Safeguarding public health

MHRA

Public Assessment Report

Repeat-Use Mutual Recognition Procedure

Solaraze™ 3% Gel

UK/H/0226/002/E02

UK licence no: PL 16973/0012

Almirall, S.A

LAY SUMMARY

This Repeat-Use Mutual Recognition Procedure (UK/H/0226/001/E02) granted a Marketing Authorisation to Almirall SA for the medicinal product Solaraze™ 3% Gel (PL 16973/0012) in Greece, Spain and Poland; the procedure concluded positively on 18th November 2010. A national licence for Solaraze™ 3% Gel was initially granted in the UK on 25th July 1997.

Solaraze is a non-steroidal anti-inflammatory gel that is applied to the skin. Solaraze gel is used to treat a skin problem known as actinic or solar keratosis that is caused by long-term sun exposure.

Solaraze contains the active ingredient diclofenac sodium, which belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs) and act by reducing fever, and inflammation as well as the ability to reduce pain.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Solaraze™ 3% Gel outweigh the risks; hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1

Product Name	Solaraze™ 3%, gel
Type of Application	Hybrid, Article 10.3
Active Substance	Diclofenac sodium
Form	Gel
Strength	3%w/w
Marketing Authorisation Holder	Almirall, S.A Ronda General Mitre, 151 08022 Barcelona Spain.
Reference Member State (RMS)	UK
Concerned Member State (CMS)	Greece, Poland and Spain
Procedure Number	UK/H/0226/001/E02
End of Procedure	18th November 2010

Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Solaraze™ 3% Gel (PL 12762/0404) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Solaraze™ 3%, gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel.

A clear, transparent, colourless or pale yellow gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of actinic keratoses

4.2 Posology and method of administration

Use in Adults: 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.

Use in the 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.

4.3 Contraindications

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

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 Solaraze is contraindicated during the last 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 Solaraze is very small compared to the frequency of side effects with oral diclofenac, owing to low systemic absorption with Solaraze. This product should be used with caution in patients with a history 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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Pregnancy and lactation

Use in pregnancy: Solaraze is contraindicated during the last trimester of pregnancy (see section 4.3) and should not be used during the first two trimesters of pregnancy unless clearly necessary. If used during pregnancy, Solaraze must not be applied to a large area of the skin (>30% of the body surface) and must not be used for long-term treatment (>3 weeks).

There are no adequate data from the use of diclofenac in pregnant women. Animal studies have shown reproductive toxicity(see section 5.3). 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 or 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.
- Inhibition of uterine contractions.
- Prolongation of pregnancy and labour.
- Increased risk of bleeding in the mother and child.
- Increased risk of oedema formation in the mother.

Use during lactation: It is not expected that any measurable amount of diclofenac sodium would occur in breast milk following topical application. Solaraze can be used at the recommended therapeutic dose. However, Solaraze should not be applied to the breast area of nursing mothers.

4.7 Effects on ability to drive and use machines

Not applicable

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.

Organ system	**Common (›1/100, <1/10)**	**Uncommon (>1/1000, <1/100)**	**Rare (>1/10000, <1/1000)**	**Very rare <1/10000**
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 and tingling or blistering at the treatment site)			
Immune System Disorders	Topical application of large amounts may result in systemic effects including hypersensitivity			
Nervous System	Hyperesthesia, hypertonia, localised paraesthesia			
Renal and Urinary System Disorders				Renal failure
Skin and Subcutaneous Tissue	Contact dermatitis, dry skin, erythema,	Alopecia, face oedema,		

Organ system	Common (›1/100, <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10000, <1/1000)	Very rare <1/10000
Disorders	oedema, pruritus, rash, scaly rash, skin hypertrophy, skin ulcer, vesiculobullous rash	maculopapular rash, photosensitivity reaction, seborrhoea		
Vascular Disorders		Haemorrhage		

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.

4.9 Overdose

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 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. 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: D11 A X 18
Other Dermatologicals
Mechanisms of action: Diclofenac is a non-steroidal anti-inflammatory drug. The mechanism of action of diclofenac in actinic keratosis 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.
Pharmacodynamic Effects: Solaraze has been shown to clear AK lesions with maximum therapeutic effect seen 30 days after cessation of drug therapy.

5.2 Pharmacokinetic properties

Absorption: Mean absorption through the skin varies between <1-12% with large inter-individual variability. Absorption is dependant 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 conjuguates. 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 ± SD) 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

Sodium hyaluronate, benzyl alcohol, macrogol monomethyl ether 350 and purified water

6.2 Incompatibilities

Not applicable.

6.3. Shelf life

3 years

After 1st opening: 6 months

6.4 Special precautions for storage

Do not store above 25°C

6.5. Nature and contents of container

The product is supplied in an epoxy-phenolic lined sealed aluminium tube with a white polypropylene screw on cap with a pierced tip, in 25 g, 50 g, 60 g, 90 g and 100 g sizes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

ALMIRALL S.A
Ronda General Mitre 151
Barcelona
E-08022
Spain

8 MARKETING AUTHORISATION NUMBER(S)

PL 16973/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 September 2000 / 25 July 2007

10 DATE OF REVISION OF THE TEXT

01/01/2010

Module 3
Product Information Leaflet
PACKAGE LEAFLET: INFORMATION FOR THE USER

Solaraze™ 3%, gel
Diclofenac Sodium 3% w/w

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Solaraze is and what it is used for

Solaraze is a non-steroidal anti-inflammatory dermatological gel. When applied to the skin, Solaraze gel is used to treat a skin problem known as actinic or solar keratosis that is caused by long-term sun exposure.

2. Before you use Solaraze

Do not use Solaraze

- If you are allergic to diclofenac or any of the ingredients in Solaraze.
- If you have had an allergic reaction such as skin rash (nettle rash), breathing difficulties (wheezing) or runny nose (allergic rhinitis) after taking aspirin or any other non-steroidal anti-inflammatory agents.
- If you are in the final 3 months of your pregnancy.

Take special care with Solaraze

- You should consult your doctor if:
  - You have, or have had in the past, a stomach ulcer or bleeding from the stomach,
  - You have heart, liver or kidney problems,
  - You have any type of bleeding disorder or bruise very easily.
- Avoid sun exposure, including tanning salons, when using Solaraze. If skin reactions occur, discontinue use.
- Do not apply to skin wounds, infected skin or dermatitis.
- Do not allow Solaraze to come into contact with your eyes or the inside of your nose or mouth.

Pregnancy/Breastfeeding

Speak to your doctor if you are, or could be pregnant. Solaraze should be used with caution during the first six months of pregnancy but **must not** be used during the last three months of pregnancy.

If you are pregnant, and your doctor considers treatment appropriate, Solaraze must not be applied to an area of the skin larger than about a third of your body and must not be used for longer than three weeks.

Solaraze can be used whilst breastfeeding but should not be used on the breasts.

Ask your doctor or pharmacist for advice before taking or using any medicine.

3. How to use Solaraze

- Solaraze is not suitable for children.
- Use the gel as directed by your doctor.
- Pierce the aluminium membrane across the tube opening with the cap before using.
- Gently smooth a small amount of gel onto the skin over the area to be treated. The amount of gel needed will vary depending upon the size of the area to be treated. Usually 0.5 grams of gel (about the size of a pea) will be enough for one area (5cm x 5cm) but not more than 8 grams should be used per day.
- You can apply Solaraze twice daily unless your doctor tells you differently. You may notice a slight cooling effect when you smooth the gel onto your skin.
- The usual period of treatment is 60-90 days. Maximum effect has been seen with treatment times closer to 90 days. Complete healing may not occur for up to a month after treatment has stopped.
- Wash your hands after applying the gel, unless your hands are being treated.

If you use more Solaraze than you should
Remove the excess gel by washing with water.

If you forget to use Solaraze
Continue to apply as directed but do not apply twice as much to make up for the missed application.

4. Possible side effects

Like all medicines, Solaraze can have side effects although not everybody gets them.

If you have any of the following side effects, stop using Solaraze and contact your doctor as soon as possible:
skin rash (nettle rash); breathing difficulties (wheezing); runny nose (allergic rhinitis). These symptoms indicate that you may be allergic to Solaraze.

If any of the following common side effects are severe or last for more than a few days you should stop using Solaraze and contact your doctor: itching, rash, skin redness, inflammation, contact dermatitis, pain and blistering.

Other Common side effects: (occur in between 1 and 10 out of every 100 patients)
Irritation or tingling at the site of treatment, conjunctivitis, allergy, a painful sensation when the skin is touched, pins and needles, muscle stiffness, dry skin, swelling, rash (including scaly or blistering), sagging of the skin, and skin ulcer.

Uncommon side effects: (occur in between 1 and 10 out of every 1,000 patients)
eye pain, weeping/dry eyes, pain in the abdomen, diarrhoea, feeling sick, hair loss, facial swelling, a skin sensitivity to sunlight, excessive bleeding or oily skin, a measles-like rash.

Very rare side effects (occur in fewer than 1 in 10,000 patients)
bleeding from your stomach or problems with your kidneys.

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

If any of the side effects becomes serious or you notice any side effects not mentioned in this leaflet please inform your doctor or pharmacist.

5. How to store Solaraze

Keep Solaraze out of the reach and sight of children.

Do not use after the expiry date (shown as 'EXP') on the tube and carton. The date refers to the last date of that month.

Do not store above 25°C.

Shelf life after opening: 6 months

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Solaraze contains

- Each gram of gel contains the equivalent of 30mg diclofenac sodium (the active substance).
- The gel also contains sodium hyaluronate, benzyl alcohol, macrogol monomethyl ether 350 and purified water.

What Solaraze looks like and contents of the pack

Solaraze gel is a clear, transparent, colourless or pale yellow gel packed in tubes containing 25 grams, 50 grams, 60 grams, 90 grams or 100 grams of product.

Marketing Authorisation Holder and Manufacturer

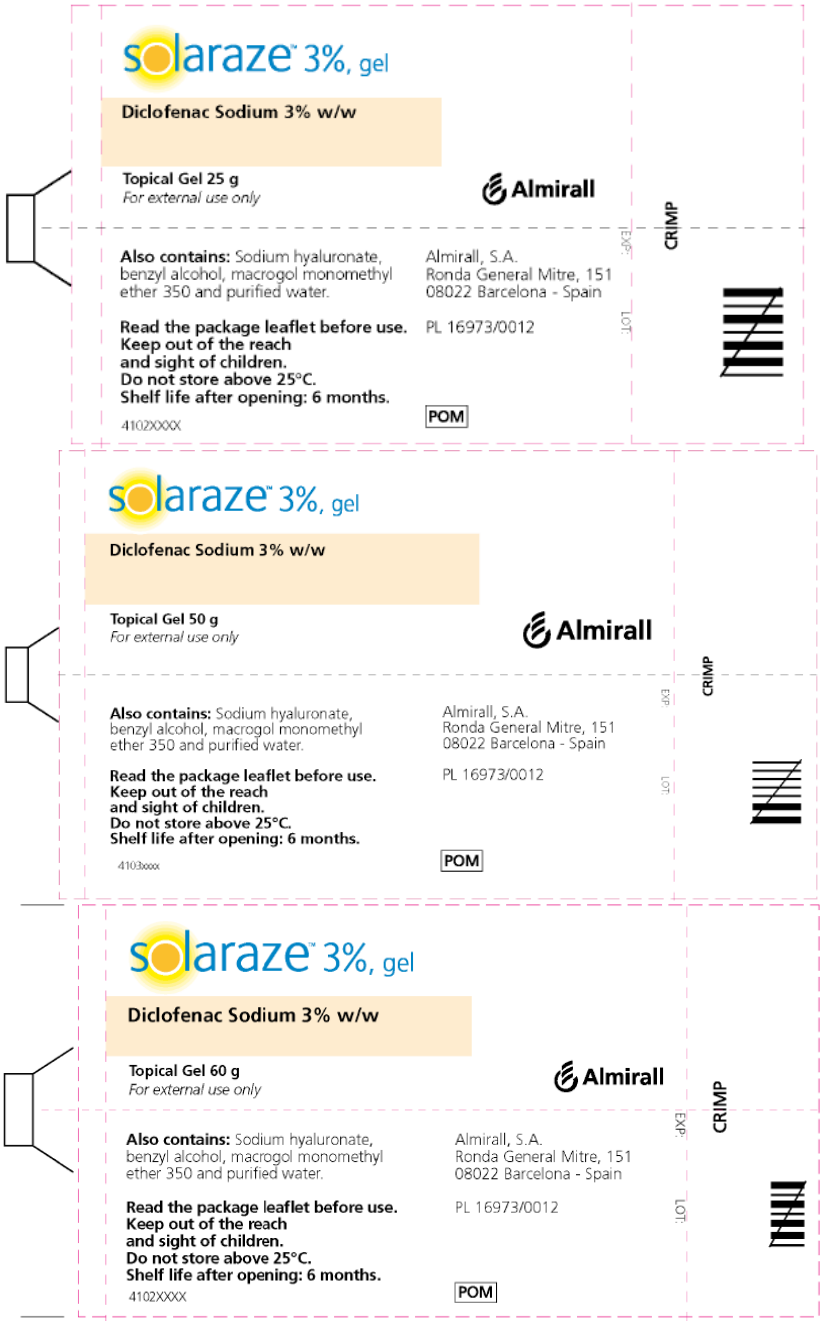
The marketing authorisation holder is Almirall, S.A.; Ronda General Mitre, 151;
08022 Barcelona; Spain

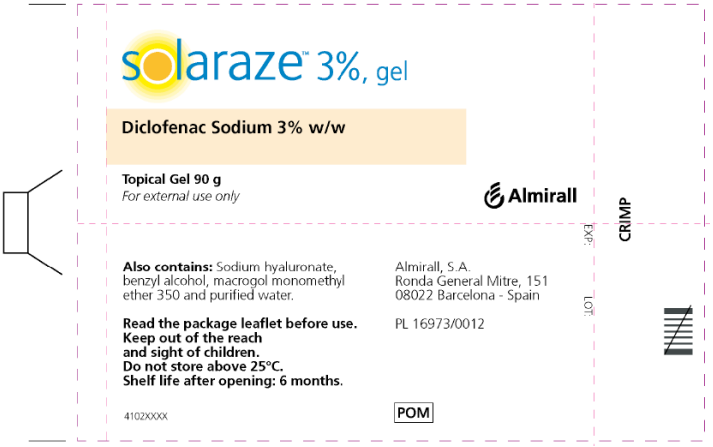
The manufacturer is Almirall Hermal GmbH, Scholtzstrasse 3, D-21465 Reinbek, Germany.

This leaflet was written on 13/01/2010

Module 4
Labelling

Carton

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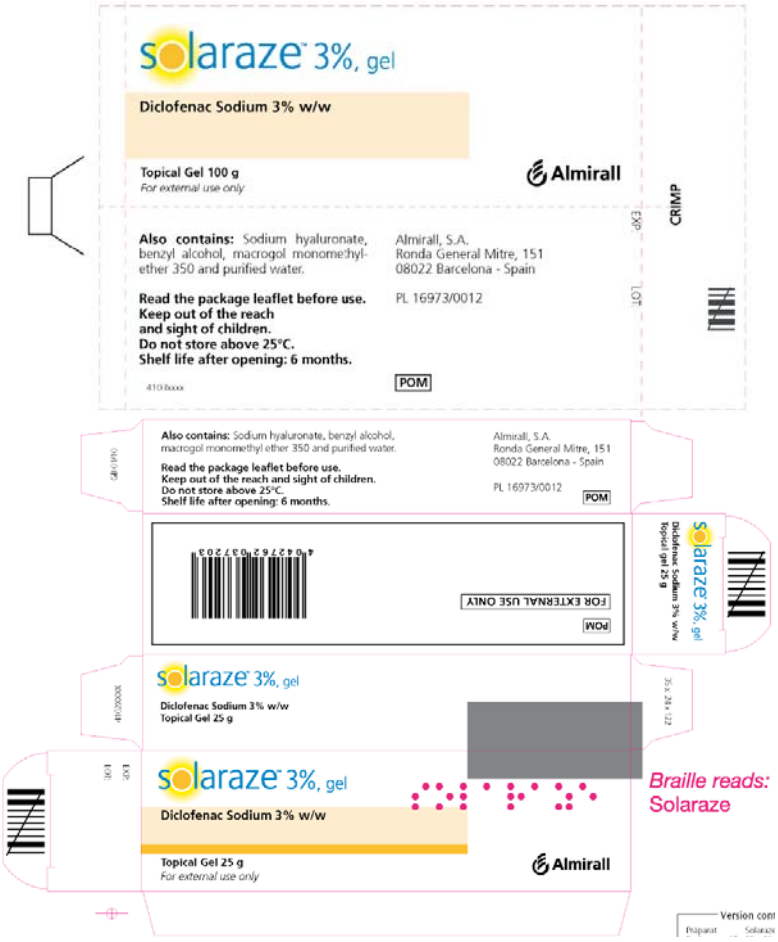
Diclofenac Sodium 3% w/w
Topical Gel 90 g
For external use only
Almirall
CRIMP
EXP
LOT
Also contains: Sodium hyaluronate, benzyl alcohol, macrogol monomethyl ether 350 and purified water.
Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona - Spain
Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not store above 25°C.
Shelf life after opening: 6 months.
PL 16973/0012
4102XXXX
POM


solaraze 3%, gel
Diclofenac Sodium 3% w/w
Topical Gel 100 g
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CRIMP
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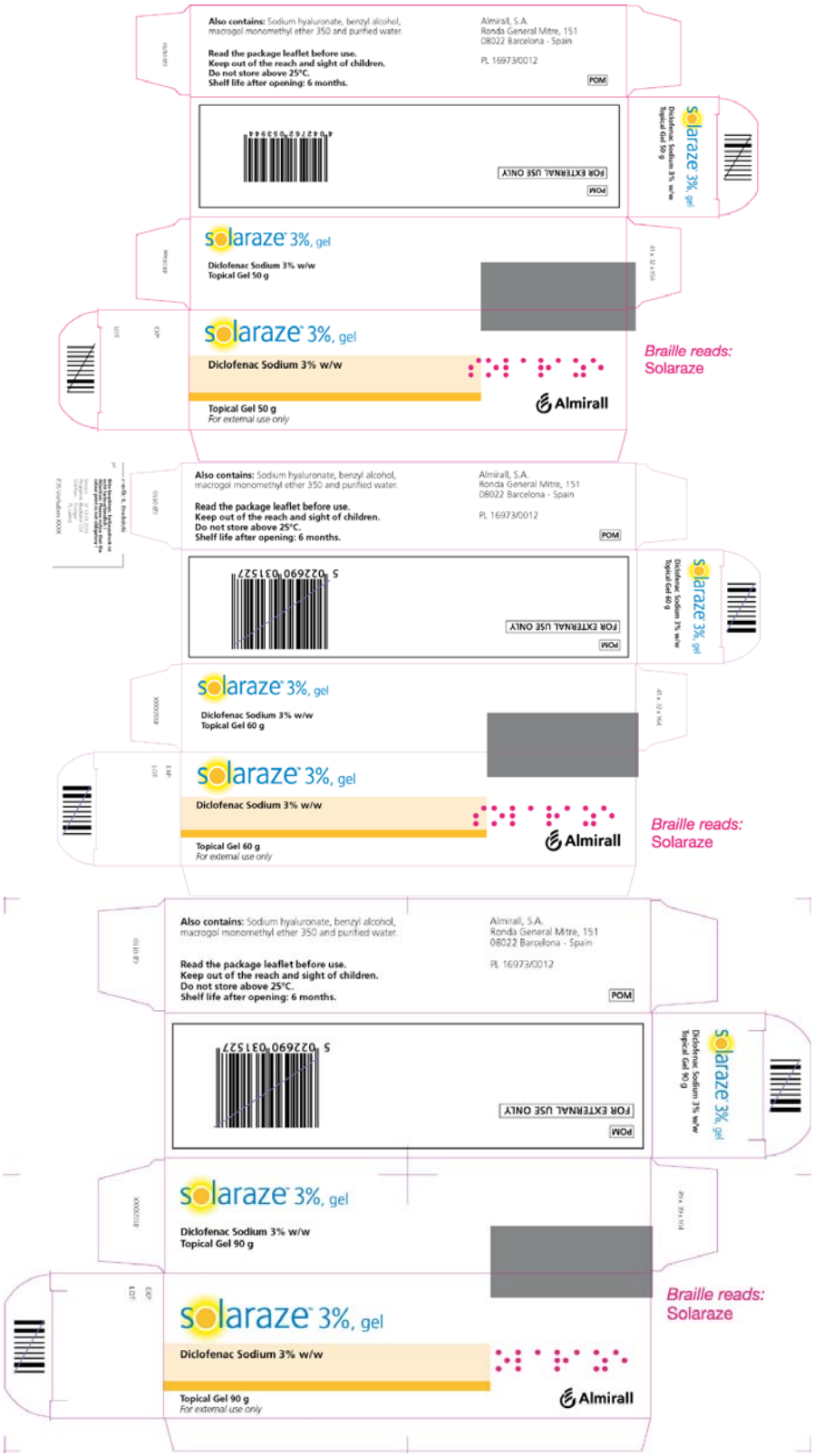
Solaraze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Almirall, S.A.
Ronda General Mitre, 151
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PL 16973/0012
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FOR EXTERNAL USE ONLY
solaraze 3%, gel
Diclofenac Sodium 3% w/w
Topical Gel 50 g
Topical Gel 50 g
For external use only
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Almirall
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Almirall
Braille reads:
Solaraze

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

On 18th November 2010, Greece, Poland and Spain granted Almirall SA a Marketing Authorisation (MA) for the medicinal product Solaraze™ 3% Gel (PL 16973/0012; UK/H/0226/001/E02). The product is available as a prescription-only medicine used to treat a skin condition known as actinic or solar keratosis.

This application was submitted under Article 10.3 of Directive 2001/83/EC (hybrid application) for Solaraze™ 3% Gel, using the mutual recognition procedure (MRP) with the UK as reference member state (RMS). The original licence had previously been granted in the UK on 25th July 1997.

The original licence for this product (PL 14507/0002, under the product name Solarase) was granted to Hyal Sweden Ltd on 25th July 1997 and was taken over by Bioglan Laboratories Ltd on 1st September 2000 (PL 00041/0117). The licence was taken over by Shire Pharmaceutical Contracts Ltd (PL 08081/0034) on 15th November 2002 when the product name changed to Solaraze. The licence was taken over by the current Marketing Authorisation Holder (ALMIRALL S.A; PL 16973/0012) on 15th July 2008.

The reference medicinal products are Voltarol Tablets 25mg (PL 00001/0036) and Voltarol Tablets 50mg (PL 00001/0082). These reference products were licensed in the UK on 27th November 1978 and 9th April 1979.

Solaraze™ 3% Gel went through a first wave Mutual Recognition Procedure (UK/H/0226/001/MR) involving Germany, France, Italy and Sweden. The procedure was completed on 3rd May 1998.

This product then went through a second wave/repeat-use Mutual Recognition Procedure (UK/H/0226/001/E01) involving Austria, Denmark, Finland, Iceland, Ireland, Luxembourg, Norway and Portugal. The procedure was completed on 4th March 2003.

The active ingredient of Solaraze TM 3% Gel, is diclofenac sodium. Solaraze™ is indicated for the treatment and management of actinic keratoses which are skin lesions caused by excessive exposure to ultraviolet radiation. It can progress to extensive epidermoid carcinoma. Diclofenac belongs to the group of non-steroidal anti-inflammatory agents (NSAIDs) and have anti-inflammatory, analgesic and anti-pyretic activities.

Solaraze™ is applied locally to the skin two 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.

The application is supported by preclinical and clinical studies.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of

these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the Marketing Authorisation Holder (MAH), fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Solaraze™ 3%, gel
Name(s) of the active substance(s) (INN)	Diclofenac sodium
Pharmacotherapeutic classification (ATC code)	Other dermataologicals (D11 AX18)
Pharmaceutical form and strength(s)	Gel 3% w/w
Reference numbers for the Decentralised Procedure	UK/H/0226/001/E02
Reference Member State	United Kingdom
Member States concerned	Greece, Poland and Spain
Marketing Authorisation Number(s)	PL 16973/0012
Name and address of the authorisation holder	ALMIRALL S.A Ronda General Mitre 151 Barcelona E-08022 Spain

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

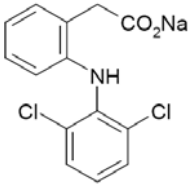
INN Diclofenac sodium

Chemical name:

1. 2-[2,6-Dichlorophenyl)amino] benzeneacetic acid monosodium salt
2. [0-(2,6-Dichloroanilino)phenyl] acetic acid sodium salt
3. Sodium2-[[(2,6-dichlorophenyl)amino]phenyl]acetate

Chemical Abstracts No.: CAS-15307-79-6

Structure:



Molecular formula: $C_{14}H_{10}Cl_2NNaO_2$
Molecular weight: 318.13

General Properties

Description: White or slightly yellowish, slightly hygroscopic, crystalline powder.
Solubility: Sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 %), slightly soluble in acetone.

The active substance, diclofenac sodium, is the subject of a European Pharmacopeia (Ph.Eur.) monograph.

Manufacture

All aspects of the manufacture and control of the active substance diclofenac sodium are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

The active substance is stored in appropriate packaging. The primary packaging is a double polyethylene bag inside a high density polyethylene (HDPE) drum. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been presented for the active substance stored in packaging representative of the proposed commercial packaging. These data demonstrate the stability of the active substance. A re-test period of 24 months has been applied when stored in the stated container closure system.

DRUG PRODUCT

Description and Composition

The finished product is presented as a clear, transparent, colourless or pale yellow gel. Each gram of gel contains 30mg diclofenac sodium (3% w/w).

Other Ingredients
Other ingredients consist of pharmaceutical excipients, namely sodium hyaluronate, benzyl alcohol, macrogol monomethyl ether 350 and purified water. Appropriate justifications for the inclusion of each excipient have been provided. All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of macrogol monomethyl ether 350 which complies with the National Formulary (NF). Satisfactory Certificates of Analysis have been provided for all the excipients. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in, or used in the manufacturing process for the proposed product. Furthermore, none of the excipients are sourced from genetically modified organisms.

Pharmaceutical Development
The aim of the pharmaceutical development programme was to produce a reproducible, therapeutically effective and cosmetically acceptable gel formulation containing 3% diclofenac sodium as the active substance. Suitable pharmaceutical development data have been provided for this application.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. Satisfactory analytical results from three consecutive commercial scale batches have been provided and are satisfactory.

Finished Product Specification
Finished product specifications are provided for both release and shelf–life, and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Batch data are provided for six batches of the finished product, which demonstrate that the batches are compliant with the proposed release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System
The finished product is licensed for marketing in epoxy-phenolic lined sealed aluminium tubes with white polypropylene screw on caps with a pierced tip. Tubes are available in pack sizes of 25g, 50g, 60g, 90g and 100g and are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 3 years (unopened) and 6 months after first opening has been set, which is satisfactory. Storage instructions are ‘Do not store above 25°C’.

Bioavailability Study
A bioavailability study to demonstrate the pharmacokinetics of diclofenac sodium from a topically applied Solaraze 3% Gel with that from orally administered Voltaren 75mg film-coated tablets (manufactured by Geigy) have been provided. The details of this study are discussed in the Clinical Aspects (Section III.3) of this report.

Quality Overall Summary
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that is contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Conclusion
There are no objections to approval of Solaraze™ 3% Gel from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS

INTRODUCTION
This application is for a gel containing 3% diclofenac sodium indicated for the treatment of actinic keratoses.

Solaraze is applied locally to the skin two times daily. 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. A maximum of 8 grams daily should not be exceeded.

The Nonclinical Overview contains a reasonable summary of the data and discussion of the results. Much of the information was derived from published papers and the US Summary Basis of Approval (SBA) of 1988 for Voltaren enteric coated tablets. There is a substantial amount of human experimental data included and one dermal tolerance study in mini-pigs using the product is reported in full. There is also a discussion of the effects of sodium hyaluronate, which is present in the formulation.

Sodium hyaluronate
No safety studies involving the dermal application of sodium hyaluronate are available in the literature. Sodium hyaluronate is naturally occurring and it has been used in humans, for instance in the eye, and is present in some cosmetic preparations. It is present in Solaraze primarily for its gel-forming and moisturising properties. However, some studies using human skin *in vitro* have suggested that it might slow the rate of dermal transfer of diclofenac resulting in the active material remaining in epidermal skin for a longer period than when buffer or another gel formulation, containing sodium carboxymethylcellulose, was used. It was also noted that sodium hyaluronate modified the binding of diclofenac to human serum albumin *in vitro*.

DICLOFENAC SODIUM

Pharmacodynamics relating to the proposed indication

The pharmacology of diclofenac is well known. It has anti-inflammatory, analgesic and antipyretic activity and is ulcerogenic to the GI tract. It appears that GI tract toxicity occurs after parenteral as well as oral dosing and is related to the inhibition of prostaglandin synthesis. Diclofenac was shown to reduce levels of PGE_2 and 6-keto-$PGF_{1\alpha}$ in the gastric wall. There was only limited pharmacodynamic information derived from the topical application of a diclofenac containing gel (1%) where anti-inflammatory activity was demonstrated in three rat models: UV-induced skin erythema, adjuvant-induced arthritis and vascular permeability. There was no appreciable activity in three other models: carrageenin-induced oedema, the cotton pellet test and pain threshold, and it was suggested that absorption was insufficient to give activity away from the site of application of the gel.

General pharmacology

A number of secondary pharmacological actions, involving oral or injected doses of diclofenac, were reported in the SBA for Voltaren and were briefly mentioned in the Nonclinical Overview.

PHARMACOKINETICS

The pharmacokinetics of diclofenac by the oral and i.v routes of administration have been summarised in the Nonclinical Overview. In animals, diclofenac is well absorbed after oral administration, and distribution studies showed highest levels in the liver and kidneys. Metabolism is extensive in laboratory species, with metabolites (phenolic compounds conjugated with glucuronide and sulphate) being regarded as inactive. The terminal half-life varies according to route of administration and species, but is generally fairly short e.g. 8-12 hours. Excretion is largely urinary in rabbits, guinea pigs and monkeys, but roughly evenly distributed between urine and faeces in rats, dogs and man, with significant enterohepatic recirculation present in rats and dogs. Percutaneous absorption does occur in man and animals.

In a study in guinea pigs involving the dermal application of a gel containing 3 % ^{14}[C] diclofenac with and without hyaluronic acid, only very low levels of radioactivity were detected in the underlying muscle tissue and in plasma. Systemic absorption appeared to occur slowly and to a limited extent but this study used too few animals and too low a dose to give more detailed information. *In vitro* studies using human skin and 1 % diclofenac gels (Voltarol Emulgel- PL 00101/0468 currently licensed Novartis Pharmaceuticals UK Limited) and gels with and without hyaluronic acid) showed similar results. For both Voltarol Emulgel and gels containing hyaluronic acid, dermal penetration was not significant until 12 hours after application, when appreciable levels of diclofenac could be detected in lower skin layers and receptor fluid. Diclofenac penetrated to a lesser degree from the gel without hyaluronic acid.

It appears that the terminal half-life may be shorter in man than in animals, but there would appear to be reasonable similarity in general between species. Direct and quantifiable comparison of the pharmacokinetics between man and animals was not possible given the limited and disparate information available.

TOXICOLOGY

Single and repeat dose studies (routes other than percutaneous)

These are summarised in the Nonclinical Overview. The main target organ in rats, dogs, rhesus monkeys and baboons was the GI tract (but apparently not in rabbits at the doses used). Other organs affected by diclofenac included the kidneys, liver and testes and red and white cell

parameters were also altered. In rats and dogs significant toxicity was seen after relatively short periods of treatment i.e. about 1 month, at dose levels close to the levels given to patients.

REPRODUCTIVE TOXICOLOGY

There are several animal studies reported using oral dosing. It appears that diclofenac sodium does not affect fertility, it caused dystocia and some embryo and foetal toxicity (e.g. increased resorptions, reduced birth weight, delayed skeletal ossification), but was not teratogenic. Maternal toxicity was sometimes, but not always, reported in conjunction with foetotoxicity.

GENOTOXICITY

A fairly comprehensive collection of mutagenicity assays was reported in the SBA of 1988, all of which were negative. There are two literature reports of Rec assays using *B. subtilis* which indicate that diclofenac had marginal activity in causing DNA damage. Diclofenac was also cytotoxic in cultured human conjunctival cells. When the lymphocytes from individuals dosed with diclofenac (100 mg/day, p.o., for 14 days) were examined, they appeared normal (no change in the rate of sister chromatid exchange was detected). Cell transformation assays using diclofenac and Solaraze gel both gave negative results. The overall conclusion is that diclofenac does not appear to possess significant genotoxic activity.

CARCINOGENICITY

Two dietary studies in rats were reported in the SBA of 1988. Although these studies were to some extent flawed, there were no clear carcinogenic effects seen. In one study there were small increases in several tumours but the incidences were all within the claimed historic control range.

LOCAL TOLERANCE

Eye irritation

A 0.3 or 0.5% buffered isotonic solution of diclofenac did not produce signs of ocular irritation in rabbits.

Dermal tolerance of Solaraze

Human data

In order to supplement the single animal study (described below), some studies in human volunteers were submitted. Following a single application of Solaraze (0.2 ml) to 19 subjects, no evidence of primary skin irritation was seen.

When the skin sensitising potential of the formulation was evaluated in 102 subjects (following nine applications of 0.2 ml), none of the application sites showed significant erythema or oedema.

Photosensitisation was evaluated in 25 subjects given a single application of Solaraze (0.2 ml), followed by exposure to UV and visible light. Slight erythema, which quickly resolved, was seen in a single subject.

Another study of photosensitisation and contact sensitisation involved 27 subjects who received repetitive application of gel followed by UV exposure over a 3 week period. After a 2 week rest period, challenge was made to untreated sites, with UV irradiation of one site. No significant reactions were seen, indicating a lack of contact and photosensitisation.

Animal data

A six month dermal toxicity study in mini pigs was carried out in accordance with GLP. Solaraze Gel was applied to shaved skin areas of mini pigs at daily dose levels of diclofenac of

0, 3, 10 or 30/45 mg/kg. A male animal from the mid-dose group and one from the high-dose group were sacrificed in poor condition after 21 and 23 weeks, respectively, due to peritonitis and ulcerative jejunitis or gastritis. Skin reactions were seen at the treatment sites at all doses, but there was no clear relationship between dose and severity. There were also some skin lesions at untreated sites in control and treated animals. A range of lesions was reported, with the more severe being ulcerative or erosive dermatitis, and as the latter only appeared at treated sites, some relationship with treatment appears probable. The main target organ for toxicity was the GI tract, with dose related erosive and ulcerative changes being found in the duodenum, jejunum and stomach, although at the low dose, the only microscopic changes were seen in the stomach. The details can be found in the Nonclinical Overview. The kidneys of mid- and high-dose animals also showed a slightly increased incidence of changes e.g. interstitial nephritis, tubular dilation, hyaline casts, mononuclear infiltrations and papillary degeneration. Although some plasma level data were provided, there were detectable levels of diclofenac in the control samples, attributed to contamination, thus making it difficult to evaluate systemic exposure.

ENVIRONMETAL RISK ASSESSMENT
The results show that the MAH meets current legal requirements with regards to environmental risk.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

EXPERT REPORT
The pre-clinical overview was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

CONCLUSIONS
Diclofenac is a well known non-steroidal anti-inflammatory drug (NSAID) which has been available for some years as an oral preparation. A 1 % diclofenac gel is also authorised; Voltarol Emulgel, licensed in May 1990 to Ciby-Geigy and has since undergone a change of ownership in July 1997 to Novartis Pharmaceuticals UK Limited.

The pharmacology of diclofenac presented in this application did not specifically address the proposed indication. The suggestion was made by the Expert that as prostaglandin E appears to be linked to the growth of neoplastic tissue, perhaps via an effect on the immune system, inhibition of the synthesis of prostaglandins, particularly E, could suppress tumour growth. This would be relevant to actinic keratoses as they are dysplastic epidermal lesions which are apparently predictive of basal cell carcinoma.

The absorption data available suggested appreciable systemic exposure to diclofenac would occur after topical application, but would not be as great as that seen after oral administration, suggesting that the usual dose of Solaraze would present a reduced risk of toxicity when compared with the usual dose of, for instance, Voltarol tablets. The inclusion of the sodium hyaluronate in the formulation appeared to delay dermal penetration, suggesting reasonable exposure of the upper layers of the skin at the application site.

The single dermal toxicity study in mini pigs did show some adverse effects, including GI tract toxicity, effects on the kidney as well as some skin lesions. Other dermal tolerance data were presented from human studies and showed that there was no significant dermal irritancy, sensitisation or photosensitisation for the preparation. The information presented suggested that diclofenac lacked significant genotoxic, carcinogenic or teratogenic activity but was foetotoxic in animals.

Although the preclinical package presented is rather limited with regard to animal studies using the product, there is considerable clinical experience with the active using different routes of administration, and thus there are no toxicological objections to the grant of a Marketing Authorisation for this product.

III.3 CLINICAL ASPECTS

CLINICLAL PHARMACOLOGY

Mode of action of Solaraze

Solaraze™ contains 3% diclofenac in a gel vehicle which includes hyaluronan (sodium hyaluronate, hyaluronic acid) as an aid to drug delivery. A naturally occurring product in most extracellular tissues, hyaluronan is capable, after hydration, of carrying water soluble drugs within a complex polysaccharide porous sphere, which is able to penetrate the epidermis carrying water and dissolved compounds with it, the former being the basis for its use as a moisturiser in cosmetics. The activity of hyaluronan as a carrier to aid epidermal absorption of diclofenac has been tested by the MAH in one *in vitro* and two *in vivo* human studies.

An *in vitro* study was conducted to determine the penetration of labelled diclofenac (C^{14}) and hyaluronan (H_3) through skin using full thickness, epidermal sheet and corneum striatum human skin sections mounted in a Franz cell.

The penetration of diclofenac from formulations including either hyaluronan or a buffer indicated that when diclofenac was given with hyaluronan most of the C^{14} label was retained for at least seven days as a depot in the epidermis, whilst diclofenac in the buffered formulation penetrated all layers of skin and was not retained.

When labelled hyaluronan was applied by itself it was observed that, whilst it penetrated all layers of the skin, most was retained in the epidermis. It is suggested that the retention of hyaluronan in the epidermis may be related to a cell surface receptor, CD44, located mainly in the epidermis, with which hyaluronan has a high affinity.

Other *in vivo* pharmacokinetic studies of the Solaraze formulation indicate very low systemic absorption of diclofenac compared to formulations not containing hyaluronan and support the hypothesis that the effect of hyaluronan is to control diffusion of diclofenac through the skin and to retain it in the epidermis. This localisation of the active ingredient in the skin is the rationale for the use of the formulation in the management of appropriate dermatological conditions.

Diclofenac pharmacodynamics

It has been reported that some NSAIDs have anti-cancer properties. In one study (Panje; 1981) the administration of indomethacin was associated with regression of advanced head and neck carcinoma. Modulation of immunity by piroxicam has been observed in cancer patients (Braun *et al*; 1989), but with modest anti-tumour effects. Diclofenac and ketorolac have been used in combination with cytodestructive therapy in patients with advanced neoplasia and a significant proportion are reported (Falk *et al*; 1992-abstract only) to have had a partial or complete response.

The mechanism of action of this effect of NSAIDs is suggested to be by inhibition of the cyclo-oxygenase pathway, specifically the reduction of PGE_2 synthesis (Brunda *et al* 1980 and Elliott *et al* 1988). PGE_2 inhibits natural killer cell cytotoxicity, mitogen induced lymphocyte

proliferation, macrophage proliferation and anti-tumour cytotoxicity. A direct action (of indomethacin) on T-lymphocyte function, independent of prostaglandin synthetase inhibition, has also been proposed (Tilden *et al* 1982).

These observations imply that diclofenac may have efficacy against malignant or pre-malignant conditions and the ability of the Solaraze formulation to concentrate it in the epidermis suggested that malignancy of the skin would be a possible target for clinical assessment.

Clinical pharmacology of diclofenac

The clinical expert has briefly reviewed the clinical pharmacology of diclofenac, particularly in regard to adverse effects (gastrointestinal, platelet aggregation, renal function). No conclusion is reached concerning the possibility of such effects being observed following application of Solaraze.

The MAH has conducted a series of studies to evaluate the dermal tolerance of Solaraze in human volunteers. These studies involved applications of Solaraze 0.2 ml (0.25g) or the gel vehicle, as follows:

1. Primary skin irritation in 19 subjects. Single application (24 hours) of Solaraze and placebo showed no oedema or erythema.

2. Contact sensitisation in 102 subjects. Nine applications (three times weekly x 3 weeks) of Solaraze and placebo and a challenge 2 weeks later showed no evidence of sensitisation.

3. Contact sensitisation in 103 subjects who were chronic users of NSAIDs. Similar design to above study; two subjects showed mild erythema and one showed papules after five applications of Solaraze, but no response to subsequent challenge test. It was concluded that this study showed no evidence of sensitisation for Solaraze.

4. Phototoxicity potential in 25 subjects. Single application of Solaraze and placebo for 24 hours followed by exposure to UVA irradiation or visible light and evaluated over next 3 days. No evidence of phototoxicity was observed.

5. Contact photoallergy potential in 27 subjects. Daily applications of Solaraze and placebo for 6 days followed by UVA irradiation one day later. After 2 weeks a single application was made and evaluated for photo-sensitisation and contact sensitisation. No significant reactions were observed during either phase of this study.

Pharmacokinetics

A two-way crossover study was carried out in 23 healthy male volunteers to compare the bioavailability of diclofenac sodium from topically applied Solaraze gel with that from orally administered Voltaren 75mg film coated tablets, currently licensed to Novartis (PL 00101/0471). Two grams of the gel was applied three times a day to the leg for 5 days, with a single administration on day 6, giving a total of 16 applications. The Voltaren tablets were taken once daily for 6 days and a nine day wash out period was allowed between treatments. Blood samples were taken immediately before dosing on days 1 and 6 and up to 24 hours after the final dose. Plasma samples were assayed for diclofenac sodium using a validated HPLC method, with UV detection. Results were as follows:

	Solaraze (180mg active per day)	Voltarern 75mg Tablet (75mg active per day)
	Mean (CV)	**Mean (CV)**
AUC_{0-t} (ng/hr/ml)	9.09	1598.8
C_{max} (ng/ml)	4.49	316.05
T_{max} (hrs)	4.5	4.72

Results were analysed using thee-way ANOVA.

This study demonstrates that systemic absorption of diclofenac sodium from Solaraze is low and highly variable.

A second study was carried out in patients with inflammatory skin disease and was designed as a cross-over comparison of the absorption of diclofenac from Solaraze when applied to affected areas of skin or to intact skin. Twelve patients with atopic dermatitis or eczema were treated with 2g gel four times a day (equivalent to 240mg diclofenac) for six days and once only on day seven, with a washout period of at least 14 days. Blood samples were collected on days 1 and 7. Results for day 7 are shown as follows:

Parameter	Compromised Skin Mean (CV%)	Intact Skin Mean (CV%)	Ratio of Means	ANOVA p-value Treatment factor
AUC_{0-t} (ng.hr/ml)	632 (91)	468 (83)	1.35	0.362
C_{max} (ng/ml)	76 (107)	58 (93)	1.32	0.352
T_{max} (hr)	13 (56)	13 (57)	1.01	0.831

There are no statistically significant differences for these parameters between compromised and intact skin. However, systemic absorption of diclofenac is stated as 12% of the administered dose for compromised skin and 9% for intact skin, demonstrating that the extent of absorption of diclofenac.

EFFICACY

The MAH has conducted three pivotal double blind studies and four studies defined as supportive.

Pivotal Studies

Study CT-1101-03

Informed patient consent was obtained and the study was conducted in accordance with GCP guidelines.

Study design and methods

The critical inclusion criterion was the clinical diagnosis of five or more actinic keratosis lesions contained in up to three 5cm² areas on face, arms or hands. Patients were excluded if they had been treated within 60 days with various medications, which may confound study results (including masoprocol, 5-FU, etretinate, etc).

Lesions were assessed for severity on a 0-3 scale (0 = not visible; 1 = visible with thin scales; 2 = moderately thick scale; 3 = thick hypertrophic/florid) and counted (target lesion number score: TLNS). Their size and location were marketed on a transparent plastic sheet placed over the area; they were also photographed.

Eligible patients were randomised double blind to receive treatment for 90 days with either:

a) Solaraze: 3% diclofenac with excipients, or
b) Vehicle: excipients only.

Dosage was 0.5g of the gel applied twice daily to each 5cm² area containing the target lesions.

Patients attended for assessment after 30, 60 and 90 days of treatment and, finally, a follow-up visit 30 days later. The number of lesions were counted, recorded and photographed on each visit. New lesions were identified (new lesion number score: NLNS) and a cumulative score calculated (TLNS + NLNS = CLNS).

The investigator scored a global improvement index (IGII) according to a 7 point scale (-2 = worse; 0 = no change; 4 = lesion cleared) and the patient also used this scale to score improvement (PGII).

Safety was monitored by adverse event reports, standard laboratory measures and evaluation of eczematous-type reactions.

Patients

One hundred and twenty patients were randomised, and 96 completed all study visits. Suitable justifications were given for drop-outs and patients that were withdrawn from the study.

Patient demographics and baseline characteristics were balanced between the two treatment groups.

Most patients were classified as having lesions of mild (Solaraze 36%; vehicle 31%) or moderate (56%, both treatments) severity.

Results

Primary efficacy outcomes were the number of patients with zero TLNS & CLNS scores at follow-up, and the number of patients 'completely improved' at follow-up by IGII and PGII assessments.

Patients (%) with a target lesion number score of zero.

Visit		Solaraze	Vehicle	Significance
Day	30	0	0	NS
	60	0	3(6)	0.05
	90	24 (41)	14 (24)	0.023
Follow-up		29 (50)	12 (20)	<0.001

Patients (%) with a cumulated lesion number score of zero.

Visit		Solaraze	Vehicle	Significance
Day	30	0	0	NS
	60	0	1(2)	NS
	90	24 (41)	13 (22)	0.014
Follow-up		27 (47)	11 (19)	<0.001

Patients (%) 'completely improved' (score=4) by investigator.

Visit		Solaraze	Vehicle	Significance
Day	30	2 (4)	0	NS
	60	1 (2)	1 (2)	NS
	90	24 (41)	13 (22)	0.014
Follow-up		27 (47)	11 (19)	<0.001

Patients (%) 'completely improved' (score=4) by patient.

Visit		Solaraze	Vehicle	Significance
Day	30	2 (4)	0	NS
	60	1 (2)	0	NS
	90	20 (34)	10 (17)	0.018
Follow-up		24 (41)	10 (17)	0.001

Secondary end points included a comparison of the number of lesions counted at each visit (TLNS & CLNS). The results for CLNS are shown below by mean (sd) lesions.

Visit		Solaraze	Vehicle	Significance
Day	0	6.7 (2.2)	7.1 (2.2)	NS
Day	30	6.0 (3.9)	5.1 (2.6)	NS
	60	4.2 (2.8)	3.7 (2.5)	NS
	90	2.8 (4.2)	2.7 (2.4)	NS
Follow-up		1.6 (2.1)	3.2 (2.0)	<0.001

Conclusion

Treatment of actinic keratoses with Solaraze provided significant benefit when compared to treatment with vehicle. A statistically significant difference was seen for all primary efficacy outcomes after 90 days treatment and these benefits became more emphatic after 30 days follow-up.

Study CT-1101-04

The major difference to the previous study was duration of treatment. Patients were randomised equally to form treatment groups as follows:

1) Solaraze bd x 30 days 2) Solaraze bd x 60 days
2) Vehicle bd x 30 days 4) Vehicle bd x 60 days.

A follow-up visit was made 30 days after completing treatment. The number of lesions were scored as before. In addition to a severity scale this study used a total thickness score (TTS) where R = resolved, 0 = visible, not palpable, to 4 = hyperkeratotic, > 2mm height. Investigator and patient Global Improvement Indices were as before. Punch biopsy specimens were obtained from one lesion per patient at baseline and follow-up for histological examination.

Safety was monitored as before.

Patients

One hundred and ninety five patients were randomised to treatment and 184 patients completed the study. Suitable justifications were given for drop-outs and patients that were withdrawn from the study.

Patient demographics and baseline characteristics were balanced between Solaraze vehicle treatments except for skin type (there were less light skinned patients in the Solaraze group than in the vehicle group).

Most patients were graded as having lesions of mild or moderate severity.

Results

Primary efficacy outcomes were the number of patients with zero TLNS, CLNS and TTS scores at follow-up, and the number 'completely improved' at follow-up by IGII and PG11 assessments.

Patients (%) with a target lesion number score of zero

	Solaraze 30	Vehicle 30	Significance	Solaraze 60	Vehicle 60	Significance
30	3 (6)	0	NS	1 (2)	2 (4)	NS
60	-			6 (13)	7 (14)	NS
Follow-up	7 (14)	2 (4)	NS	16 (33)	5 (10)	0.0126

Overall, i.e., for all patients, Solaraze had significantly more patients with a zero score at follow-up than vehicle (p=0.011). Similar results were obtained with CLNS, except the difference at follow-up was significant for Solaraze 30 ($p < 0.05$).

Patients (%) with total thickness core of zero (lesion resolved)

	Solaraze 30	Vehicle 30	Significance	Solaraze 60	Vehicle 60	Significance
30d	2 (4)	0	NS	1 (2)	1 (2)	NS
60d	-	-		5 (10)	5 (10)	NS
Follow-up	7 (14)	2 (4)	NS	12 (25)	3 (6)	0.034

Overall, Solaraze had significantly more patients with a zero score than vehicle (p=0.0192). The basis for this analysis is confusing since the TTS scale provided in the Methods section indicated that R represents 'lesion resolved' whilst zero represents 'visible, not palpable'.

Patients (%) 'completely improved' (score =4) by investigator

	Solaraze 30	Vehicle 30	Significance	Solaraze 60	Vehicle 60	Significance
30d	2 (4)	0	NS	2 (4)	4 (9)	NS
60d	-	-		7 (15)	8 (16)	NS
Follow-up	8 (16)	1 (2)	NS	14 (29)	5 (10)	0.027

Overall, Solaraze was significantly better at follow-up than vehicle (p=0.0114).

Patients (%) completely improved (score=4) by patient

	Solaraze 30	Vehicle 30	Significance	Solaraze 60	Vehicle 60	Significance
30	3 (6)	0	NS	3 (7)	2 (4)	NS
60	-	-		6 (13)	7 (14)	NS
Follow-up	8 (16)	2 (4)	NS	15 (31)	5 (10)	0.0213

Overall, Solaraze was significantly better at follow-up than vehicle (p=0.0089).

Conclusion

The results of this study confirm that Solaraze provides significant benefit to patients with actinic keratoses when compared to treatment with vehicle alone. Statistically significant benefit was seen for all primary efficacy outcomes in patients treated for 60 days, but only at the 30 day follow up visit.

Efficacy in those treated for 30 days was less in terms of percentage response to those treated for 60 days but significant benefit was only seen for one primary efficacy outcome (CLNS) at the follow-up visit.

5.1.3 Study CT-1101-07

This was a single-centre, double blind, placebo controlled study involving 112 patients randomised in a 1:1 ratio to treatment with either Solaraze (0.5g bid in each treatment area for 90 days) or gel vehicle (at the same dose and duration). The study included a follow up visit at 30 days after end of treatment. Efficacy was based on target and cumulative lesion scores, as well as investigator and patient global improvement indices. To evaluate sensitisation to diclofenac, serum samples obtained at screening and end of treatment were evaluated for antibodies to the active. Unfortunately, baseline target lesion scores were significantly greater in the diclofenac group than in the vehicle group (p=0.032). Nevertheless, the study results are statistically significant, with the Solaraze group showing greater reductions in TLNS and CLNS values than the vehicle group (p=0.006 for both outcome measures). The investigator global improvement index was also significantly greater in the Solaraze group than in the vehicle group (p=0.009), while the patient global improvement index did not demonstrate a statistically significant advantage of Solaraze (p=0.119). Biochemical analyses did not find any evidence of sensitisation to diclofenac. The clinical expert concludes that this study supports the conclusions of the original pivotal studies.

Supportive Studies

Study AK-LDN-093-001

This was an open study in which 30 patients with actinic keratoses were treated with Solaraze 1G bd for up to 180 days, or up to the time lesions were cleared, if less. Response to treatment was rated on a 7 point scale (from 'cure' to 'much worse') and the number of lesions was counted. Assessments were carried out at 60 day intervals and 30 days after stopping treatment.

One patient dropped out early. Of the remaining 29 patients, 81% were 'cured' at the follow-up visit. Treatment was discontinued because of adverse events in 11 patients but 9 of these were graded 'cured' and 2 'markedly improved' at the follow-up visit. The mean duration of treatment was 84 days. Compliance for applying the full dose of Solaraze was poor (50%).

Study AK CT 1101-01

A randomised double blind comparison of Solaraze 0.25G bd against vehicle in 150 patients with actinic keratoses. Duration of therapy was 12 weeks; the follow-up visit 30 days later was only added after the study had begun and just over half the patients were evaluated at that visit. In these patients the mean lesion count was significantly reduced (p=0.001) for Solaraze compared to vehicle. The number of patients whose lesions were cured was significantly greater with Solaraze at 12 weeks (21 Solaraze, 10 vehicle) and at the follow-up visit, (17 Solaraze, 4 vehicle).

Study ST-5101-GRK-01

An open study similar to that of Study AK-LDN-093-001. Solaraze 1G bd applied for up to 180 days to 20 patients with actinic keratoses. Efficacy was based on the investigators opinion of

lesion response. Compliance with this high dose was poor but response was rated as excellent in 74% and good in 16%.

Study ST-5101-AUS-01

A randomised, double blind study in which a single lesion was identified, measured, assessed and treated for 8 to 24 weeks with Solaraze or vehicle. A sunscreen was applied to the lesion after the Solaraze or vehicle gel.

Complete response rates at cessation of treatment (no follow-up) in the 130 patients recruited were 29% for Solaraze and 17% for vehicle, the difference not being significantly different. The low degree of efficacy in this study may have been associated with the use of sunscreen with the Solaraze, and no follow up assessment.

Conclusion

To provide an overall view of the results from the two pivotal studies the percentages of patients with a target lesion score of zero at the various time points are shown as follows:

Percentage patients with zero target lesion score

Visit	Study CT-1101-03 - 90 days			Study CT-1101-04, Dr Ribers - 30 days			Study CT-1101-04, - 60 days		
	Solaraze	Vehicle	Significance	Solaraze	Vehicle	Significance	Solaraze	Vehicle	Significance
30 days	0	0	-	6	0	NS	2	4	NS
60	0	6	0.05	-	-		13	14	NS
90	41	24	0.02	-	-		-	-	
Follow up	50	20	<0.001	14	4	NS	33	10	0.02

Treatment for 90 and 60 days provide significant benefit, whereas the results from 30 days treatment is low and less than the vehicle response (90 days). Optimum duration is 90 days treatment and optimum response 30 days later.

Results from the supportive studies, all conducted over at least 56 days but using different dosage regimens, show efficacy (cure) from 29% to 81%.

SAFETY

Safety data presented in this application relate only to the studies conducted in patients with actinic keratoses, as detailed in the previous section.

Pivotal Studies

Study CT-1101-03

Adverse events were reported by 90% Solaraze and 81% vehicle patients. Most were related to skin (79% Solaraze, 64% vehicle) and nervous system (31% Solaraze, 34% vehicle); for the latter the majority were also skin related i.e. paraesthesia, hyperaesthesia and tingling at the site of application.

The most frequent skin related adverse events were as follows:

Body System	**Treatment**	
	Solaraze n=58 n (% of group)	**Vehicle n=59 n (% of group)**
Pruritus	32 (55)	29 (49)
Application site reaction	20 (34)	12 (20)
Dry skin	21 (36)	10 (17)
Rash	19 (33)	9 (15)
Erythema	15 (26)	4 (7)

Rash vesiculobullous	3 (5)	0 (0)
Skin exfoliation	3 (5)	0 (0)
Ulcer skin	3 (5)	0 (0)

Eczematous type reactions were assessed separately and described as a 'clinically significant dermal reaction'. Definite erythema with or without induration was observed in 24 Solaraze patients (35 treatment blocks) but in only 6 vehicle patients (9 blocks).

A number of patients in each group were withdrawn from treatment because of adverse reactions. Whilst the study report is very detailed it is difficult to identify exactly how many had their treatment stopped, when, why and for how long. However, it is clear that more Solaraze patients were withdrawn than vehicle patients (8 vs 4), but in the study report it states 'the drug was stopped' in 13 vs 4 for skin reactions and 5 vs 2 for other events.

Most Solaraze patients (87%) and all vehicle patients recovered fully from their skin related adverse events. Two Solaraze patients recovered 'with sequelae' and four were 'not yet recovered'.

Most events were recorded as mild (Solaraze 72%, vehicle 84%) or moderate (24%, 13%); only one patient in each group was graded severe.

Overall it is clear that skin related effects occurred quite frequently with both treatments but the incidence with Solaraze was higher (79% vs 64%).

Patients were closely monitored for changes in haematological or biochemical values. Although a lot of minor abnormalities were noted there was no evidence of significant treatment related effects.

Conclusion
Adverse events were frequent, generally of mild severity and mostly skin related. The incidence was higher with Solaraze than with vehicle.

Study CT-1101-04
Adverse events were reported by 81% Solaraze and 87% vehicle patients. As in the previous study, most were skin related. Paraesthesia and hyperaesthesia were classed as nervous system events. The most frequent events were pruritus (Solaraze 36%, vehicle 59%) rash (34%, 29%) dry skin (27%, 16%) and application site reactions (23%, 19%).

Most were rated as mild or moderate severity but 7 Solaraze patients experienced 10 severe reactions (rash, pruritus, site reaction, contact dermatitis, oedema, and paraesthesia). Of patients reporting skin related adverse events almost all recovered without problem; the condition in 9 patients (2 Solaraze, 7 vehicle) had not resolved by the end of the study (mostly rash or dry skin).

Eczematous type reactions were observed more frequently in Solaraze patients (25-31%) than in vehicle patients (8-12%).

The histological data were reported as being consistent with clinical response.

Conclusion
Adverse events were frequent in all treatment groups, mostly skin related and of mild to moderate severity. The incidence of severe adverse reactions was higher in Solaraze patients.

Study CT-1101-07
The profile of adverse events seen in the additional study presented in the second wave MR dossier (CT-1101-07) is consistent with that seen in the studies reported above.

Supportive Studies

Study AK-LDN-093-001
The most common adverse events were skin related (70% of 30 patients) and were the reason for stopping treatment in 11 patients. Rash, eczema and pruritus were the most frequent diagnoses.

Study AK-CT-1101-01
Adverse events in 150 patients were more frequent with Solaraze (81 events in 30 patients) than with vehicle (31 events in 18 patients). Most common were rash, pruritus and dry skin.

Study 5101-GRK
Skin related adverse reactions were reported by only two of 20 treated patients (one rash, one ulcer; both mild).

Study 5101-AUS-01
Adverse reactions in the 130 patients were mostly skin related, 29% Solaraze and 5% vehicle.

Conclusion
Adverse events were very common in nearly all studies and were predominantly skin related. Although more events were reported by Solaraze patients the vehicle was also responsible for quite a high incidence of similar reactions, as can be seen in the following table:

Incidence (% patients) of skin reactions in controlled studies

	Study CT-1101-03		Study CT-1101-04	
	Solaraze	Vehicle	Solaraze	Vehicle
Pruritis	55	49	36	59
Rash	33	15	34	29
Application site reaction	34	20	23	19

Severe reactions were uncommon and nearly all reactions resolved when treatment was stopped.

The possibility that eczematous-type reactions may reflect hypersensitivity has been addressed by measuring anti-diclofenac antibodies in 150 patients participating in the two controlled studies. None was detected after exposure to Solaraze and it was concluded that there is no evidence of an allergic basis to these skin reactions. Also, the question of whether a topical NSAID could act as a sensitiser was looked at by patch testing patients who had previously been exposed to Solaraze (or Hyanalgese-D). Only one of 248 patients tested showed evidence of classical contact dermatitis after 48 hours and the MAH concludes that allergic sensitisation is of low risk potential with Solaraze.

No pattern of systemic adverse events with Solaraze was observed and no haematological or biochemical abnormalities were identified which suggested treatment related effect.

DISCUSSION

Introduction

The inclusion of hyaluronan in the Solaraze formulation has been adequately shown in preclinical studies to localise or retain most of the active ingredient, diclofenac, in the epidermis and this observation has been confirmed to some extent by pharmacokinetic studies which show unexpectedly low systemic absorption of diclofenac following topical application.

However, accepting that diclofenac may be relatively retained in the epidermis, the logical target for a therapeutic effect would be in the skin rather than in deeper or remote tissues. The company has identified from the literature publications which suggest that NSAIDs have anti cancer activities, possibly by reducing PGE_2 synthesis, and have taken the next step by suggesting that malignancy in the skin is a possible target for Solaraze.

Actinic or solar keratoses are dysplastic epidermal lesions commonly occurring in pale skinned individuals exposed to strong sunlight. Histologically they demonstrate hyperkeratotic atypia, hyperkaratosis and parakeratosis. The granular layer is disrupted and the basal layer may show changes in cell morphology. They are clinically important lesions since they are risk factors for basal cell carcinoma and melanoma and are thought to be precursors to squamous cell carcinoma. They are subject to spontaneous remission but more lesions persist than remit and the threat of malignant transformation is the spur to treatment.

Excision, curettage, cryotherapy and chemical destruction by topical agents such as 5-fluorouracil or masoprocol are the bases of current therapy. The latter pharmacological agents have severe dermal side effects which may reduce compliance (and, therefore, efficacy) and an alternative, less toxic, therapy would be of value. The potential of Solaraze to fill this therapeutic gap is the basis of this application.

Efficacy

The two pivotal double blind studies show statistically significant benefit for Solaraze compared to vehicle for the primary efficacy variables. The studies were conducted to a satisfactory standard and the measures of efficacy were appropriate.

A delayed response has also been observed following treatment with topical 5-fluorouracil. A late immunological response to treatment has been suggested for this phenomenon but it is not known whether such a mechanism applies to diclofenac. The product literature for Solaraze makes it clear that complete healing of lesions may not be evident for up to 30 days following cessation of treatment and this statement would appear appropriate.

The other clinical trials also indicate significant benefit for Solaraze. These studies suggest that doses of 1G bd may be too high, since compliance was poor, and doses of 0.25G bd too low (no difference between treatment groups). The choice of 0.5G bd seems acceptable in that it provides significant efficacy and is reasonably absorbed into the skin.

From all studies there is consistent evidence of efficacy in patients treated with the vehicle. Mostly the response is greatest during treatment, sometimes better than for Solaraze, but the improvement declines after stopping treatment. There are three possible explanations for this effect; first, that the vehicle itself has therapeutic properties; secondly, the natural regression of actinic keratoses; and, thirdly, probably the most likely explanation, the effect of the moisturising action of hyaluronan which has the ability to attract and absorb water into its molecule. This is the basis for its use in moisturisers and results in 'plumping' of the skin, thus giving the illusion of improvement to keratotic lesions. Natural regression of lesions may

contribute to some of the improvement observed during treatment, but not at follow up, and a therapeutic effect of hyaluronan is possible but speculative.

Safety

Whilst the incidence of skin related adverse reactions was high, few were severe and most recovered without problem. There was no evidence of significant hypersensitivity reactions, of sensitisation to diclofenac, or of systemic adverse events. It appears that most patients tolerated Solaraze without major problems and without the need to stop treatment.

Risk benefit analysis

Actinic keratosis is a fairly common condition which requires early treatment to prevent malignant transformation. Efficacy of Solaraze has been established by the MAH.

Overall, the mild adverse event profile balanced against a moderate degree of therapeutic efficacy indicates a positive benefit to risk ratio for Solaraze for the indication requested.

Expert Report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The *curriculum vitae* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

MAA form

The MAA form is medically satisfactory.

Conclusion

There are no objections to approval of Solaraze™ 3% Gel from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Solaraze™ 3% Gel are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL

Diclofenac is a well known NSAID which has been available for some years as an oral preparation. Dermal studies carried out in mini-pigs demonstrated that the principal adverse effect of Solaraze 3% Gel is on the gastrointestinal tract. Other dermal tolerance data were presented from human studies and showed that there was no significant dermal irritancy, sensitisation or photosensitisation for the preparation. The information presented suggested that diclofenac lacked significant genotoxic, carcinogenic or teratogenic activity but was foetotoxic in animals.

EFFICACY

The active ingredient, diclofenac sodium, is well-established. The clinical efficacy is supported by a series of clinical studies demonstrating the improvement in patients with keratotic lesions when treated with Solaraze™ 3% Gel. Studies have also been submitted demonstrating the safety of the product. No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The SmPC and PIL are acceptable, and consistent with those for the reference product. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with diclofenac sodium is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome