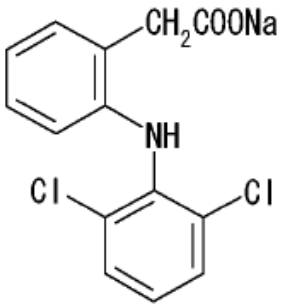
SOLARAZE® 3% gel
(diclofenac sodium)

NAME OF THE MEDICINE

Solaraze (diclofenac sodium) Gel 3% contains the active ingredient, diclofenac sodium, in a clear, transparent, colourless to light orange gel base.

The chemical name for diclofenac sodium is: Sodium [o-(2,6-dichloranilino)phenyl]acetate



Molecular weight: 318.13

CAS number: CAS-15307-79-6

DESCRIPTION

Diclofenac sodium is a white to slightly yellow crystalline powder. It is freely soluble in methanol, soluble in ethanol, sparingly soluble in acetone, and partially insoluble in ether.

Active. Diclofenac sodium

Inactive. Sodium hyaluronate, benzyl alcohol, polyethylene glycol monomethyl ether (350) and purified water.

PHARMACOLOGY

Diclofenac is a non-steroidal anti-inflammatory drug. The mechanism of action of diclofenac in actinic keratoses is not known but may be related to the inhibition of the cycloxygenase pathway leading to reduced prostaglandin E_2 (PGE_2) synthesis. Efficacy of the treatment has only been demonstrated in placebo-controlled studies. Comparative studies with topical 5-fluorouracil have not been conducted. The long term beneficial effects of Solaraze has not been proven.

Pharmacokinetics

Absorption:

When Solaraze is applied topically, diclofenac is absorbed into the epidermis. In a study in patients with compromised skin (mainly atopic dermatitis and other dermatitic conditions) of the hands, arms or face, approximately 10% of the applied dose (2 grams of 3% gel over 100 cm^2) of diclofenac was absorbed systemically in both normal and compromised epidermis after seven days, with four times daily applications.

After topical application of 2 g Solaraze three times daily for six days to the calf of the leg in healthy subjects, diclofenac could be detected in plasma. Mean bioavailability parameters were $AUC_{0\text{-}t}$ 9±19 ng.hr/mL (mean±SD) with a C_{max} of 4±5 ng/mL and a T_{max} of 4.5±8 hours.

In comparison, a single oral 75 mg dose of diclofenac (Voltaren) produced an AUC of 1600 ng.hr/mL. Therefore, the systemic bioavailability after topical application of Solaraze is lower than after oral dosing.

Blood drawn at the end of treatment from 60 patients with AK lesions treated with Solaraze in three adequate and well-controlled clinical trials were assayed for diclofenac levels. Each patient was administered 0.5g of Solaraze gel twice a day for up to 105 days. There were up to three 5 cm x 5 cm treatment sites per patient on the face, forehead, hands, forearm, and scalp. Serum concentrations of diclofenac were on average at, or below 20 ng/mL. These data indicate that systemic absorption of diclofenac in patients treated topically with Solaraze is much lower than that occurring after oral daily dosing of diclofenac sodium.

No information is available on the absorption of diclofenac when Solaraze is used under occlusion.

Distribution:

Diclofenac binds highly to serum albumin. The volume of distribution of diclofenac following oral administration is approximately 550 mL/kg.

Metabolism:

Biotransformation of diclofenac following oral administration involves conjugation at the carboxyl group of the side chain or single or 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 smaller extent than diclofenac. Metabolism of diclofenac following topical administration is thought to be similar to that after oral administration. The small amounts of diclofenac and its metabolites appearing in the plasma following topical administration makes the quantification of specific metabolites imprecise.

Elimination:

Diclofenac and its metabolites are excreted mainly in the urine after oral dosing. Systemic clearance of diclofenac from plasma is 263 ± 56 mL/min (mean value ± SD). The terminal plasma half-life is 1-2 hours. Four of the metabolites also have short terminal half-lives of 1-3 hours.

Pharmacokinetics in special patient groups:

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*:*

CLINICAL TRIALS

Management of actinic keratoses.

The efficacy of Solaraze was established in two placebo controlled trials involving a total of 231 patients with actinic keratoses.

Study 1 comprised a total of 112 subjects of which 111 subjects were treated with study medication and 93 subjects completed the study. Of the 111 subjects, 56 were enrolled in the Solaraze group and 55 in the vehicle group. Patients were treated with 0.5 g Solaraze or placebo twice a day for 90 days followed by a 30 days follow-up. The primary efficacy endpoint of the study was to evaluate the changes in CLNS (cumulative lesion number score) and TLNS (target lesion number score) between baseline and follow up, and proportion of patients with CLNS=0 and TLNS=0. The percentage of patients with CLNS = 0 at follow-up was 34% of patients treated with Solaraze and 18% of patients treated with placebo, the percentage of patients with TLNS = 0 at follow-up was 34% of patients treated

with Solaraze and 20% of patients treated with placebo. The percentage of patients treated with diclofenac with CLNS = 0 at follow up was significantly greater (p=0.061) than in the vehicle group. The percentage of patients treated with diclofenac group with TLNS = 0 at follow up was greater than in vehicle group, but statistical significance could not be shown (p=0.102).

In study 2, a total of 120 subjects were enrolled and treated with study medication, with 113 patients completing the study. Of the 120 subjects, 61 were treated with Solaraze and 59 with placebo, 0.5 g of Solaraze or placebo was applied twice a day for 12 weeks followed by a follow-up period of 12 weeks. The primary efficacy endpoint of the study was to assess the clearance of actinic keratoses lesions after 12 weeks of treatment and 12 weeks of follow up, calculating the percentage of subjects with CLNS = 0 at week 24. The percentage was higher in the diclofenac group (10%) compared with the vehicle group (4%), although this difference was not statistically significant. Histopathological assessments were also carried out in this study with ratings from 0=normal to 3=severe, biopsies were performed at screening and week 24. At week 24, there was a mean decrease in screening lesions of -0.7 in the Solaraze group and -0.4 in the placebo group. 13 Solaraze treated subjects (23%) demonstrated a resolved target lesion biopsy (grade = 0) at week 24 compared with 6 vehicle control subjects (11%) (p=0.679). There was a significant correlation (p=0.0004) between the histopathological data and the efficacy data.

Additionally, two studies were performed in healthy subjects, all treated with Solaraze.

Study 1 assessed the photosensitisation and sensitisation potentials of Solaraze combined or not with sunscreen. 32 subjects were enrolled in the study of which 30 subjects completed the study. Photosensitation and sensitation reactions were assessed using a 5-point scale. No such reactions were observed at irradiated or non-irradiated sites combined or not with sunscreen.

Study 2 evaluated the phototoxicity potential of Solaraze alone or in combination with sunscreen. 32 subjects were enrolled in the study and all 32 completed the study. Phototoxicity was assessed using a 6-point scale. No phototoxicity reactions were observed for Solaraze alone or in combination with sunscreen products.

INDICATIONS

Management of actinic keratoses.

CONTRAINDICATIONS

Solaraze is contraindicated in patients with a known hypersensitivity to diclofenac, benzyl alcohol, macrogolmonomethyl ether 350 and/ or sodium hyaluronate.

Because of cross-reactions, 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, should not use the gel.

The use of Solaraze is contraindicated during the third trimester of pregnancy (see **Use in Pregnancy**).

PRECAUTIONS

The likelihood of systemic side effects occurring following the topical application of Solaraze is small compared to the frequency of side effects with oral diclofenac, owing to low systemic absorption with Solaraze. 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 NSAIDs can interfere with platelet function. Although the likelihood of systemic side effects 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.

Solaraze 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.

Drug interactions of topical application of Solaraze have not been studied but since systemic absorption of diclofenac is low, drug interactions applied to orally administered NSAIDs are unlikely (see **Interactions**). Concomitant oral administration of other NSAIDs should be minimized.

No data are available on the recurrence of actinic keratoses after cessation of treatment with Solaraze.

No studies evaluating the long-term efficacy of Solaraze have been conducted.

Use in elderly

The usual adult dose may be used.

Use in children

Dosage recommendations and indications for the use of Solaraze have not been established for use in children.

Effects on fertility

Diclofenac inhibited ovulation in rabbits and impaired implantation and early embryonic development in rats. Diclofenac had no obvious effects on fertility in male rats dosed at up to 4 mg/kg/day.

Use in pregnancy **(Category C)**

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.

Solaraze is contraindicated during the last trimester of pregnancy and should not be used during the first two trimesters of pregnancy 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).

There are no adequate data from use of diclofenac in pregnant women. In embryofetal toxicity studies in mice, rats and rabbits, fetal death and growth retardation occurred at maternal toxic doses, although on the basis of the available data, diclofenac is not considered teratogenic. The gestation period and the duration of parturition were prolonged by diclofenac treatment. Doses lower than maternal toxic level did not affect postnatal development. The potential risk for humans is unknown.

The use of prostaglandin synthetase inhibitors in the second and third trimesters of pregnancy may result in:

- 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 and prolonged exposure).
- Pulmonary and cardiac toxicity in the foetus (pulmonary hypertension with preterm closing 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:

- Increased risk of bleeding in the mother and child.
- 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 for the mother.

Use in lactation

Diclofenac sodium is excreted in breast milk after oral administration. The extent to which diclofenac sodium is excreted into the milk after topical administration of the Solaraze gel is unknown. Since no experience has been acquired with Solaraze, it is not recommended for use in breast-feeding women.

Carcinogenicity

Dietary administration of diclofenac to mice and rats at doses up to 0.5 mg/kg/day revealed no carcinogenic activity. However, the plasma concentration of diclofenac at this dose level was only 1-5% of that observed in humans. Administration of higher doses to the animals resulted in increased mortality due to gastrointestinal ulceration.

Diclofenac applied topically to the skin of mice was not tumourigenic at doses up to 2 mg/kg/day, which resulted in plasma diclofenac levels 1- to 8-times (males) and 4- to 13-times (females) the human concentration. When applied topically to the skin of hairless mice, diclofenac at 2.8 mg/kg/day has been shown to slightly reduce the median onset time of UV-induced skin tumours. Caution should be exercised to avoid sun exposure of the application site(s).

Genotoxicity

Diclofenac showed no genotoxic effects in an adequate battery of studies.

Effect on ability to drive or operate machinery

Not applicable.

INTERACTIONS WITH OTHER MEDICINES

No drug interactions during treatment with Solaraze have been reported. After topical administration, systemic absorption is limited. Drug interactions applied to orally administered NSAIDs are improbable.

ADVERSE EFFECTS

In studies examining a total of 229 subjects of which 112 were treated with Solaraze, no serious adverse events related to Solaraze was reported.

Adverse events related to Solaraze (>1%) are summarized in table 1.

Table 1: Patients with adverse events related to Solaraze by body system

Preferred Term	Placebo n = 114 (%)	Solaraze n = 117 (%)
Burning sensation	0 (0)	2 (1.7)
Dermatitis NOS	2 (1.8)	2 (1.7)
Dermatitis contact	1 (0.9)	5 (4.3)
Dermatitis exfoliative NOS	0 (0)	2 (1.7)
Erythema	0 (0)	3 (2.6)
Administration site reactions	53 (46.5)	79 (67.5)
Burning	2 (1.8)	1 (0.9)
Exfoliation	9 (7.9)	14 (12.0)
Dryness	13 (11.4)	14 (12.0)
Erythema	1 (0.9)	10 (8.5)
Pain	21 (18.4)	12 (10.3)
Paraesthesia	12 (10.5)	12 (10.3)
Hyperesthesia	2 (1.8)	1 (0.9)
Pruritus	27 (23.7)	37 (31.6)
Rash	9 (7.9)	37 (31.6)
Vesiculobullous rash	1 (0.9)	1 (0.9)
Swelling	0 (0)	2 (1.7)
Contact dermatitis	3 (2.6)	30 (25.6)
Alopecia	1 (0.9)	1 (0.9)
Photosensitivity	2 (1.8)	0 (0)

Most frequently reported reactions include localised 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 (Table 2) 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 2: Adverse events based on post marketing studies and post marketing surveillance

System Organ Class	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1,000, <1/100)**	**Rare (≥1/10,000, <1/1000)**	**Very rare <1/10,000**
Eye Disorders	Conjunctivitis	Eye pain, lacrimation disorder		
Gastrointestinal Disorders		Abdominal pain, diarrhoea, nausea		Gastrointestinal haemorrhage
General Disorders and Administration Site Conditions	Application site reactions (including inflammation, irritation, pain, itching and tingling or blistering at the treatment site)			
Immune System Disorders				Topical application of large amounts may result in systemic effects including hypersensitivity (including urticaria, angioneurotic oedema)
Infections and infestations				Rash pustular
Nervous System	Hyperesthesia, hypertonia, localised paraesthesia			
Renal and Urinary System Disorders				Renal failure
Respiratory, Thoracic and Mediastinal Disorders				Asthma
Skin and Subcutaneous	Dermatitis (including contact	Alopecia, face oedema,	Dermatitis bullous	

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1000)	Very rare <1/10,000
Tissue Disorders	Dermatitis), eczema, dry skin, erythema, oedema, pruritus, rash, scaly rash, skin hypertrophy, skin ulcer, vesiculobullous rash, exfoliation, urticaria	maculopapular rash, photosensitivity reaction, seborrhoea		
Vascular Disorders		Haemorrhage		

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.

DOSAGE AND ADMINISTRATION

Solaraze is applied locally to the skin 2 times daily and smoothed into the skin gently. The amount needed depends on the size of the lesion. 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.

OVERDOSAGE

Due to the low systemic absorption of Solaraze, 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 Solaraze inducing overdosage.

In the event of accidental ingestion (25 g Solaraze gel contains the equivalent of 750 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. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Specific therapies such as forced diuresis and dialysis will probably not be therapeutic in eliminating NSAIDs due to their high rate of protein binding.

PRESENTATION AND STORAGE CONDITIONS

The product is supplied in an epoxy-phenolic lined sealed aluminium tube with a white polypropylene screw on cap with a pierced tip, in a 25 g or 50 g size.

Not all presentations may be marketed in Australia.

NAME AND ADDRESS OF THE SPONSOR

A.Menarini Australia Pty Ltd

Level 8, 67 Albert Ave,

Chatswood NSW 2067

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS(THE ARTG)

15 May 2007

DATE OF MOST RECENT AMENDMENT

19 January 2015