Public Assessment Report

Mutual Recognition Procedure

Diclofenac Sodium 4% Spray Gel

UK/H/0562-3/001/E01

Mika Pharma GmbH

Diclofenac Sodium 4% Spray Gel

LAY SUMMARY

Czech Republic, Poland, Slovak Republic, Estonia, Hungary, Latvia, Lithuania, Slovenia today granted Mika Pharma GmbH Marketing Authorisations (licences) for the medicinal products Diclofenac Sodium 4% Spray Gel (PL 18017/0001-2). These are prescription only medicines (POM) for the relief of acute pain and swelling affecting small or medium-sized joints and surrounding tissues.

Diclofenac Sodium 4% Spray Gel contain the active ingredient diclofenac sodium, which belongs to a group of drugs called non-steroidal anti-inflammatory drugs (NSAID).

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Diclofenac Sodium 4% Spray Gel outweigh the risks, hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1

Product Name	Diclofenac Sodium 4% Spray Gel
Type of Application	Article 10a (formerly Article 10.1(a)(ii)
Active Substance	Diclofenac Sodium Ph Eur
Form	Cutaneous Spray Solution
Strength	40mg/g Diclofenac Sodium
MA Holder	MIKA Pharma GmbH, Chenoverstrasse 3, 67117 Limburgerhof, Germany
RMS	UK
CMS	UK/H/562/01/E01: Czech Republic, Poland, Slovak Republic UK/H/563/01/E01: Estonia, Hungary, Latvia, Lithuania, Slovenia
Procedure Number	UK/H/0562-3/001/E01
Timetable	Day 90 – 15th February 2006

Module 2

Summary of Product Characteristics

European Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Diclofenac Sodium 4 % Spray Gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1g of solution contains 40 mg of diclofenac sodium.
For excipients see 6.1.

3. PHARMACEUTICAL FORM

Cutaneous spray, solution.

A golden-yellow, transparent solution, which turns to a gel-like consistency after administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the local symptomatic relief of mild to moderate pain and inflammation following acute blunt trauma of small and medium-sized joints and periarticular structures.

4.2 Posology and method of administration

For cutaneous use only. Not to be administered orally.

Adults
Sufficient solution should be sprayed onto the skin to ensure a generous covering of Diclofenac Sodium 4 % Spray Gel over the affected site. Normally, 4-5 pump strokes (0.8-1.0 g of spray containing 32-40 mg of diclofenac sodium) would be required. The treatment should be repeated 3 times a day at regular intervals. The maximum daily dose is 15 pump strokes (3.0 g of spray containing 120 mg of diclofenac sodium).

Diclofenac Sodium 4 % Spray Gel should be massaged gently into the skin. After this the hands should be washed unless they are the site to be treated. After application some minutes for drying should be allowed before dressing or binding the treated area.

The treatment may be discontinued when the symptoms (pain and swelling) have subsided. Treatment should not be continued beyond 7-8 days without review. The patient is requested to consult the doctor if no improvement is seen after 3 days.

Elderly
The posology is the same as for adults.

Children
The use in children under the age of 15 years is not assessed and therefore not recommended.

Patients with hepatic or renal insufficiency
For the use of Diclofenac Sodium 4 % Spray Gel in patients with hepatic or renal insufficiency see section 4.4.

4.3 Contra-indications

Hypersensitivity to diclofenac, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs) or any excipients of the finished medicinal product.

Patients with or without asthma in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.

In the last trimester of pregnancy.

4.4 Special warning and precautions for use

Patients should be warned against excessive exposure to sunlight in order to reduce the incidence of photosensitivity. Discontinue if any rash develops. Not for use with occlusive dressings.

Diclofenac Sodium 4 % Spray Gel should only be administered onto intact skin, not on open wounds or diseased skin areas. Contact with eyes and mucous membranes as well as oral use should be avoided.

The concomitant use of Diclofenac Sodium 4 % Spray Gel with oral NSAIDs should be cautioned as the incidence of systemic side effects may increase (see interactions).

Where Diclofenac Sodium 4 % Spray Gel is applied to a relatively large area of skin (i.e. more than 600 square centimetres of the body surface) and over a prolonged period (i.e. more than 4 weeks), the possibility of systemic side-effects cannot be completely excluded. If such usage is envisaged, the data sheet on diclofenac oral dosage forms should be consulted (for example, there is the potential for hypersensitivity, asthmatic and renal adverse reactions).

Bronchospasm may be precipitated in patients suffering from or with previous history of bronchial asthma or allergenic disease.

Diclofenac Sodium 4 % Spray Gel should only be used with caution in patients with a history of peptic ulcer, hepatic or renal insufficiency, or bleeding diathesis, or inflammatory bowel disease, as isolated cases with topical diclofenac have been reported.

Diclofenac Sodium 4 % Spray Gel contains propylene glycol which may cause skin irritation.

Diclofenac Sodium 4 % Spray Gel contains peppermint oil which may cause allergic reactions.

4.5 Interactions with other medicinal product and other forms of interaction

The systemic availability of diclofenac from this pharmaceutical presentation is very low. Hence the risk of interactions with other medicinal products is small. Concurrent aspirin or other NSAIDs may result in an increased incidence of adverse reactions.

4.6 Pregnancy and lactation

There is insufficient experience for the use during pregnancy and lactation. Therefore the use is not recommended.

Use in pregnancy: No evidence of a malformative effect was observed with diclofenac. However, additional epidemiological data is necessary to assess safety. During the last trimester of pregnancy, the use of prostaglandin synthetase inhibitors may result in:

- pulmonary and cardiac toxicity in the foetus (pulmonary hypertension with preterm closing of the ductus arteriosus)
- renal insufficiency in the foetus with oligohydramnios
- and increased possibility of bleeding in the mother and child.

Therefore, Diclofenac Sodium 4 % Spray Gel should be used with caution and only if clearly necessary during the first six months of pregnancy and must not be applied to a large area of the skin (i.e. more than 600 square centimetres of the body surface). It must not be used for long-term treatment (> three weeks). Treatment with Diclofenac Sodium 4 % Spray Gel is contraindicated during the last trimester of pregnancy.

Use during lactation: It is not expected that any measurable amount of diclofenac will occur in breast milk following topical application. However, NSAIDs are excreted in human milk. Therefore Diclofenac Sodium 4 % Spray Gel is not recommended for use in nursing mothers. An application to the breast area of nursing mothers is contraindicated.

In preclinical studies of toxicity to reproduction, diclofenac showed adverse effects (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients who experience dizziness or other central nervous disturbances while taking NSAIDs should refrain from driving or operating machinery, but this would be very unlikely using topical preparations.

4.8 Undesirable effects

Skin disorders are commonly reported.

Skin: Application site reactions, rashes, pruritus and urticaria, drying, reddening, burning sensations, contact dermatitis.

In a clinical trial 236 patients with ankle distortions were treated with 4-5 pump strokes of Diclofenac Sodium 4 % Spray Gel t.i.d. (120 patients) or placebo (116 patients) for 14 days. The following adverse drug reactions were reported for Diclofenac Sodium 4 % Spray Gel:

Organ system	**Very common (> 1/10)**	**Common (> 1/100, <1/10)**	**Uncommon (>1/1000, <1/100)**	**Rare (>1/10000, <1/1000**
Skin and subcutaneous disorders				
Pruritus			0.9 %	

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration. The total single dose of product should not exceed 1.0 g of spray.

Nevertheless during long term treatment (> three weeks) and/or when treating large areas (i.e. more than 600 square centimetres of the body surface) there is a possibility of systemic adverse reactions. Reactions like abdominal pain, dyspepsia, gastric and renal disorders may occur.

In patients using topical NSAID preparations asthma has been reported rarely. In isolated cases generalised skin rash, hypersensitivity reactions such as angioedema and photosensitivity reactions have been reported.

4.9 Overdose

During recommended use there is practically no risk due to overdosage. If accidentally Diclofenac Sodium 4 % Spray Gel has been administered orally symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory preparations, non-steroids for topical use.

ATC code: M02AA 15

Sodium diclofenac is a non-steroidal anti-inflammatory drug (NSAID) which has also analgesic properties. The inhibition of prostaglandin synthesis is considered to be an essential part of its mode of action.

5.2 Pharmacokinetic properties

After cutaneous application of 1.5 g Diclofenac Sodium 4 % Spray Gel a rapid onset of diclofenac absorption can be observed leading to measurable plasma levels of about 1 ng/ml as early as 30 minutes and to maximum levels of about 3 ng/ml at about 24 hours after application.

The achieved systemic concentrations of diclofenac are about 50 times lower than those achieved following oral administration of equivalent amounts of diclofenac. Systemic plasma levels are not supposed to contribute to the efficacy of Diclofenac Sodium 4 % Spray Gel.

Diclofenac is extensively bound to plasma proteins (about 99 %).

5.3 Preclinical safety data

In rabbit skin, Diclofenac Sodium 4 % Spray Gel is classified as non-irritant.

Preclinical data based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential of diclofenac reveal no special hazard for humans other than already mentioned in earlier sections of this SPC.

In rats and rabbits oral doses of diclofenac were not teratogenic but caused embryotoxicity at maternally toxic doses.

Diclofenac did not affect fertility in rats but inhibited ovulation in rabbits and reduced implantation in rats.

In rats, diclofenac resulted in dose-dependent constriction of the fetal ductus arteriosus, dystocia and delayed parturition.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isopropyl alcohol
Soy bean lecithin
Ethanol
Disodium phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Disodium edetate
Propylene glycol
Peppermint oil
Ascorbyl palmitate
Hydrochloric acid 10% (w/w)
Sodium hydroxide 10% (w/w)
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Unopened bottle (30 ml and 15 ml):	3 years
Unopened bottles (10 ml)	2 years
In-use:	6 months

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Glass bottle with metering pump/nozzle/spray valve and cap, 7.5 g, 12.5 g and 25 g solution.

Not all pack sizes may be marketed.

6.6 Instructions for use/handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

MIKA Pharma GmbH
Chenoverstraße 3
67117 Limburgerhof
GERMANY

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Module 3

Product Information Leaflet

PATIENT INFORMATION LEAFLET

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, please ask your doctor or your 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.

In this leaflet

Diclofenac Sodium 4 % Spray Gel

The active substance is diclofenac sodium 4 % (w/w).

Also contains: isopropyl alcohol, soy bean lecithin, ethanol, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, disodium edetate, propylene glycol, peppermint oil, ascorbyl palmitate, hydrochloric acid 10 % (w/w), sodium hydroxide 10 % (w/w) and purified water.

Marketing authorisation holder: MIKA Pharma GmbH, Chenoverstraße 3, 67117 Limburgerhof, Germany.

Manufacturer: Pharbil Waltrop GmbH, 45731 Waltrop, Germany.

1. What your medicine is and what it is used for

Diclofenac Sodium 4 % Spray Gel is a liquid, which turns to a gel-like consistency when sprayed onto the skin.

It contains the active substance diclofenac sodium, which belongs to the group of non-steroidal anti-inflammatory drugs (NSAID). Diclofenac Sodium 4 % Spray Gel is used to relieve the acute pain and swelling affecting small or medium-sized joints and surrounding tissues.

Each bottle contains 7.5 g, 12.5 g or 25 g cutaneous spray.

2. Before you use this medicine

Do not use your medicine

- If you are allergic to diclofenac sodium or any other ingredient of the medicinal product.
- If you have ever had an allergic reaction to aspirin (acetylsalicylic acid) or any other NSAID such as ibuprofen with difficulty in breathing, skin rash and runny nose.
- In the last three months of pregnancy – please see section on pregnancy and breast-feeding.

Take special care with your medicines

- If you have or have had stomach ulcers, liver or kidney problems, a tendency for bleeding or inflammatory bowel disease.
- If you have previously suffered from bronchial asthma or allergies.
- Do not use in eyes, nose or mouth and on open wounds or infected skin areas. If you accidentally get some spray into your eyes rinse thoroughly with clear water and inform your doctor.
- Never swallow Diclofenac Sodium 4 % Spray Gel.
- Do not sunbathe or use sunlamps whilst using this medicine.

This medicinal product contains propylene glycol which may cause skin irritation and peppermint oil which may cause allergic reactions.

This medicine is not to be used by children under 15 years of age.

If you are not sure what to do, ask your doctor or pharmacist.

Pregnancy and breast-feeding

This medicine must not be used by women who are in the last three months of pregnancy and must not be applied to the breast whilst breast-feeding.

Diclofenac Sodium may be excreted in human milk. Therefore Diclofenac Sodium 4% Spray Gel is not recommended for use in nursing mothers and must not be applied to the breast-area of nursing mothers.

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Consult your doctor for further information if you are pregnant or breast-feeding.

Driving and using machines

It is unlikely that Diclofenac Sodium 4 % Spray Gel will make you feel dizzy or drowsy but if you are affected do not drive or use machinery.

Taking other medicines

Speak to your doctor before you use Diclofenac Sodium 4 % Spray Gel

- If you are taking tablets, capsules or suppositories for pain including any containing diclofenac sodium, aspirin or any other anti-inflammatory agent, as for example ibuprofen.
- If you are taking any other medicines even those bought without a prescription.

3. How to use this medicine

Follow your doctor's instructions.

- Remove the protective cap.
- Apply the prescribed number of spray strokes onto the painful or swollen site.
- The usual dose is 4 to 5 strokes of Diclofenac Sodium 4 % Spray Gel applied 3 times daily. The number of strokes depends on the size of the affected area. The maximum number of pump strokes is 15 times daily.
- Diclofenac Sodium 4 % Spray Gel should be massaged gently into the skin. Wash your hands afterwards unless they are the site being treated.
- Wait until Diclofenac Sodium 4 % Spray Gel has dried before covering the skin with clothes or bandage. Take care as the spray can stain your clothes if wet.
- Discontinue treatment when your symptoms (pain and swelling) improve. Do not use for more than 7-8 days without consulting your doctor.
- If there is no improvement in your symptoms after 3 days, talk to a doctor.

If you are not sure how to apply Diclofenac Sodium 4 % Spray Gel, ask your doctor or pharmacist.

If you use more of your medicine than you should

- If you use more of your medicine than you should wipe the surplus Diclofenac Sodium 4 % Spray Gel off with a tissue.
- If you swallow some of the spray inform your doctor immediately or go to the nearest hospital casualty. Take the bottle and this leaflet with you.

If you forgot to use your medicine

- Use the spray as soon as you remember, but do not apply more than the recommended dose at once. Then carry on as before.

4. Possible Side Effects

Like all medicines, Diclofenac Sodium 4 % Spray Gel can have side-effects.

- Skin disorders such as reactions at the application site, rashes, itching, reddening, burning sensations or scaling of the skin are commonly reported.
- In a clinical trial patients using Diclofenac Sodium 4 % Spray Gel reported itchy skin as an uncommon side effect.
- Asthma has been reported rarely in patients using topical NSAID preparations.

In isolated cases the following side effects were reported:

- generalised skin rash and hypersensitivity reactions such as swelling of skin and mucous membranes (angioedema) and hypersensitivity to light.

If the product is used for a long time (longer than three weeks) and/or it is used on large areas of the skin, systemic side effects such as stomach pain and disorders, heartburn and kidney problems may occur.

Discontinue use if any rash develops.

If you notice any side effect not mentioned in this leaflet, please inform your doctor or pharmacist.

5. Storing your medicine

Store in the original package.

Do not use Diclofenac Sodium 4 % Spray Gel after the expiry date stated on the carton and bottle as well as longer than 6 months after first use.

KEEP THIS MEDICINE OUT OF THE REACH AND SIGHT OF CHILDREN.

This leaflet was last revised on: 03 June 2003.

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Module 4

Labelling

Each 1 g of spray contains 40 mg diclofenac sodium

Other ingredients: Isopropyl alcohol, soy bean lecithin, ethanol, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, disodium edetate, propylene glycol, peppermint oil, ascorbyl palmitate, hydrochloric acid (10%), sodium hydroxide (10%), purified water

Store in the original package.

DICLOFENAC SODIUM 4% SPRAY GEL

25 g cutaneous spray, solution

For cutaneous use

PL 18017/0002

MIKA PHARMA

MIKA Pharma GmbH
Chenoverstrasse 3
67117 Limburgerhof
Germany

To be applied as directed by a doctor.

This medicine should not be used by women who are pregnant or are breast-feeding. Consult your doctor for advice.

Do not exceed the stated dose.
Keep out of reach and sight of children.

POM

Batch No:
Use before:

Module 5

Scientific discussion during initial procedure

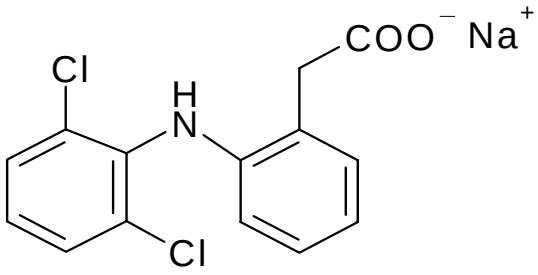
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted marketing authorisations for Diclofenac Sodium 4% Spray Gel, from Mika Pharma GmbH for the local symptomatic relief of mild to moderate pain and inflammation following acute blunt trauma of small and medium-sized joints and periarticular structures.

This is an application made under Article 10a (formerly Article 10.1(a)(ii)) of Directive 2001/83 EC for Diclofenac Sodium 4% Spray Gel. Diclofenac Sodium 4% Spray Gel comprises of a 40mg/g cutaneous spray solution of Diclofenac Sodium Ph Eur.

Diclofenac Sodium 4% Spray Gel is a 4% (w/w) diclofenac sodium cutaneous spray, solution that develops a gel-like consistency after being sprayed onto the skin. The applied drug product belongs to the group of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for topical use with diclofenac sodium as drug substance.

Chemical name: Sodium 2-[(2,6-dichlorophenyl)amino]phenyl]acetate
Chemical formula: $C_{14}H_{10}Cl_2NNaO_2$
Relative molecular mass: 318.1
Structural formula:



Diclofenac is a phenylacetic acid derivative and belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs) that also exhibit analgesic and antipyretic properties. NSAIDs are inhibitors of the enzyme cyclo-oxygenase, and so directly inhibit the biosynthesis of prostaglandins and thromboxanes from arachidonic acid.

Preclinical studies were carried out in accordance with Good Laboratory Practice (GLP), and in accordance with recognised guidelines. No toxicity was demonstrated, and no new toxicological problems for these products were found. Clinical studies on diclofenac sodium were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that diclofenac sodium provides satisfactory clinical benefits.

The products were granted marketing authorisations in the UK on 13th May 2002 and have gone through a first-wave MRP in Belgium, Finland, France, Luxembourg and Portugal (PL 18017/0001), and Austria and Ireland (PL 18017/0002). With the UK as

the Reference Member State in this second-wave Mutual Recognition Procedure (MRP), marketing authorisations were granted in the Czech Republic, Poland and Slovak Republic (PL 18017/0001) and Estonia, Hungary, Latvia, Lithuania and Slovenia (PL 18017/0002).

The UK acting as reference member state (RMS) has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

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.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Diclofenac Sodium 4% Spray Gel
Name(s) of the active substance(s) (INN)	Diclofenac Sodium Ph Eur
Pharmacotherapeutic classification (ATC code)	Topical products for joint and muscular pain, anti-inflammatory preparations, non-steroidal for topical use, diclofenac (M02A A15)
Pharmaceutical form and strength(s)	40mg/g cutaneous spray solution
Reference numbers for the Mutual Recognition Procedure	UK/H/0562-3/01/E01
Reference Member State	United Kingdom
Member States concerned	UK/H/562/01/E01: Czech Republic, Poland, Slovak Republic UK/H/563/01/E01: Estonia, Hungary, Latvia, Lithuania, Slovenia
Name and address of manufacturer responsible for batch release in the EEA	Pharbil Waltrop GmbH, Im Wirrigen 25, 45731 Waltrop, Germany
Date of first authorisation	13th May 2002
Marketing Authorisation Number(s)	PL 18017/0001-2
Date of assessment report	20th March 2006
Name and address of the authorisation holder	MIKA Pharma GmbH, Chenoverstrasse 3, 67117 Limburgerhof, Germany

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Diclofenac Sodium

Diclofenac sodium is the subject of a European Pharmacopoeia monograph. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the European Pharmacopoeia. The analytical methods used for quality control of the active substance are appropriately described and validated. Adequate stability data have been provided and a re-test period of 5 years has been set by the active substance manufacturer. In addition, the finished product manufacturer has set a re-test period of 1 year.

FINISHED PRODUCT

Formulation and Manufacture

The product Diclofenac Sodium 4% Spray Gel is a gold-yellowish, transparent solution. Each gram contains 40mg diclofenac sodium. The formulation of the spray gel contains the following other ingredients: Isopropyl alcohol, Soy bean lecithin, Ethanol, Disodium phosphate dodecahydrate, Sodium dihydrogen phosphate dehydrate, Disodium edentate, Propylene glycol, Peppermint oil, Ascorbyl palmitate, Hydrochloric acid 10% (w/w), Sodium hydroxide 10% (w/w), Purified water. Hydrochloric acid and sodium hydroxide are used as pH adjusters during manufacturing, if needed.

All excipients except soy bean lecithin 76% comply with the European Pharmacopoeia standards. A satisfactory in-house specification has been applied to soy bean lecithin, together with analytical methods. No analytical methods are given for the Ph.Eur grade excipients where reference is made to the Ph.Eur. Certificates of Analysis are provided for compendial and non-compendial ingredients in support of their specifications. No excipients of animal origin are used in the product. The source and origin of ascorbyl palmitate and propylene glycol is stated on Certificates of Analysis.

The objective of the development programme was to formulate a stable, acceptable formulation of diclofenac sodium as a 4% cutaneous spray, which turns to a gel-like consistency upon spraying the solution onto the skin.

The formulation and functions of ingredients are defined. The solvent system employed makes the addition of a preservative agent unnecessary. The product has been subjected to preservative efficacy testing, described under the stability section.

The manufacturing process is given both in descriptive and flow chart form. Satisfactory manufacturing formulae are provided. In-process controls are described with adequate specifications.

In support of the process validation, batch analysis data are provided on pilot scale batches and industrial batches produced at the site of manufacture in Germany. In-process controls and batch analysis data indicate the manufacturing process to be satisfactory.

The immediate packaging is an amber glass (Type III glass Ph.Eur) bottle fitted with a snap on spray pump closure. Results from batch records of tests carried out by the supplier of the spray pump bottles are detailed in the dossier. Copies of certificates of analysis from suppliers confirming that the packaging materials are suitable for use with the product are provided in support of the specifications proposed.

Finished Product Specification
The finished product specifications proposed for both release and shelf life are acceptable and provide an assurance of quality and consistency of the finished product. Analytical methods used have been suitably validated and batch analysis data demonstrate compliance of the product with the proposed specification.

Stability of the Finished Product
Up to 36 months long-term (25ºC/60%RH), 6 months accelerated (40ºC/75%RH) and 12 months at 4 ºC stability data have been generated for batches of diclofenac sodium stored in the packaging for marketing. Samples were tested according to appropriate, stability-indicating finished product specifications. Based on these data, a shelf life of 36 months has been implemented for the 25 gram and 12.5 gram pack size, and a shelf life of 24 months has been implemented for the 5 gram and 7.5 gram pack size.

Further in-use stability trials have been performed on all pack sizes covering a period of 6 months. All results comply and an in-use shelf life of 6 months has been imposed.

BIOEQUIVALENCE
The applicant has provided details of the analytical method and validation report for the pharmacokinetics study used to show bioequivalence. This study comprised of one pharmacokinetics study in 12 volunteers, and an efficacy and safety clinical trial study in 236 patients over 14 days duration is reported. These studies indicated that the active is absorbed into the applied area from the diclofenac spray gel 4%.

PART I - ADMINISTRATIVE PARTICULARS
Completed European Application Forms are provided.

GMP statement
There are no GMP issues. The manufacturing and packaging sites are all in Germany and are satisfactory for this type of product.

Product labelling & leaflets
Contain satisfactory pharmaceutical details.

Summary of Product Characteristics
Satisfactory pharmaceutical details.

EXPERT REPORT
The Pharmaceutical Expert Report is satisfactory and represents an adequate critical summary of the data. An appropriate CV of the Pharmaceutical Expert has been provided.

COMPLIANCE WITH GUIDELINES

The application complied with the guidelines available at the time of initial assessment by the UK Licensing Authority.

CONCLUSION ON QUALITY

The pharmaceutical assessor concluded that marketing authorisations may be granted for these products.

III.2 PRE-CLINICAL ASPECTS

PHARMACODYNAMICS

The pharmacology of diclofenac sodium, an NSAID, is well established and has been adequately reviewed by the expert. Diclofenac sodium inhibits prostaglandin synthesis through inhibition of cyclo-oxygenase (COX). Diclofenac is a more potent inhibitor of COX-2 than COX-1 and has anti-inflammatory, analgesic and antipyretic activity. Some of the metabolites of diclofenac have anti-inflammatory activity but are less potent than diclofenac. 4′-Hydroxy-diclofenac, the major metabolite in man, has anti-inflammatory, analgesic and antipyretic activity but is 15-60 times less potent than diclofenac.

In rat and hen models of osteo-arthritis, diclofenac sodium produced a dose-dependent anti-degenerative effect indicating good cartilage tolerance of diclofenac.

The expert has discussed the interaction of oral diclofenac with a number of medicines in several animal models.

PHARMACOKINETICS

After oral administration, diclofenac is rapidly absorbed and undergoes first pass metabolism. Systemic availability of unchanged diclofenac is 38% and 60% in dog and man, respectively. After the topical application of diclofenac solution and diclofenac aqueous gel containing 0.25% phospholipid (not identical to DSG 4%) to rats, plasma C_{max} was reached within 4h and systemic availabilities were 4% and 26%, respectively. Apparently, the phospholipid component increased penetration of diclofenac through the stratum corneum.

The *in vitro* skin permeation (using abdominal skin from human volunteers) of DSG 4% was compared with that of Voltaren® Emulgel (1.16% diclofenac diethylammonium), and formulations containing 1, 2 or 4% diclofenac sodium, using a modification of the method developed by Maibach and Reifenrath. Permeation of DSG 4% into the receptor fluid occurred with a lag period of 80min. The maximum concentrations detected in the receptor fluid were 7.7μg/cm^2 and 0.43μg/cm^2 with DSG 4% and Voltaren® Emulgel, respectively. Within 8h, up to 2.5% of DSG 4% was completely absorbed through the skin, as opposed to 0.12% with Voltaren® Emulgel. Permeation of deeper skin layers was more pronounced with DSG 4% (36% of dose, 148μg/cm^2) than with Voltaren® Emulgel (9% of dose, 34μg/cm^2). In contrast, diclofenac concentrations in the stratum corneum were higher with Voltaren® Emulgel (78% of dose, 291μg/cm^2) than with DSG 4% (47% of dose, 195μg/cm^2). Absorption from DSG 4%, therefore, was about 21 times that of Voltaren® Emulgel, and resulted in higher diclofenac concentrations in the deeper skin layers.

Apparently a second *in vitro* skin permeation study showed that active ventilation of skin samples increased the penetration rate of DSG 4% but not that of Voltaren® Emulgel.

In a local tolerance study in rabbits, pharmacokinetic parameters for diclofenac were estimated following topical application of DSG 4% and Voltaren® Emulgel.

Table 1. Pharmacokinetic parameters estimated following topical application of different diclofenac formulations to NZW rabbits.

	Group 1	Group 2	Group 3	Group 4	Group 5
AUC (ng.h)/ml	2370	4113	1319	891	1399
C_{max} (ng/ml)	595	1059	233	102	536
t_{max} (h)	0.5	0.8	1.5	3	0.5

Values are mean of six animals
Group 1: 1.6g Voltaren® Emulgel on 160cm^2 equivalent to 18.6mg diclofenac diethylamine salt
Group 2: 0.4ml DSG 4% on 160cm^2 equivalent to 16mg diclofenac sodium
Group 3: 0.4ml DSG 4% on 40cm^2 equivalent to 16mg diclofenac sodium
Group 4: 0.2ml DSG 4% on 80cm^2 equivalent to 8mg diclofenac sodium
Group 5: 0.1ml DSG 4% on 40cm^2 equivalent to 4mg diclofenac sodium

Peak plasma concentrations were attained within 30 minutes post-dose and thereafter slowly decreased over a 24h period. After topical application of equivalent doses of Voltaren® Emulgel and DSG 4% (groups 1 and 2), plasma C_{max} and AUC attained with DSG 4% were two-fold higher than those attained with Voltaren® Emulgel.When identical doses of DSG 4% were applied to rabbit skin, the extent of systemic absorption was proportional to application site surface area (comparison of PK data of groups 2 and 3).

In healthy volunteers, however, plasma C_{max} and AUC attained after topical administration of DSG 4% were considerably lower than those attained after an equivalent oral dose of Voltaren 50mg tablets (see Medical Assessment). Therefore, given the low systemic exposure anticipated with DSG 4% in humans, it is unlikely that topical administration of DSG 4% would be of safety concern.

In a tissue distribution study in mice (iv dose), the highest levels of radioactivity were detected in blood and highly perfused tissues including liver, kidneys, heart and lungs. Radioactive levels in liver, bile and kidneys exceeded blood levels. The percutaneous absorption of Voltaren® Emulgel (1.16% diclofenac diethylammonium) and Voltaren Cream (1% diclofenac sodium in a cream formulation) in guinea pigs, rabbit and man was investigated. In guinea pigs, between 3-6% of the dose of Voltaren Cream (40, 100 or 320mg, applied to 10cm^2 of occluded skin) was absorbed through the skin. Diclofenac applied topically on the knee joint of rabbits penetrated the patellar ligament, the adipose corpus and the synovial fluid. In man, 6% of Voltaren® Emulgel (5mg/cm^2 applied to non-occluded skin) was absorbed through the skin. Diclofenac steady state plasma concentrations after repeat topical administration of Voltaren Cream (2.5g three times daily, equivalent to daily dose of 75mg diclofenac sodium) were 20-40nmol/l. After topical application of Voltaren® Emulgel (2.5g four times daily for 3-4 days equivalent to a daily dose of 93mg diclofenac) to arthritic patients, diclofenac concentrations in plasma (≥20nmol/l) were considerably lower than that in synovial fluid (≥370nmol/l) and synovial tissues (≥410nmol/l).

Diclofenac is highly bound to serum proteins (>99% in rats, dogs, baboons, monkeys and man), crosses the placenta and the blood-brain barrier and is secreted in breast milk. Within 24h of oral administration of diclofenac (5mg/kg) to pregnant rats, the milk to plasma exposure ratio for unchanged diclofenac was 0.14, whilst fetal concentrations were the same as maternal blood levels.

There are species differences in the metabolism of diclofenac. Diclofenac is either directly conjugated or oxidised at various positions (position 3′ or 4′ of the dichlorophenyl moiety, position 5' of the phenyl ring or simultaneously at positions 5′ and 4′) prior to conjugation.

The more important route of elimination in rat and dog is through bile, as opposed to renal excretion in monkey and man. The terminal plasma elimination half-life (t½β) of unchanged diclofenac after an iv dose, was 1.3h in dogs. In man also, unchanged diclofenac had a short plasma t½β (1-2h).

TOXICOLOGY

This section briefly discusses the toxicity of diclofenac after acute, sub-acute and chronic exposure. A rare complication of NSAIDs is idiosyncratic hepatotoxicity. The mechanism of this hepatotoxic effect of diclofenac may be due to covalent binding of one of its metabolites, diclofenac acyl glucuronide, to hepatic proteins (*Cf* Special Toxicity below).

Sub-chronic administration of diclofenac (3, 6 or 12mg/kg/day) to rats (using the Urist model), inhibited heterotopic, but not orthotopic, bone formation. The mechanism of this effect of diclofenac may be through the inhibition of inflammatory response to trauma.

REPRODUCTIVE TOXICITY

Diclofenac did not affect the fertility of male or female rats at 4mg/kg but a dose of 75µg/ml was potentially embryotoxic. Pre-treatment of blastocysts and dams with diclofenac (40µg/ml and 3mg/kg ip, respectively), reduced implantation rate (35% and 41%, respectively) and retarded growth of the fetus (23% and 34%, respectively).

In pregnant rats, diclofenac sodium is a potent constrictor of fetal ductus arteriosus (more potent than indomethacin, mefenamic acid or aspirin). There is, therefore, a risk of premature closure of fetal ductus arteriosus, causing congenital cardiac damage or persistent pulmonary hypertension of the newborn. Diclofenac should not be used during the third trimester of pregnancy. The use of DSG 4% during the last trimester of pregnancy is contraindicated under section 4.6.

MUTAGENICITY

Diclofenac sodium was potentially non-mutagenic in the bacterial reverse mutation assays (*Salmonella Typhimurium* strains TA1537, TA1538, TA100 or TA98; or *Escherichia Coli* strain B/r WP2 uvr^-) with or without metabolic activation. However, in a Rec-assay using *B. subtilis*, equivocal results were obtained.

Intraperitoneal doses of diclofenac sodium (up to 80mg/kg) tested negative in an *in vivo* mouse micronuclei assay and a mouse sperm morphology test.

CARCINOGENICITY

According to Physician’s Desk Reference (1990), long-term administration of diclofenac sodium (up to 2mg/kg) to rats did not significantly increase the incidence of tumours but increased the incidence of benign mammary fibroadenomas at 0.5mg/kg/day. In addition, in a 2-year study, diclofenac sodium was potentially non-carcinogenic in male (up to 0.3mg/kg/day) and female (up to 1mg/kg/day) mice.

Diclofenac sodium, in contrast to other NSAIDs, had no effect on the activities of peroxisomal enzymes or mitochondrial carnitine palmitoyltransferase.

LOCAL TOLERANCE

The local tolerance of DSG 4% was compared with Voltaren® Emulgel (1.16% diclofenac diethylammonium) in a single dermal application study in male NZW rabbits. This was a GLP-compliant study performed by the Toxicological Research Centre based in Hungary. Diclofenac spray gel 4% had comparable dermal irritating potential to Voltaren® Emulgel, and both were classified as non-irritant (primary irritation index of 0.17).

SPECIAL TOXICITY

Immunotoxicity

Intraperitoneal administration of diclofenac sodium to mice for three consecutive days and prior to immunisation with sheep erythrocytes (T-cell dependent antigen) markedly reduced the humoral antibody titre and the number of rosette-forming cells in the spleen.

Diclofenac (20μg/ml) reduced allergen-induced histamine release in isolated perfused guinea pig lungs but stimulated the antigen-dependent first phase and calcium-dependent second phase of allergic histamine release from human leucocytes.

Hepatotoxicity

Long term clinical use of diclofenac increases serum alanine transaminase levels and may cause hepatotoxicity. The expert has reviewed possible mechanisms of diclofenac hepatotoxicity studied *in vitro*, *in vivo* and *ex-vivo*.

Diclofenac (1-10mM), like other NSAIDs, produced dose-dependent and time-dependent hepatotoxicity *in vitro*. Reactive metabolites formed either through cytochrome P450 or UDP-glucuronosyl transferase catalysis have been implicated. In fact, pre-treatment of rats with phenobarbitone increased the hepatoxicity of diclofenac *in vitro*. Acute *in vitro* cytotoxicity of diclofenac, has been attributed to its potential oxidative metabolite(s) formed through constitutive CYP2C11 in rat; whereas covalent binding of diclofenac acyl glucuronide to rat hepatocellular proteins could be responsible for its hepatotoxicity. Plasma membrane proteins were the major target of such adducts and it is postulated that the protein adducts may stimulate an immune reaction against the liver.

In view of the potential hepatotoxicity of diclofenac, especially after long-term use, patients should be carefully monitored during diclofenac therapy.

Phototoxicity

Diclofenac was weakly photoactive (UVA exposure) after a single ip sub-lethal dose of 50-200mg/kg.

IMPURITIES AND COMPONENTS OF THE SPRAY GEL

The source of diclofenac sodium is a known source already used in other UK licensed medicines. Drug substance and finished product specification limits proposed for impurities are acceptable as well as the specification limit for residual solvents and does not raise any safety concerns.

At the maximum recommended daily dose, up to 3.6mg sodium is applied to the skin, which is considerably lower than the threshold for declaring the amount of sodium on the label and

PIL. All of the excipients used in DSG 4% are regularly used in pharmaceutical formulations and do not raise any safety concerns at the proposed levels and dose regimen.

EXPERT REPORT
A satisfactory pharmaco-toxicological Expert Report has been submitted with an appropriate CV. The report consists of a review of published literature on the pharmacology and toxicology of diclofenac sodium. In addition, preclinical studies performed with the proposed formulation are discussed; these include a local tolerance study in rabbits and an *in vitro* skin penetration study using human abdominal skin.

SUMMARY OF PRODUCT CHARACTERISTICS
The SPC is satisfactory.

DISCUSSION
DSG 4% was well absorbed after *in vitro* topical administration, 2.5% completely permeated the skin, 47% in the stratum corneum and 36% in the deeper skin layers. *In vitro* percutaneous absorption of DSG 4% was about 21 times that of Voltaren® Emulgel (1.16% diclofenac diethylammonium), and resulted in higher diclofenac concentrations in the deeper skin layers. Given the synovial fluid/tissue concentrations obtained with Voltaren® Emulgel, it is anticipated that after the application of DSG 4% to arthritic patients, plasma levels of parent drug would be lower than in synovial fluid/tissues.

In rabbits, systemic availability of diclofenac attained with DSG 4% was twice that attained with an equivalent dose of Voltaren® Emugel. However, in human volunteers, systemic availability of diclofenac achieved with DSG 4% was considerably lower than that attained after an equivalent oral dose of Voltaren 50mg tablets. Therefore, previous safety margins estimated for oral diclofenac formulations are unlikely to be eroded following topical administration of DSG 4% to humans.

DSG 4% was non-irritant to rabbit skin and would probably be well tolerated after topical administration.

CONCLUSIONS
There are no preclinical objections to the granting of Marketing Authorisations for Diclofenac Spray 4% Gel.

III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY
The clinical expert report provides a bibliographic review of the clinical pharmacology of diclofenac, including a brief summary of two pharmacokinetic studies in 12 volunteers.

Pharmacodynamics
Diclofenac is a phenylacetic acid derivative, one of the group of non-steroidal anti-inflammatory drugs whose action is mediated by inhibition of enzymes of the cyclo-oxygenase type that are essential for the production of prostaglandins. Reduced prostaglandin synthesis is believed to be responsible for the anti-inflammatory and analgesic activities.

As with other NSAIDs, diclofenac has been found to be an effective analgesic across the range of musculo-skeletal pathologies.

This particular product contains the mono-sodium salt of the drug substance.

Pharmacokinetics
In the applicant's clinical expert report, it is stated that this preparation (similar to the reference product Voltarol Emulgel) utilises 'diadermal application'. This is explained as implying a predominately local effect of the active rather than one through systemic absorption ('transdermal' application). Whilst there were some earlier investigative data on the reference product gel formulation to the contrary, the applicant has performed a further study with this test product, which provides evidence that permeation of diclofenac to the 'local' target tissue appears significantly greater than systemic circulation.

Quantitatively for topical applications of diclofenac (5g of 1% gel administered twice daily), it is estimated that the maximum plasma level is about 10%, and total AUC amounts correspond to 25 to 50% of the values seen after parenteral administration.

Diclofenac is well absorbed after oral administration and undergoes first-pass metabolism in the liver, only 60% of the absorbed dose reaching the general circulation. In the plasma, the drug is extensively protein bound (>99%).

Elimination is by hepatic metabolism followed by urinary and biliary excretion. The principal metabolite has negligible activity. The terminal half-life of elimination is about 1.8 hours.

Pharmacokinetic studies
Two studies are included in this application

Study Summary [A]. An open, randomised, two-way cross-over study in 12 female subjects was performed in 1996.

It was carried out in accordance with current EC GCP/GLP guidelines, under the Declaration of Helsinki and was approved by the local Ethics Committee.

The study is described in the clinical expert report (pages 10-11), in the tabulated summaries (pages 55-7) and fully in Module 5, volumes 5-6 of the supporting documents.

The study was designed to compare the pharmacokinetic parameters of test and reference (Voltarol Emulgel) products after single (in all subjects) and multiple doses (in a subset of 4 subjects) were administered topically. The stated aim was "to prove the safety of the test preparation" or to show that systemic plasma levels are of the same 'pharmacologically irrelevant' order.

The subjects were all female between 19 and 41 years old, but one was withdrawn before the second phase (pregnant – data not used for pharmacokinetics) and replaced for the second half of the study.

Eight subjects underwent the single dose cross-over treatment (60 mg diclofenac sodium or its equivalent on the paravertebral skin area), while four were administered the equivalent of 15 mg diclofenac sodium qds in addition from days 2 to 4 in the multiple dose cross-over part of the investigation.

Results. Regarding skin tolerability, four reports of low grade erythema were made (two subjects after completing day 4 of the test product and two during or following single administration of the reference product).

Plasma samples 30 minutes after administration showed diclofenac concentrations of between 0.17 and 6.52 ng/ml after the test product and between 0.77 and 4.65 ng/ml after the reference gel. After this transdermal diffusion, the initial peak concentrations occurred between 0.5 and 1.5 hours, followed by a decrease of some 50% and then a continuous increase to C_{max} at around 24 hours after administration.

The plasma levels of diclofenac were initially greater for the reference product but this difference did not appear to be maintained beyond the third day when both products were administered qds.

In this small population sample, the steady state plasma concentrations for both products were of the order of 2ng/ml – and it is reported that the effective plasma level for therapeutic effects is around 50ng/ml.

Study Summary [B]. The second pharmacokinetic study included in this dossier is an open, single-centre, two period, non-randomised comparison of the relative bioavailability in subcutaneous and muscular tissue, versus plasma of the topically-applied test product and an orally administered formulation of diclofenac. Equivalent doses were tested on 12 male subjects.

Endpoints included the bioavailability differences and secondarily, changes in laboratory standard tests, basic safety information and local tolerability.

Results. Relative bioavailability (Treatment A – Topical vs Treatment B-Oral of diclofenac at steady state based upon AUC_{∞} (Geometric mean and 95% confidence intervals.

Plasma	2.23% [1.55% - 3.20%]
Subcutaneous tissue (thigh)	324% [232% - 453%]
Muscular Tissue (thigh)	209% [130% - 337%]

Safety data. There were no significant adverse findings in this small sample.

Conclusion. The results support the claim that this spray-gel preparation permeates through the skin to the target tissues in significantly greater amounts than is distributed to the systemic circulation.

SPECIAL POPULATIONS

There is said to be inadequate experience of topical diclofenac in children. No formal data have been submitted.

EFFICACY

The clinical expert report includes a bibliographic review of diclofenac clinical trials plus one placebo-controlled clinical trial of the product (4% Diclofenac Spray Gel before peppermint flavouring was added to the excipients). This involved 236 patients with accidental injuries of the ankle.

Peppermint Oil has been added as a fragrance. The applicant states that this is a minor variation and that this will not affect the pharmacodynamic or pharmacokinetic properties.

Study Summary [C]. A placebo-controlled, parallel-group, randomised, multicentre study of Diclofenac Spray Gel 4% in 236 patients with sports/accidental injuries of the ankle.

Main criterion for inclusion. Acute unilateral and uncomplicated 'ankle distortion' – swelling not less than 12 mm compared to the contralateral ankle.

Endpoint. Objective measurement of swelling (50% decrease by day 10), marked with tattooing points and based on the ITT population.

Further efficacy objectives were the decrease of spontaneous pain VAS and verbal score, pain on active movement, impairment of joint movability, tenderness, the consumption of analgesics and global assessments of therapeutic efficacy by investigator and patients.

Duration. Two weeks, measurements at days 3/4, 7/8, 10/11 and 14 +/- 1.
Dose. Four to five actuations of the pump tds, corresponding to between 96 –120 milligrams diclofenac sodium or placebo.

Results. One centre including 40 patients was excluded, having shown signs of false documentation. In the circumstances and as justified in the study final report it appears reasonable to exclude this group from the ITT efficacy analysis. Five other patients were excluded to leave the 'Full Analysis Set' with 97 patients on the active, and 94 on placebo.

There was a trend towards less swelling in those patients on the 'active' medication at baseline, so this assessment was evaluated as relative change calculated as a percentage.

The **defined primary criterion** response expressed as a decrease in swelling of at least 50% during 10 days of treatment for the 'Full Analysis Set' was reached in 87 of 97 patients (89.7%) on diclofenac SG compared to 74 of 94 on placebo (78.7%, $p = 0.029$ (one-tail) and $p = 0.0467$ (two-tail)).

The analyses with and without the patients excluded from centre 9 appeared to show that the data were sufficiently robust to justify the favourable results for the test product.

At each visit, there was also a statistically significant difference in favour of the diclofenac spray gel in terms of decrease in swelling.

In all of the other efficacy measurements, there was either a clear trend or statistically significant difference favouring the test product over the placebo treatment. The active treatment was NOT associated with a decreased consumption of rescue medication.

The safety analysis was also conducted with the exclusion of the 40 patients from one centre, as it was concluded that these patients did not actually exist and had not received any trial medication.

Seven AEs occurred in six patients on diclofenac while eight events occurred in eight patients taking placebo. One patient from each group was prematurely withdrawn, moderate stomach pain being reported in one patient who had also resorted to taking oral diclofenac, whilst a case of flu occurred in the placebo group. Laboratory tests, including a minority of patients tested for the presence of blood in the stool, showed no clinically significant occurrences.

In conclusion, this study showed beneficial effects in favour of diclofenac SG over placebo in treating patients with acute ankle trauma as well as adequate tolerability.

The expert report also contains a review of the efficacy and safety of similar products containing diclofenac and NSAIDs in general including a meta-analysis of randomised trials involving topical NSAIDs.

SAFETY
Considering that it is one of the most potent NSAIDs, diclofenac is relatively well tolerated, its gastrointestinal toxicity being generally rated as medium-risk. One of the main reasons for the development of cutaneous formulations of NSAIDs is to lessen the risk of systemic side effects, such as the many gastrointestinal complications, as well as pulmonary, renal and various other adverse reactions.

The clinical expert has reviewed the literature with regard to cutaneous NSAIDs, as well as diclofenac topical products and the relatively small experience with diclofenac spray gel.

Such evidence as exists points to a reduced risk of the typical adverse reaction profile associated with systemic use of NSAIDs.

The local tolerability of this product appears satisfactory on the limited animal tests and clinical experience reported so far.

EXPERT REPORT
The clinical expert report has been written by a suitable qualified expert.

The clinical expert supplies a bibliographic review of the clinical pharmacology and the clinical trials, and the applicant has also submitted three sets of clinical data of relevance: two pharmacokinetic studies and a placebo-controlled clinical trial involving 236 patients with accidental injuries of the ankle

Tabulated summaries are provided for these studies.

Sufficient validation has been presented to permit claims for this product to be used for the local and temporary treatment of acute trauma to the ankle shown in the clinical study described above.

SUMMARY OF PRODUCT CHARACTERISTICS

The Summary of Product Characteristics is satisfactory.

POST-MARKETING EXPERIENCE

Approximately 1.1 million patients have been treated with an identical topical formulation marketed since 1999 and 2001, respectively.

From August 1999 until March 2004 three spontaneous reports of adverse events after topical administration are known. One of the cases was described as “tongue oedema and sense of respiratory obstruction”. The adverse event was considered as drug related, due to an individual hypersensitivity to the drug. The second event was a “cutaneous dyschromia with subcutaneous adipose necrosis preceded by a local erythema”. The event occurred after one week of treatment and cleared up with permanent after-effects. It was therefore considered serious. The third event was described as “pruritus and erythmatous exanthema on the site of application”. It occurred after 14 days topical treatment. The seriousness of the reaction was not defined in the report.

There have been four periodic safety update reviews (PSURs) since the original national licence was granted, covering periods between 13 May 2002 to 13 November 2002, 14 November 2002 to 13 May 2003, 14 May 2003 to 13 November 2003 and 14 November 2003 to 13 May 2004.

DISCUSSION AND RECOMMENDATIONS

There are no medical reasons why these applications should not be granted.