Vascular disorders		Haemorrhage (skin bleeding)		
Respiratory, thoracic and mediastinal disorders				Asthma
Gastrointestinal disorders		Abdominal pain, diarrhoea,		Gastrointestinal haemorrhage

		feeling sick		
Skin and subcutaneous tissue disorders	Dermatitis (including contact dermatitis), eczema, dry skin, erythema, oedema, pruritus, rash, scaly rash, skin hypertrophy, skin ulcer, vesiculobullous rash	Alopecia, facial oedema, maculopapular rash, seborrhoea	Bullous dermatitis	Photosensitivity reactions
Renal and urinary disorders				Renal insufficiency
General disorders and administration site conditions	Application site reactions (including inflammation, skin irritation, pain and tingling or blistering at the treated site)			

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

Skin tests in a previously treated patient population indicated a 2.18% probability of sensitisation to diclofenac, triggering allergic contact dermatitis (type IV). The clinical relevance is as yet unknown. Cross-reactions with other NSAIDs are unlikely.

Serum tests in more than 100 patients revealed no (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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The low systemic absorption of topical diclofenac renders overdose very much unlikely. However, the skin should be rinsed with water. There have been no reports of clinical cases of overdosage from ingestion of diclofenac-containing gel.

However, undesirable effects similar to those observed following an overdose of diclofenac tablets can be expected if topical diclofenac is inadvertently ingested (1

tube of 100 g contains the equivalent of 3,000 mg diclofenac sodium). In the event of accidental ingestion resulting in significant systemic adverse effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory medicinal products should be used.

Supportive and symptomatic treatments should be administered for the management of 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 treatments (such as forced diuresis and dialysis) will probably not be effective at eliminating NSAIDs because of the high rate of protein binding of NSAIDs.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatologicals

ATC code: D11AX18

Mechanism of action

Diclofenac is a non-steroidal anti-inflammatory medicinal product.

The mechanism of action of diclofenac in actinic keratosis is not known but may be related to inhibition of the cyclo-oxygenase pathway leading to reduced prostaglandin E2 (PGE2) synthesis. In addition, immunohistochemistry (IHC) from skin biopsies 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

Diclofenac-containing gel has been shown to clear AK lesions with maximum therapeutic effect seen 30 days after cessation of medicinal product therapy.

Clinical efficacy and safety

Data from 3 company-sponsored, randomised, double-blind clinical trials in which a diclofenac 30 mg/g gel was used as a comparator arm (Studies 0908, 1004 and 0702) provide further evidence on the efficacy of diclofenac 30 mg/g gel in the treatment of AK lesions (including hyperkeratotic lesions) across a number of endpoints. Specifically the diclofenac 30 mg/g gel 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 30 mg/g gel 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 30 mg/g gel 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 30 mg/g gel treatment.

Observational 1-year follow-up data indicate that following treatment with diclofenac 30 mg/g gel, 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 30 mg/g gel has been investigated in 32 patients (24 on diclofenac 30 mg/g gel, 8 on placebo) who had previously undergone organ transplantation, and now had a currently stable graft. diclofenac 30 mg/g gel 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 of diclofenac through the skin ranges from <1% to 12% with large interindividual variability. Absorption depends on the topically applied dose and the site of application.

Distribution

Diclofenac binds highly to serum albumin.

Biotransformation

Biotransformation of diclofenac partly involves conjugation of the intact molecule, but mainly consists of 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, but 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. Following oral administration, the systemic clearance of diclofenac from plasma is 263 ± 56 ml/min (mean ± standard deviation). Terminal plasma half-life is short (1-2 hours). The metabolites also have short terminal half-lives of 1-3 hours.

Pharmacokinetics in special patient populations

Following topical application, the absorption rates of diclofenac on normal and compromised epidermis are similar although there are large interindividual differences. The 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 diclofenac is administered orally, adverse reactions affect mainly the gastrointestinal tract. Diclofenac inhibited ovulation in rabbits and impaired implantation as well as early embryonic development in rats. The embryotoxic/foetotoxic potential of diclofenac was evaluated in three animal species (rat, mouse, rabbit). Foetal death and growth retardation occurred at materno-toxic doses. However, based on the available data, diclofenac is not considered to be teratogenic. The gestational period and the duration of parturition were prolonged with diclofenac. Doses lower than materno-toxic doses did not affect postnatal development. Results from extensive genotoxicity and carcinogenicity testing suggest that it is unlikely that diclofenac poses a significant carcinogenic hazard to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hyaluronate
Macrogol 400
Benzyl alcohol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After first opening: 6 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium tube with original sealing membrane and internal protective lacquer and HDPE screw cap

10 g gel

25 g gel

26 g gel

30 g gel

50 g gel

60 g gel

90 g gel

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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