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LAY SUMMARY

The MHRA granted Pinewood Laboratories Limited a Marketing Authorisation for the medicinal product Ketoprofen 2.5% w/w Gel (PL 04917/0069) on 31st December 2008. Ketoprofen 2.5% w/w Gel is a prescription-only medicine (POM) and is used to relieve pain in soft tissue injuries including sports injuries, sprains and strains, as well as musculo-tendonitis, swelling, backache and rheumatic pain.

The active ingredient, ketoprofen, belongs to a non-steroidal group of anti-inflammatory drugs (NSAIDs) which help to reduce pain and inflammation.

This application is identical to a previously granted application for Ketoprofen 2.5% w/w Gel (PL 06934/0064, granted to Ethypharm SA on 1st March 2001 as a change of ownership, which in turn demonstrated equivalence to the approved product, Ketoprofen Gel Hi Pharmtech 2.5% and as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Ketoprofen 2.5% w/w Gel outweigh the risks; hence a Marketing Authorisation has been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Ketoprofen 2.5% w/w Gel (PL 04917/0069) to Pinewood Laboratories on 31st December 2008. The product is a prescription-only medicine.

The application was submitted as a simple abridged application according to Article 10c of Directive 2001/83/EC, cross-referring to Ketoprofen 2.5% w/w Gel (Ethypharm SA, PL 04917/0069), approved on 1st March 2001 as a change of ownership. The original product had previously been shown to be essentially similar to Ketoprofen Gel Hi Pharmtech 2.5% licensed in the UK since 15th December 1993.

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) has been generated for it.

The product contains the active ingredient ketoprofen which is a non-steroidal anti-inflammatory drug (NSAIDs) which is used to manage and reduce pain and inflammation.
1. INTRODUCTION
This is a simple, informed consent application for Ketoprofen 2.5%w/w Gel submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Pinewood Laboratories Limited, Ballymacarbry, Clonmel, County Tipperary, Ireland.
The application cross-refers to Solpaflex Gel, granted to Ethypharm SA on 1st March 2001 as a change of ownership. The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed name of the product is Ketoprofen 2.5%w/w Gel. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The product contains ketoprofen, equivalent to 2.5%w/w. It is to be stored in varnished aluminium tubes with a polyethylene cap and is available in pack sizes of 50g or 100g. The proposed shelf-life (30 months) and storage conditions (“Do not store above 25°C.”) are consistent with the details registered for the cross-reference product.

2.3 Legal status
On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
Pinewood Laboratories Limited, Ballymacarbry, Clonmel, County Tipperary, Ireland.
The QP responsible for pharmacovigilance is stated and CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.
2.8 Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
No materials of animal or human origin are included in the product. This is consistent with the cross-reference product.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summary is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet 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 it contains.

7. CONCLUSIONS
The data submitted with the application are acceptable. A Marketing Authorisation should be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Ketoprofen is a well known drug and has been used to reduce pain and inflammation for many years. This application is identical to previously granted application for Ketoprofen 2.5% Gel (PL 04917/0069) granted to Ethypharm SA.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with ketoprofen is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

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<thead>
<tr>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 31st October 2003.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 5th November 2003.</td>
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<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 2nd May 2005 and 30th October 2008.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 27th February 2008 and 24th November 2008.</td>
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<td>5</td>
<td>The application was determined on 31st December 2008.</td>
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STEPS TAKEN AFTER ASSESSMENT

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<th>Date submitted</th>
<th>Application type</th>
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KETOPROFEN 2.5% W/W GEL  
PL 04917/0069

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT  
Ketoprofen 2.5% w/w Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION  
Ketoprofen 25 mg/g  
For excipients, see 6.1

3 PHARMACEUTICAL FORM  
Gel  
Homogenous transparent gel with an odour of lavender and alcohol

4 CLINICAL PARTICULARS  
Symptomatic relief of pain in such conditions as soft tissue injuries, including sport injuries, sprains, strains, musculo-tendonitis, swelling, backache and rheumatic pain.

4.2 Posology and method of administration  
For cutaneous use.  
Penetration of the gel by gentle and prolonged massage on the painful or inflamed surface for up to seven days.  
Two to four daily applications of approximately 2 to 4g gel, representing approximately 5 to 10cm.  
The usual maximum dose is 15g per day.  
Children (under 15 years): Not recommended, as safety in children has not been established.

4.3 Contraindications  
Known allergy to Ketoprofen, to substances of similar activity to aspirin.  
Known allergy to excipients.  
Patients in whom attacks of asthma, urticaria or rhinitis are precipitated by aspirin or other NSAIDs (including when taken by mouth).  
Dermatosis, eczema, infected skin lesion, wounds.  
Not to be applied on mucous membranes nor on the eyes.

4.4 Special warnings and precautions for use  
For topical use only. The appearance of cutaneous eruption following application of the gel requires interruption of treatment.  
Hands should be washed before use and immediately after use (unless they are being treated).  
Not for use with occlusive dressing. Topical application of large amounts may result in systemic effects including hypersensitivity and asthma (renal disease has also been reported).

The label will state:  
Do not exceed the stated dose.  
For external use only.  
Keep out of the reach and sight of children.  
If symptoms persist consult your doctor or pharmacist.
Do not use if you are allergic to ketoprofen or any of the ingredients, aspirin or any other pain killers.

Consult your doctor before use if:
You are taking aspirin or any other pain-relieving medication.
You are pregnant or breast feeding.

4.5 **Interaction with other medicinal products and other forms of interaction**
Interactions are unlikely, as serum concentrations following topical application are low. However concurrent aspirin or other NSAIDs may result in increased incidence of adverse reaction.

4.6 **Pregnancy and lactation**
No embryopathic effects have been demonstrated in animals and there is epidemiological evidence of the safety of ketoprofen in human pregnancy. Nevertheless, it is recommended that ketoprofen should be avoided during pregnancy. Non-steroidal anti-inflammatory drugs may also delay labour. Trace amounts of ketoprofen are excreted in breast milk following oral administration, therefore the gel should not be used during breast feeding.

4.7 **Effects on ability to drive and use machines**
Not applicable.

4.8 **Undesirable effects**
Rare allergy type pruritic or localised erythematous skin reactions, urticaria and photosensitivity (avoid excessive exposure to sunlight).

4.9 **Overdose**
Overdosage is unlikely to be caused by topical administration. If accidentally ingested, the gel may cause systemic adverse effects depending on the amount ingested. However, if they occur, treatment should be supportive and symptomatic.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
Ketoprofen is a non-steroidal anti-inflammatory of the propionics group, derivative of aryl-carboxylic acid.

It has anti-inflammatory and analgesic properties.

5.2 **Pharmacokinetic properties**
Applied locally in the form of a gel, ketoprofen is absorbed very gradually and is not accumulated in the body. The systemic passage of the gel compared to that of the oral formulations of ketoprofen is around 5 per cent, which enables a local effect to be obtained without systemic incidence.

5.3 **Preclinical safety data**
The main acute side effect seen during the safety studies after oral, sc and ip routes is the ulcerogenic potential. The target organs for chronic toxicity are the gastro-intestinal tract, the kidney and, to a lesser degree the liver. Due to low systemic passage of ketoprofen from the gel such safety data are not relevant for local administration. Studies on the local tolerance have shown that ketoprofen is well tolerated.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
Carbomer
Triethanolamine
Lavender essential oil
Ethanol 95%
Purified water

6.2 **Incompatibilities**
None stated.

6.3 **Shelf life**
30 months

6.4 **Special precautions for storage**
Do not store above 25°C.

6.5 **Nature and contents of container**
Varnished aluminium tube – polyethylene screw cap.
50g or 100g.

6.6 **Special precautions for disposal**
None stated.

7 **MARKETING AUTHORISATION HOLDER**
Pinewood Laboratories Limited,
*Trading as: Pinewood Healthcare*
Ballymacarbry,
Clonmel,
Co. Tipperary,
Ireland.

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 04917/0069

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
31/12/2008

10 **DATE OF REVISION OF THE TEXT**
31/12/2008
KETOPROFEN 2.5% W/W GEL
PL 04917/0069

PATIENT INFORMATION LEAFLET

KETOPROFEN 2.5% W/W GEL
Ketoprofen 25 mg/g

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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What Ketoprofen Gel is and what it is used for
2. Before you use Ketoprofen Gel
3. How to use Ketoprofen Gel
4. Possible side effects
5. How to store Ketoprofen Gel
6. Further information

1. WHAT KETOPROFEN GEL IS AND WHAT IT IS USED FOR

Ketoprofen Gel is a homogenous and colourless gel for application to the surface of the skin only. It contains ketoprofen which belongs to a non-steroidal group of anti-inflammatory drugs (NSAIDs), like aspirin, which help to reduce pain and inflammation.

Ketoprofen Gel is used for pain relief in:
- soft tissue injuries including sports injuries and sprains and strains
- muscle-tendinitis
- swelling
- backache
- rheumatic pain

2. BEFORE YOU USE KETOPROFEN GEL

Do not use Ketoprofen Gel
- if you are allergic to ketoprofen or to aspirin or other NSAIDs, or to any of the other ingredients of Ketoprofen Gel (see Section 6).
- if you have ever had asthma, urticaria (skin rash), or tummy ache and sneezing after taking aspirin or other NSAIDs.
- on an area where you have any skin conditions, eczema, wounds or infections.
- in your eyes, mouth, nose, or on the anal or genital areas, if this happens, wash with plenty of clean water.

Take special care with Ketoprofen Gel
Tell your doctor if you:
- are, or may be pregnant, or if you are breast-feeding.
- have taken aspirin, or any other pain-relieving medicine recently.

If you have to go to a hospital, tell the medical staff that you are using this product.

You should STOP using Ketoprofen Gel if you notice spots or a rash on the skin at the site of application, and consult your doctor immediately.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, especially those for pain relief, such as aspirin or other NSAIDs.

Pregnancy and breast-feeding
Tell your doctor if you are or may be pregnant. Ask your doctor for advice before taking any medicine during pregnancy. Ketoprofen Gel must not be used if you are breast-feeding.

3. HOW TO USE KETOPROFEN GEL

FOR EXTERNAL USE ONLY
Always use Ketoprofen Gel exactly as your doctor has told you. Your doctor will tell you how much to apply and how often, but you must check with your doctor if you are not sure.
Do not exceed the stated dose.

For application to the surface of the skin only:
1. Wash your hands thoroughly before use.
2. Unscrew the cap, turn it upside down and use the spike of the cap to puncture the top of the tube.
3. Apply the correct dose. Massage the gel gently into the painful or inflamed area to ensure absorption into the skin, and there may be a slight cooling effect as the gel is applied. Apply 2 to 4g of Ketoprofen Gel (equivalent to a 5-10cm strip) to the affected area two to four times a day. Do not apply more than 15g of gel (equivalent to approximately 35cm strip) in any one day.

The usual dose is:

| Adults, the elderly and children over 15 years. | Apply 5 - 10 cm of the gel to the affected area 2 - 4 times a day for up to 7 days. |
| Children under 15 years: | Not recommended. |

4. Replace the cap tightly immediately after use.
5. Wash your hands again, unless your hands are being treated with the gel.
6. Once applied, do not cover the area with a dressing or plaster.
7. If your symptoms remain at the end of 7 days, stop your treatment and consult your doctor or pharmacist.

Do not exceed the recommended maximum daily dose of 15g (equivalent to a 35cm strip) of Ketoprofen Gel in one day.

If you do, you may experience allergy (hypersensitivity) and asthma or other effects including kidney disease.

If you get the gel in your eyes, mouth, nose or on the anal or genital areas, wash with plenty of water.

If you use more Ketoprofen Gel then you should

If you or your child accidentally swallow the gel, contact your doctor or nearest hospital immediately.

If you apply more than 15g of gel in any one day, you may experience an allergic reaction (hypersensitivity), asthma or other effects including kidney disease. If you accidentally use more gel than recommended or if you or your child accidentally swallow the gel, contact your doctor or nearest hospital casualty department immediately. Take any remaining gel with you and keep it in the original packaging to help identification.

If you forget to use Ketoprofen Gel

If you miss a treatment, apply the gel as soon as you remember, but do not use more than 4 times a day.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ketoprofen Gel can cause side effects, although not everybody gets them.

You may notice the following:
- rash, itching, swelling of the lips, eyes, tongue, or difficulty in breathing may be signs of an allergic reaction.

Side effects may include:
- redness of the skin, itching, urticaria (skin rash) or sensitivity to sunlight (avoid exposure).

If any of the side effects become severe, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE KETPROFEN GEL

Keep Ketoprofen Gel away from naked flames.

Keep out of the reach and sight of children.

Do not store above 25°C. Store in the original package and keep the tube in the outer carton.

Do not use this medicine after the expiry date stated on the tube/carton.

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 Ketoprofen Gel contains:
- The active substance is ketoprofen and the gel contains 25mg in every 1g.
- The other ingredients are: water, propylene glycol and purified water.

What Ketoprofen Gel looks like and contents of the pack
- The gel is homogenous and colourless and is available in tubes containing 50g or 100g. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Manufacturer
Chemieux Laboratories, 93 Route De Monmaule, Vouvray 37210, France.

PL 04917/0069 This leaflet was last revised in 11/2008
Ketoprofen 2.5% w/w Gel

Each 15 g of the gel contains 375 mg Ketoprofen

This medicine contains Ketoprofen 25 mg/g. It also contains carbomer, triethanolamine, lavender oil, ethanol and purified water.

Directions: Use as directed by the physician. Do not exceed the stated dose, if symptoms persist consult your doctor or pharmacist. Please read the patient information leaflet carefully before use. Replace the cap tightly after use. Do not use if you are allergic to Ketoprofen or any of the ingredients, aspirin or any other pain killers. Consult your doctor before use if you are taking aspirin or any other pain relieving medication; you are pregnant or breast feeding.

Storage: Do not store above 25°C.

Keep out of the reach and sight of children.

For external use only.

Product Licence Holder/Manufacturer:
Pinewood Laboratories Ltd., Ballymacarbry, Clonmel, Co. Tipperary, Ireland.
PL 04917/0069
SEC