SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diclofenac Glenmark 3% gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of gel contains 30 mg diclofenac sodium (3 % w/w).

Excipient with known effect:

1 gram of gel contains 10 mg of benzyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

gel
A clear, transparent, and colourless to slightly yellow gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of actinic keratosis (AK) in adults.

4.2 Posology and method of administration

Posology

Use in Adults:

Diclofenac 3% gel is applied locally to the affected area twice daily, with the gel smoothed into the skin gently. The amount needed depends on the size of the affected area. Normally 0.5 g (the size of a pea) of the gel is used on a 5 cm x 5 cm lesion site. The maximum daily amount of 8 g of gel allows simultaneous treatment of up to 200 cm^2 skin surface area.

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.

Use in the Elderly:

The usual adult dose may be used.

Paediatric population:

Actinic keratosis (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 30 mg/g gel in children and adolescents have not been established. No data are available.

Method of administration

For cutaneous use.

4.3 Contraindications

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

Because of cross-reactions, the gel must 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 the medicinal product is contraindicated during the third trimester of pregnancy (see Section 4.6).

4.4 Special warnings and precautions for use

The likelihood of systemic adverse reactions occurring following the topical application of diclofenac gel is very small compared to the frequency of adverse reactions with oral diclofenac, owing to low systemic absorption with diclofenac gel. 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 medicinal 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, have been reported with topically administered anti-inflammatory medicinal products.

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

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

The gel 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.

The treatment should be discontinued 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 10 mg benzyl alcohol in each g. Benzyl alcohol may cause 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

<u>Pregnancy</u>

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.

There are no clinical data from the use of Diclofenac Glenmark 3% gel during pregnancy. Even if systemic exposure is lower compared with oral administration, it is not known if the systemic Diclofenac Glenmark 3% gel exposure reached after topical administration can be harmful to an embryo/fetus. During the first and second trimester of pregnancy, Diclofenac Glenmark 3% gel should not be used unless clearly necessary. If used, the dose should be kept as low and duration of treatment as short as possible.
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).

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, systemic use of prostaglandin synthetase inhibitors including diclofenac may induce cardiopulmonary and renal toxicity in the fetus. At the end of the pregnancy prolonged bleeding time in both mother and child may occur, and labour can be delayed. Therefore, Diclofenac Glenmark 3% gel is contraindicated during the last trimester of pregnancy (see Section 4.3).

Breastfeeding
Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at the recommended therapeutic doses of diclofenac gel 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, diclofenac 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

Diclofenac 3% gel has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Most frequently reported adverse 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	Rash pustular
Immune system disorders	
Very rare	Topical application of large amounts may result in systemic effects including all types of hypersensitivity (including urticaria, angioneurotic oedema)
Nervous system disorders	
Common	Hyperesthesia, hypertonia, localised paraesthesia
Eye disorders	
Common	Conjunctivitis
Uncommon	Eye pain, lacrimation disorder
Vascular disorders	
Uncommon	Haemorrhage
Respiratory, thoracic and mediastinal disorders	
Very rare	Asthma
Gastrointestinal disorders	
Uncommon	Abdominal pain, diarrhoea, nausea

Very rare	Gastrointestinal haemorrhage
Skin and subcutaneous tissue disorders	
Common	Dermatitis (including contact dermatitis), eczema, dry skin, erythema, oedema, pruritus, rash, scaly rash, skin hypertrophy, skin ulcer, vesiculobullous rash
Uncommon	Alopecia, face oedema, maculopapular rash, seborrhoea
Rare	Dermatitis bullous
Very rare	Photosensitivity reaction
Renal and urinary disorders	
Very rare	Renal failure
General disorders and administration site conditions	
Common	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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the **Google Play or Apple App Store.**

4.9 Overdose

Due to the low systemic absorption of diclofenac gel, overdose 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 diclofenac gel inducing overdosage.

In the event of accidental ingestion (100 g gel contain the equivalent of 3000 mg diclofenac sodium) resulting in significant systemic *adverse reactions*, 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

Pharmacotherapeutic group: dermatologicals; other dermatologicals

ATC code: D11AX18

Mechanism 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 cycloxygenase pathway leading to reduced prostaglandin E_2 (PGE_2) 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 3 % gel 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 3 % gel was used as a comparator arm (Studies 0908, 1004 and 0702) provide further evidence on the efficacy of diclofenac 3 % gel in the treatment of AK lesions (including hyperkeratotic lesions) across a number of endpoints. Specifically the diclofenac 3 % 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 3 % 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 3 % 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 3 % gel treatment.

Observational 1-year follow-up data indicate that following treatment with diclofenac 3 % 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 3 % gel has been investigated in 32 patients (24 on diclofenac 3 % gel, 8 on placebo) who had previously undergone organ transplantation, and now had a currently stable graft. diclofenac 3 % 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 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

Non-clinical data based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential reveal no special hazards for humans beyond those already outlined in other sections of the Summary of Product Characteristics.

In animal studies, chronic toxicity of diclofenac following systemic administration mainly manifested as gastrointestinal lesions and ulcers. In a 2-year toxicity study, rats treated with diclofenac showed a dose-related increase in thrombotic occlusion of the cardiac vessels.

In animal studies on reproductive toxicity, systemically administered diclofenac caused inhibition of ovulation in rabbits and impairment of implantation and early embryonic development in rats. The gestational period and duration of parturition were prolonged by diclofenac. The embryotoxic potential of diclofenac was studied in three animal species (rat, mouse, rabbit). Foetal death and growth retardation occurred at maternotoxic dose levels. Based on the available non-clinical data, diclofenac is regarded as non-teratogenic. Doses below the maternotoxic threshold had no impact on the postnatal development of the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium hyaluronate

benzyl alcohol

polyethylene glycol monomethyl ether 350

purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After first opening: 6 months

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

The gel is supplied in aluminium tubes with white HDPE ribbed stand up cap having piercing point.

Pack sizes: 25 g, 50 g, 60 g, 90 g or 100 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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PL 25258/0442

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