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LAY SUMMARY

The MHRA granted McNeil Products Limited Marketing Authorisation (licence) for the medicinal product Daktarin 2% Cream on 1st April 2009. This product is indicated for the treatment of fungal and bacterial infections of the skin and nails.

This product is a pharmacy (P) only medicine and contains miconazole nitrate. This medicine is used to treat fungal and bacterial infections of the skin and nails. Miconazole nitrate works by destroying both the fungus that causes the infection and some of the associated bacteria which may also be present.

This application is a duplicate of a previously granted application for Daktarin Cream (PL 00242/0016), which was originally approved to Janssen-Cilag Limited on 13th May 1974.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Daktarin 2% Cream outweigh the risks; hence a Marketing Authorisation has been granted.
DAKTARIN GOLD 2% CREAM
PL 15513/0307

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted McNeil Products Limited Marketing Authorisation for the medicinal product Daktarin 2% Cream (PL 15513/0307) on 1st April 2009. The product is available on a Pharmacy (P) only licence.

The application was submitted as a simple abridged application according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Daktarin Cream (PL 00242/0016), which was originally approved to which was originally approved to Janssen-Cilag Limited on 13th May 1974.

No new data were submitted nor were they necessary for this simple application, as the data is identical to that of the previously granted cross-reference product.

This suspension contains the active ingredients miconazole nitrate and is indicated for the treatment of myotic infections of the skin and nails and superinfections due to Gram-positive bacteria.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 15513/0307
PROPRIETARY NAME: Daktarin 2% Cream
ACTIVE(S): miconazole nitrate
COMPANY NAME: McNeil Products Limited
LEGAL STATUS: P

1. INTRODUCTION
This is a simple, piggy back application for Daktarin 2% Cream (PL 15513/0307) submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is McNeil Products Limited, Foundation Park, Roxborough Way, Maidenhead, Berkshire, SL6 3UG, United Kingdom.

The application cross-refers Daktarin Cream (PL 00242/0016), which was originally approved to which was originally approved to Janssen-Cilag Limited on 13th May 1974.

The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed name of the product is Daktarin 2% Cream. 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 miconazole nitrate. The finished product is packaged in aluminium tubes, inner lined with heat polymerised epoxy-phenol resin. These are closed with a white polypropylene cap in sizes of 15g, 30g or 70g of cream, or with a high density polyethylene cap in a size of 5g.

The proposed shelf-life (24 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 product will be available on a pharmacy (P) only licence.

2.4 Marketing authorisation holder/Contact Persons/Company
McNeil Products Limited, Foundation Park, Roxborough Way, Maidenhead, Berkshire, SL6 3UG, United Kingdom.

The QP responsible for pharmacovigilance is stated and their 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 for each product 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 information 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
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product. The 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 they contain.
Labelling
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 packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the application is acceptable. The grant of a Marketing Authorisation is recommended.
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 applications of this type.

EFFICACY
This application is identical to a previously granted application Daktarin Cream (PL 00242/0016), which was originally approved to which was originally approved to Janssen-Cilag Limited on 13th May 1974.

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 miconazole nitrate is considered to have demonstrated the therapeutic value of the compound. The risk:benefit is, therefore, considered to be positive.
DAKTARIN 2% CREAM  
PL 15513/0307

### STEPS TAKEN FOR ASSESMENT

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<tr>
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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 15\textsuperscript{th} March 2008.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 18\textsuperscript{th} March 2008.</td>
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<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the quality dossier on 15\textsuperscript{th} August 2008.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 2\textsuperscript{nd} October 2008 for the quality sections.</td>
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<td>5</td>
<td>The application was determined on 1\textsuperscript{st} April 2009.</td>
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## STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Daktarin 2% Cream.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Miconazole nitrate 2% w/w.
Excipients: Benzoic acid, Butylated hydroxyanisole
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Cream
White homogeneous cream.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of mycotic infections of the skin and nails and superinfections due to Gram-positive bacteria.

4.2 Posology and method of administration
Route of administration: Cutaneous use.
Recommended dosage:
For all ages:
Skin infections: Apply the cream twice daily to the lesions. Treatment should be prolonged for 10 days after all lesions have disappeared to prevent relapse.
Nail infections: Apply the cream once or twice daily to the lesions. Treatment should be prolonged for 10 days after all lesions have disappeared to prevent relapse.

4.3 Contraindications
Daktarin Cream is contraindicated in individuals with a known hypersensitivity to miconazole or another ingredient in this product.

4.4 Special warnings and precautions for use
Daktarin Cream must not come into contact with the eyes.
If a reaction suggesting sensitivity or irritation should occur, the treatment should be discontinued.
Benzoic acid (E210) is mildly irritant to the skin, eyes and mucous membranes.
Butylated hydroxyanisole (E320) may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction
Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to the limited systemic availability after topical application, clinically relevant interactions are rare. However, in patients on oral anticoagulants, such as warfarin, caution should be exercised and anticoagulant effect should be monitored.

4.6 Pregnancy and lactation
Pregnancy
In animals miconazole nitrate has shown no teratogenic effects but is foetotoxic at high oral doses. Only small amounts of miconazole nitrate are absorbed following topical administration. However, as with other imidazoles, miconazole nitrate should be used with caution during pregnancy.

Lactation
Topically applied miconazole is minimally absorbed into the systemic circulation, and it is not known whether miconazole is excreted in human breast milk. Caution should be exercised when using topically applied miconazole products during lactation.
4.7 Effects on ability to drive and use machines
Not relevant.

4.8 Undesirable effects
Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience with Daktarin that meet threshold criteria are included. The adverse drug reactions are ranked by frequency, using the following convention:
Very common \( \geq 1/10 \)
Common \( \geq 1/100 \) and \( < 1/10 \)
Uncommon \( \geq 1/1,000 \) and \( < 1/100 \)
Rare \( \geq 1/10,000 \), \( < 1/1,000 \)
Very rare \( < 1/10,000 \), including isolated reports

The frequencies provided below reflect reporting rates for adverse drug reactions from spontaneous reports, and do not represent more precise estimates of incidence that might be obtained in clinical or epidemiological studies.

Immune system disorders
*Very rare:* anaphylactic reaction, hypersensitivity, angioneurotic edema

Skin and subcutaneous tissue disorders
*Very rare:* urticaria, contact dermatitis, rash, erythema, pruritus, skin burning sensation

General disorders and administration site conditions
*Rare:* application site reactions, including application site irritation

4.9 Overdose
**Symptoms**
Cutaneous use: Excessive use can result in skin irritation, which usually disappears after discontinuation of therapy.

**Treatment**
Daktarin cream is intended for cutaneous use, not for oral use. If accidental ingestion of large quantities of the product occurs, an appropriate method of gastric emptying may be used if considered necessary.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic classification: (Antifungals for dermatological/topical use; imidazole derivative) *ATC code:* D01A C02.

Miconazole nitrate is an imidazole antifungal agent and may act by interfering with the permeability of the fungal cell membrane. It possesses a wide antifungal spectrum and has some antibacterial activity.

5.2 Pharmacokinetic properties
**Absorption:** There is little absorption through skin or mucous membranes when miconazole nitrate is applied topically.
**Distribution:** Absorbed miconazole is bound to plasma proteins (88.2%) and red blood cells (10.6%).
**Metabolism and Excretion:** The small amount of miconazole that is absorbed is eliminated predominantly in faeces as both unchanged drug and metabolites.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of local irritation, single and repeated dose toxicity, genotoxicity, and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
PEG-6, PEG-32 and glycol stearate
Oleoyl macroglycerides
Liquid paraffin
Benzoic acid (E210)
Butylated hydroxyanisole (E320)
Purified water

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
24 months.

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

6.5 **Nature and contents of container**
Aluminium tube inner lined with heat polymerised epoxy-phenol resin with a white polypropylene cap containing 15 g, 30 g or 70 g of cream, or aluminium tube inner lined with heat polymerised epoxy-phenol resin with a high density polyethylene cap containing 5 g of cream.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
McNeil Products Limited
Foundation Park
Roxborough Way
Maidenhead
Berkshire
SL6 3UG
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 15513/0307

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
01/04/2009

10 **DATE OF REVISION OF THE TEXT**
01/04/2009
Daktarin® 2% CREAM
miconazole nitrate

- This medicine is used to treat fungal and bacterial infections of the skin and nails.
- This medicine is for use by adults and children of all ages.
- Do not use this medicine:
  - There are some people who should not use this medicine. To find out if you are one of them, see Section 2.
  - If you have ever had a bad reaction to any of the ingredients. For the list of ingredients, see Section 6.
  - If you suffer from any of the conditions mentioned in Section 2.
  - If you are taking any other medicines. See Section 2.
  - Follow the instructions on how to use this product carefully. See Section 3.

Now read this whole leaflet carefully before you use this medicine. Keep the leaflet: you might need it again.

1 What the medicine is for

Daktarin 2% Cream is a medicine which is used in the treatment of fungal and associated bacterial infections of the skin and nails. Skin infections may appear on the hands, feet, outer ear, trunk or groin and include athlete’s foot, dhoibie itch and intertrigo. Daktarin 2% Cream is also effective against infected nappy rash. The cream contains miconazole nitrate which works by destroying both the fungus that causes the infection and some of the associated bacteria which may also be present. It also has moisturising properties to help soothe cracked, red skin. This medicine is for use in adults and children of all ages.

2 Before using this medicine

This medicine is suitable for most adults and children but a few people should not use it. If you are in any doubt, talk to your doctor or pharmacist.

- Do not use this medicine...
  - If you have ever had a bad reaction to any of the ingredients.
  - If this applies to you, get advice from a doctor or pharmacist without using Daktarin 2% Cream.

- Talk to your doctor or pharmacist if you are taking...
  - Oral anticoagulants (drugs used to thin the blood, such as warfarin).
  - If you are not sure about any of the medicines you are taking, show the bottle or pack to your pharmacist.

- If you are pregnant or breast-feeding
  - Ask your doctor or pharmacist for advice before using this medicine if you are pregnant or breast-feeding.

- Special warnings about this medicine
  - Do not let the cream get into your eyes.
  - If you experience any irritation or sensitivity to the cream, stop using this medicine.

- Some of the ingredients can cause problems
  - Benzoic acid (E210) can mildly irritate the skin, eyes and mucosal membranes.
  - Butylated hydroxyanisole (E320) may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

3 How to use this medicine

Check the table below to see how often to use.

- Each tube of cream is sealed – use the cap to pierce the seal.
- For cutaneous use only, which means it is applied directly to the affected area of skin.
- Do not use more often than the stated dose shown in the table.

How to apply the cream

- Wash the infected area and dry it well. As many skin conditions are contagious, you should keep a towel and flannel for your own use and not share it so that you do not infect anyone else.
- Apply the cream onto the infected area and surrounding skin.
- Wash your hands carefully after applying the cream to avoid spreading the infection to other parts of the body or to other people. Similarly, clothing which comes into contact with the infected areas, such as socks, should be washed and changed frequently.

<table>
<thead>
<tr>
<th>Adults and children of all ages</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and children of all ages</td>
<td>Skin infections: Apply the cream to the infected skin twice a day. Nail infections: Apply the cream to the infected area once or twice daily.</td>
</tr>
</tbody>
</table>

- Continue treatment for 10 days after all the symptoms have cleared to prevent them from coming back.
- If symptoms persist talk to your doctor.

- turn over -
If anyone has swallowed this product
If anyone accidentally swallows Daktarin 2% Cream, contact a doctor or your nearest Accident and Emergency department (Casually), taking this leaflet and pack with you.

If you forget to use the medicine
If you forget to use a dose, use the next dose when needed. Do not use a double dose.

4 Possible side-effects
Daktarin 2% Cream can have side-effects, like all medicines, although these don’t affect everyone and are usually mild.

If you experience any of the following, stop using the medicine and seek immediate medical help:
Very rarely: (less than 1 in 10,000 people are affected)
- Severe allergic reactions including swelling of the face, lips, tongue or throat.
- Light headedness, generalised itch, wheezing or difficulty in breathing.

If you experience any of the following, stop using the medicine and talk to your doctor:
Very rarely: (less than 1 in 10,000 people are affected)
- Allergic reactions such as skin rash, itchiness, hives, swelling, redness or a burning feeling.

Other mild effects which may occur include:
Rarely: (less than 1 in every 1,000 people are affected)
- Sensitivity reactions (such as rash) at the application site. If this occurs stop using the medicine.

If you experience any side-effects not included in this leaflet or are not sure about anything, talk to your doctor or pharmacist.

5 Storing this medicine
Do not store above 25°C.
Keep the product out of the reach and sight of children.
Do not use your medicine after the date shown as the expiry date on the packaging.
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’s in this medicine?
The active ingredient in 1 g of Daktarin 2% Cream is:
Miconazole nitrate 20 mg.
Other ingredients are: PEG-6, PEG-32 and glycol stearate, oleoyl macroglycerides, liquid paraffin, benzoic acid (E210), butylated hydroxyanisole (E320), purified water.

What the medicine looks like
Daktarin 2% Cream is a white cream available in tubes of 15 g.

Product Licence holder: McNeil Products Ltd,
Maidenhead, Berkshire, SL6 3UG, UK.
Manufacturer: Janssen Pharmaceutica NV,
Turnhoutseweg 30, B2340, Beerse, Belgium.
This leaflet was revised December 2008.
Daktarin is a registered trade mark.
FOR EXTERNAL USE ONLY

Directions: Cutaneous cream. Apply to skin and nails only. Skin infections: Apply to the affected area twice daily. Nail infections: Apply to the affected area once or twice daily. Continue treatment for 10 days after symptoms have cleared to prevent them coming back. For further information see leaflet. If symptoms persist, consult your doctor. Keep out of the reach and sight of children. Do not store above 25°C.

Also contains PEG-6, PEG-32 and glycol stearate, oleoyl macroglycerides, liquid paraffin, E210, E320, water.

McNeil Products Ltd, Maidenhead, Berkshire, SL6 3UG, UK.

McNeil Products Ltd, Maidenhead, Berkshire, SL6 3UG, UK.

Batch No: PL 15513/0307

Expiry:

PL 15513/0307