Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Difene 1% w/w Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diclofenac sodium 1 % w/w

Excipients with known effect: Propylene glycol 25 % w/w

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gel.
A slightly turbid, colourless gel with the odour of isopropyl alcohol.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For local symptomatic relief of pain and inflammation in

1. Trauma of the tendons, ligaments, muscles and joints e.g. due to sprains, strains and bruises.
2. Localised forms of soft tissue rheumatism.

4.2 Posology and method of administration

Topical administration.

Adults: Diclofenac Gel should be rubbed gently into the skin. Depending on the size of the site to be treated, 2 to 4 g (a circular shaped mass approximately 2 to 2.5 cm in diameter) should be applied 2 to 4 times daily. After the application the hands should be washed unless they are the site being treated.

It is recommended that the treatment be reviewed after 14 days. These indications should not warrant treatment for more than 6 weeks.

Elderly: NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed.

Children and adolescents below 14 years: Not recommend. There are insufficient data on efficacy and safety available for children and adolescents below 14 years of age (see also contraindications section 4.3).

4.3 Contraindications

Hypersensitivity to diclofenac or any of the excipients.

Patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or ether non-steroidal anti-inflammatory drugs (NSAIDs).

Third trimester of pregnancy.

Children and adolescents:
The use in children and adolescents ages less than 14 years is contraindicated.

4.4 Special warnings and precautions for use

Application over extensive areas for prolonged periods or application in excess of recommended dosage may give rise to systemic effects. These include gastrointestinal disturbances, irritability, fluid retention, rash, renal dysfunction, anaphylaxis and rarely gastrointestinal bleeding, hepatitis, blood dycrasis, bronchospasm and erythema multiform.

The product should be applied only to intact skin and not to skin wounds or open injuries. It should not be allowed to come into contact with the eyes or mucous membranes and should never be taken by mouth.

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration. Patients treated with NSAIDs longterm should undergo regular medical supervision to monitor for adverse events.

Diclofenac should be used with great caution in patients with a history of peptic ulceration or inflammatory bowel disease, gastrointestinal bleeding, hepatic or oral insufficiency or bleeding diathesis. Circulating levels of active drug are low but the theoretical increased risk in patients should be considered.

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 the product information on systemic forms of diclofenac).

Topical diclofenac should be applied only to intact non-diseased skin, and not to skin wounds or open injuries. 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 skin rash develops after applying the product.

Difene 1% w/w gel contains 250 mg propylene glycol in each gram of gel, which may cause skin irritation.

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

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions occur with oral forms of diclofenac.

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

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Care should be taken in patients treated with any of the following drugs as interactions have been reported:

Anti-hypertensives: reduced anti-hypertensive effect.

Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Lithium: decreased elimination of lithium.

Methoterexate: decreased elimination of methotrexate.

Cyclosporin: increased risk of nephrotoxicity with NSAIDs.

Other NSAIDs: avoid concomitant use of two or more NSAIDs.

Corticosteroids: increased risk of gastrointestinal bleeding.

Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAID and metabolites.

Oral hypoglycemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking Difene Suppositories concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

To date, no drug interactions during treatment with Difene Gel have been reported but the theoretical risk of the above interactions occurring should be borne in mind.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no clinical data from the use of Difene 1% w/w gel during pregnancy. Even if systemic exposure is lower compared with oral administration, it is not known if the systemic Difene 1% w/w gel exposure reached after topical administration can be harmful to an embryo/fetus. 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 dose and duration of therapy. 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. During the first and second trimester of pregnancy, Difene 1% w/w gel should not be given unless clearly necessary. If used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may
expose
the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy, 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.

Therefore, Difene 1% w/w gel is contraindicated during the last trimester of pregnancy.
Lactation
Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at therapeutic doses of (product) 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, (product) 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

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: 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: cannot be estimated from the available data.

Table 1

Immune system disorder	
Very rare	Hypersensitivity (including urticaria), angioneurotic oedema
Infections and infestations	
Very rare	Rash pustular
Respiratory, thoracic and mediastinal disorders	
Very rare	Asthma
Skin and subcutaneous tissue disorders	
Common Rare Very rare	Rash, eczema, erythema, dermatitis (including dermatitis contact), pruritus Dermatitis bullous Photosensitivity reaction

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

The low systemic absorption of topical diclofenac renders overdose very unlikely.
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 1000 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 medicines should be used. Gastric decontamination and the use of activated charcoal should be considered, especially within a short time of ingestion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Diclofenac sodium is a non-steroidal agent with marked analgesic, antipyretic and anti-inflammatory properties. It is an inhibitor of prostaglandin synthesis (cyclo-oxygenase).

5.2 Pharmacokinetic properties

The use of a topical application of diclofenac sodium allows the percutaneous absorption of therapeutic concentrations of the active to penetrate to, and accumulate at, the target site of action. The dose to be delivered in a concentration of a 1% gel, is comparable to the normal daily doses of oral administration. As with other percutaneously applied NSAIDs, it is the concentration reached at the target area that is important for the therapeutic action rather than the plasma concentration. Hence the systemic load produced by oral or parenteral administration can be avoided through local application.

The comparison of the excretion of diclofenac and its metabolities after oral and cutaneous administration gave almost the same pattern of metabolities.

5.3 Preclinical safety data

Animal studies have been carried out in a number of species to determine the toxicity of diclofenac sodium. Acute toxicity studies have been carried out in the rat and when administered orally an LD50 of 53 mg/kg produced behavioural effects and respiratory stimulation. Acute oral toxicity studies in the rabbit showed no toxic effect at a dose of 157 mg/kg.

Toxicity by the intravenous route has been measured in the rat, an administered dose of 117 mg/kg has been shown to have no adverse effect. Intraperitoneal studies have shown an no adverse effect level of 25 mg/kg in the rat, and subcutaneous toxicity in the rat shows a no toxic effect level of 83 mg/kg.

Rectal toxicity has been measured in the rat. An administered dose of 85 mg/kg has been shown to have no adverse effect.

Reproductive toxicity has been studied in both the rat and the rabbit; a dose of 1 mg/kg/day for 21 days in rats has been shown to produce developmental abnormalities of the cardiovascular system. In the rabbit a dose of 10 mg/kg has been shown to reduce fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Propylene glycol
PEG-7-glyceryl-cocoate
Isopropyl alcohol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
Once opened - 6 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

30g/50g/100g: Conical flexible tubes with membrane, tube nozzles with treads with internal protection and end seal lacquer or latex seal.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Glenwood GmbH
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Arabellastrasse 17
81925 Munich
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8 MARKETING AUTHORISATION NUMBER

PA2256/001/005

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