Daktarin Sugar Free 2% Oral Gel

PL 15513/0296

UKPAR

TABLE OF CONTENTS

Daktarin Sugar Free 2% Oral Gel

PL 15513/0296

LAY SUMMARY

The MHRA granted McNeil Product Limited Marketing Authorisation (licence) for the medicinal product Daktarin Sugar Free 2% Oral Gel (PL 15513/0296) on the 15th October 2008. This is a Pharmacy (P) only medicine.

Daktarin sugar free 2% Oral Gel is a medicine which is used to prevent and treat fungal and bacterial infections of the mouth and throat. The gel contains miconazole which works by destroying the fungus and associated bacteria which may be present.

This is 'informed consent' application submitted under article 10.c Directive 2001/83/EC as amended. This application refers to the marketing authorisation held by Janssen-Cilag Ltd (PL 00242/0048).

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Daktarin outweigh the risks, hence Marketing Authorisation has been granted.

Daktarin Sugar Free 2% Oral Gel

PL 15513/0296

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

The UK granted marketing authorisation for the medicinal product Daktarin Sugar Free 2% Oral Gel (PL 15513/0296) to McNeil Products Limited on 15th October 2008. This product is Pharmacy only Medicine (P).

The application was submitted as simple abridged application according to article 10.1(c) of Directive 2001/83/EC, cross-referring to Daktarin Oral Gel (PL 00242/0048) approved to Janssen-Cilag Ltd.

No new data was submitted nor was it necessary for this simple application, as the data is 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 PAR was generated.

Miconazole possesses an antifungal activity against the common dermatophytes and yeasts as well as an antibacterial activity against certain gram-positive bacilli and cocci.

Its activity is based on the inhibition of the ergosterol biosynthesis in fungi and the change in the composition of the lipid components in the membrane, resulting in fungal cell necrosis.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 15513/0296
PROPRIETARY NAME: Daktarin Sugar Free 2% Oral Gel
ACTIVE(S): MICONAZOLE
COMPANY NAME: McNeil Products Limited
E.C. ARTICLE: Article 10 (c) of Directive 2001/83/EC
LEGAL STATUS: P

1. INTRODUCTION

This is a simple abridged application for Daktarin Sugar Free 2% Oral Gel submitted under Article 10 (c) of Directive 2001/83/EC. The proposed MA holder is McNeil Product Limited, Foundation Park, Roxborough way, Maidenhead, Berkshire, SL6 3UG.

This application refers to marketing authorisation granted to Janssen-Cilag Ltd (Daktarin Oral Gel PL 00242/0048).

A letter of access has been provided from Janssen-Cilag Ltd authorising the MHRA to refer to PL 00242/0048 as the reference for the purpose of this informed consent application. McNeil Products Ltd has also confirmed that they are in possession of all the necessary data to support this application including the quality dossier.

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the product is identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Daktarin Sugar Free 2% Oral 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 Daktarin Sugar Free 2% Oral Gel equivalent to 20mg of miconazole respectively.

The products will be packaged into aluminium tubes. The packagings are identical to the packaging for the reference product. The pack sizes are also identical to the reference product.

The respective SPC have indicated that Daktarin Sugar Free 2% Oral Gel will be packed into aluminium tubes containing 5g or 15g gel.

The same pack sizes are stated in the reference product. The proposed shelf life of 3 years is identical to the reference product. The proposed storage conditions are also identical to the reference product.

2.3 Legal status

The product is Pharmacy (P).

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is McNeil Products Limited, Foundation Park, Roxborough Way, Maidenhead, Berkshire, SL6 3UG, United Kingdom.

2.5 Manufacturers

The proposed manufacturing sites are consistent with that registered for the cross-reference product and evidence of GMP compliance has been provided.
A flow diagram showing the sequence and activities of the different sites involved in the manufacturing process has been provided.

2.6 Qualitative and quantitative composition

The proposed compositions are consistent with the details registered for the cross-reference products.

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 products.

2.9 Drug substance specification

The proposed drug substance specification conformed to current Ph Eur monograph for miconazole as consistent with that of the reference product.

Current Ph Eur certificates of suitability for all drug substance manufacturers have been provided to support the sources of active substance. These manufacturers are in line with the reference product.

2.10 TSE Compliance

The applicant has stated in the cover letter that no excipients of human or animal origin have been used.

2.11 Bioequivalence / Bioavailability

No bioavailability and bioequivalence data are required to support this informed consent application as the proposed product is manufactured to the same formula utilising the same process. The finished product manufacturing site is also identical to that used by the reference product.

3. EXPERT REPORTS

The applicant has included detailed expert reports of the application. Signed declarations and copies of the experts' CVs are enclosed 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 appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed SmPCs are consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/BLISTER

PIL

The patient information leaflet has been prepared in-line with the details registered for

the cross-reference products.

The result of user testing has been provided.

The proposed artwork complies with the relevant 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.

7. CONCLUSIONS

The data submitted with the application is acceptable. 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 and none are required.

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 application of this type.

EFFICACY

These applications are identical to previously granted applications for Daktarin Oral Gel 2%w/w (PL 00242/0048-0054).

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the product is identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from these applications.

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 Daktarin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 22/04/2008
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 01/05/2008.
3	Following assessment of the application the MHRA requested further information on 04/06/2008
4	The applicant responded to the MHRA's requests, providing further information on 03/10/2008
7	The application was determined on 15/10/2008

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

Daktarin Sugar Free 2% Oral Gel

PL 15513/0296

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
DAKTARIN Sugar Free 2% Oral Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gram of Daktarin Sugar Free 2% Oral Gel contains 20mg of miconazole.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Oral gel.

White gel with orange taste.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Oral treatment and prevention of fungal infections of the oropharynx and of superinfections due to Gram-positive bacteria.

4.2 Posology and method of administration
For oral administration

For topical treatment of the oropharynx

Treatment should be continued for up to 2 days after the symptoms have cleared.

Adult, Elderly and Children aged 6 years and over

Apply a small amount of gel directly to the affected area with a clean finger four times a day. The gel should be kept in the mouth for as long as possible.

For oral candidosis, dental prostheses should be removed at night and brushed with the gel.

Children aged 4 months – 6 years:

Apply a small amount of gel directly to the affected area with a clean finger twice daily. The gel should be kept in the mouth for as long as possible.

The lower age limit should be increased by 1-2 months for infants who are pre-term, or infants exhibiting slow neuromuscular development.

4.3 Contraindications
Known hypersensitivity to miconazole or to any of the excipients.

In infants less than 4 months of age or in those whose swallowing reflex is not yet sufficiently developed.

In patients with liver dysfunction.

Coadministration of the following drugs that are subject to metabolism by CYP3A4: (See Section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction)

- Substrates known to prolong the QT-interval e.g., astemizole, cisapride, dofetilide, mizolastine, pimozide, quinidine, sertindole and terfenadine
- Ergot alkaloids
- HMG-CoA reductase inhibitors such as simvastatin and lovastatin

- Triazolam and oral midazolam

4.4 Special warnings and precautions for use

If the concomitant use of Daktarin and oral anticoagulants such as warfarin is envisaged, the anticoagulant effect should be carefully monitored and titrated (see section 4.5).

It is advisable to monitor miconazole and phenytoin levels, if these two drugs are used concomitantly.

In patients using certain oral hypoglycaemics such as sulphonylureas, an enhanced therapeutic effect leading to hypoglycaemia may occur during concomitant treatment with miconazole and appropriate measures should be considered (See Section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction).

Particularly in infants and young children, caution is required to ensure that the gel does not obstruct the throat. Hence, the gel should not be applied to the back of the throat and each dose should be divided into smaller portions. Observe the patient for possible choking.

The lower age limit should be increased by 1-2 months for infants who are pre-term, or infants exhibiting slow neuromuscular development.

4.5 Interaction with other medicinal products and other forms of interaction

When using any concomitant medication the corresponding label should be consulted for information on the route of metabolism. Miconazole can inhibit the metabolism of drugs metabolised by the CYP3A4 and CYP2C9 enzyme systems. This can result in an increase and/or prolongation of their effects, including adverse effects.

Oral miconazole is contraindicated with the coadministration of the following drugs that are subject to metabolism by CYP3A4 (See Section 4.3 Contraindications);

- Substrates known to prolong the QT-interval e.g., astemizole, cisapride, dofetilide, mizolastine, pimozide, quinidine, sertindole and terfenadine
- Ergot alkaloids
- HMG-CoA reductase inhibitors such as simvastatin and lovastatin
- Triazolam and oral midazolam

When coadministered with oral miconazole the following drugs should be used with caution because of a possible increase or prolongation of the therapeutic outcome and/or adverse events. If necessary, their dosage should be reduced and, where appropriate, plasma levels monitored:

Drugs subject to metabolism by CYP2C9 (see Section 4.4 Special Warnings and Precautions for Use);

- Oral anticoagulants such as warfarin,
- Oral hypoglycaemics such as sulphonylureas
- Phenytoin

Other drugs subject to metabolism by CYP3A4;

- HIV Protease Inhibitors such as saquinavir;
- Certain antineoplastic agents such as vinca alkaloids, busulfan and docetaxel;
- Certain calcium channel blockers such as dihydropyridines and verapamil;
- Certain immunosuppressive agents: cyclosporin, tacrolimus, sirolimus (= rapamycin)
- Others: carbamazepine, cilostasol, disopyramide, buspirone, alfentanil, sildenafil, alprazolam, brotizolam, midazolam IV, rifabutin, methylprednisolone, trimetrexate, ebastine and reboxetine.

4.6 Pregnancy and lactation

In animals, miconazole has shown no teratogenic effects but is foetotoxic at high oral doses. The significance of this to man is unknown. However, as with other imidazoles, Daktarin Sugar Free 2% Oral Gel should be avoided in pregnant women if possible. The potential hazards should be balanced against the possible benefits.

It is not known whether miconazole is excreted in human milk. Caution should be exercised when prescribing Daktarin Sugar Free 2% Oral Gel to nursing mothers.

4.7 Effects on ability to drive and use machines

Daktarin should not affect alertness or driving ability.

4.8 Undesirable effects

Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience with Daktarin that meet threshold criteria are included below. The adverse drug reactions are ranked by frequency, using the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <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 Allergic conditions, including angioneurotic edema and anaphylactic reactions; Lyell syndrome (Toxic Epidermal Necrolysis), Stevens Johnson syndrome, urticaria, rash

Gastrointestinal system disorders

Very rare Choking (see Section 4.3 Contraindications), nausea*, vomiting* and diarrhoea

Hepatobiliary disorders

Very rare Hepatitis

*Nausea and vomiting were observed commonly during clinical trials.

4.9 Overdose

Symptoms:

In the event of accidental overdose, vomiting and diarrhoea may occur.

Treatment:

Treatment is symptomatic and supportive. A specific antidote is not available.

In the event of accidental ingestion of large quantities of Daktarin an appropriate method of gastic emptying may be used, if considered necessary (See Section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction.)

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: A01A B09 and A07A C01

Miconazole possesses an antifungal activity against the common dermatophytes and yeasts as well as an antibacterial activity against certain gram-positive bacilli and cocci.

Its activity is based on the inhibition of the ergosterol biosynthesis in fungi and the change in the composition of the lipid components in the membrane, resulting in fungal cell necrosis.

5.2 Pharmacokinetic properties

Absorption:

Miconazole is systemically absorbed after administration as the oral gel. Administration of a 60 mg dose of miconazole as the oral gel results in peak plasma concentrations of 31 to 49 ng/mL, occurring approximately two hours post-dose.

Distribution:

Absorbed miconazole is bound to plasma proteins (88.2%), primarily to serum albumin and red blood cells (10.6%).

Metabolism and Elimination:

The absorbed portion of miconazole is largely metabolized; less than 1% of an administered dose is excreted unchanged in the urine. The terminal half-life of plasma miconazole is 20 to 25 hours in most patients. The elimination half-life of miconazole is similar in renally impaired patients. Plasma concentrations of miconazole are moderately reduced (approximately 50%) during hemodialysis. About 50% of an oral dose may be excreted in the faeces partly metabolized and partly unchanged.

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

Purified water
Pregelatinised potato starch
Ethanol (96%)
Polysorbate 20
Sodium saccharin
Cocoa flavour
Orange flavour
Glycerol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Aluminium tubes containing 5g* or 15g gel.

* *not marketed*

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
McNeil Products Limited

Foundation Park

Roxborough Way

Maidenhead

Berkshire

SL6 3UG

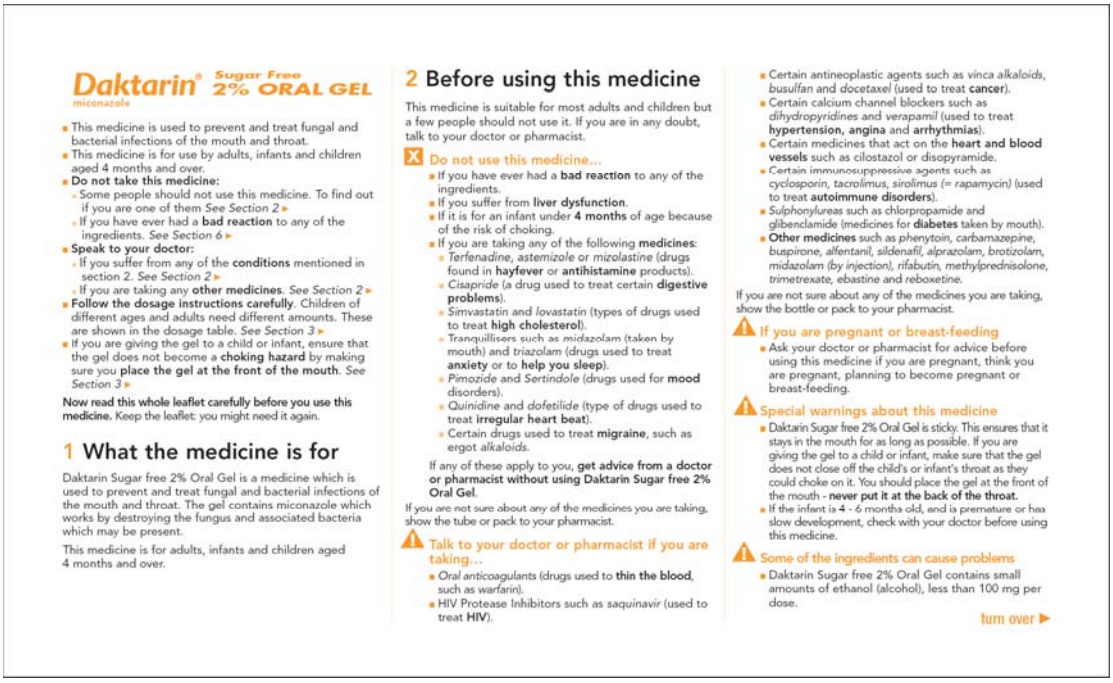
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 15513/0296

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/10/2008

10 DATE OF REVISION OF THE TEXT
15/10/2008

Patient Information Leaflet



Daktarin® Sugar Free 2% ORAL GEL
miconazole

- This medicine is used to prevent and treat fungal and bacterial infections of the mouth and throat.
- This medicine is for use by adults, infants and children aged 4 months and over.
- **Do not take this medicine:**
  - Some people 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. *See Section 6* ▸
- **Speak to your doctor:**
  - If you suffer from any of the **conditions** mentioned in section 2. *See Section 2* ▸
  - If you are taking any **other medicines**. *See Section 2* ▸
- **Follow the dosage instructions carefully**. Children of different ages and adults need different amounts. These are shown in the dosage table. *See Section 3* ▸
- If you are giving the gel to a child or infant, ensure that the gel does not become a **choking hazard** by making sure you **place the gel at the front of the mouth**. *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 Sugar free 2% Oral Gel is a medicine which is used to prevent and treat fungal and bacterial infections of the mouth and throat. The gel contains miconazole which works by destroying the fungus and associated bacteria which may be present.

This medicine is for adults, infants and children aged 4 months and over.

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 you suffer from **liver dysfunction**.
- If it is for an infant under **4 months** of age because of the risk of choking.
- If you are taking any of the following **medicines**:
  - *Terfenadine, astemizole or mizolastine* (drugs found in **hayfever** or **antihistamine** products).
  - *Cisapride* (a drug used to treat certain **digestive problems**).
  - *Simvastatin* and *lovastatin* (types of drugs used to treat **high cholesterol**).
  - Tranquillisers such as *midazolam* (taken by mouth) and *triazolam* (drugs used to treat **anxiety** or to **help you sleep**).
  - *Pimozide* and *Sertindole* (drugs used for **mood** disorders).
  - *Quinidine* and *dofetilide* (type of drugs used to treat **irregular heart beat**).
  - Certain drugs used to treat **migraine**, such as ergot *alkaloids*.

If any of these apply to you, **get advice from a doctor or pharmacist without using Daktarin Sugar free 2% Oral Gel.**

If you are not sure about any of the medicines you are taking, show the tube or pack to your pharmacist.

Talk to your doctor or pharmacist if you are taking...

- *Oral anticoagulants* (drugs used to **thin the blood**, such as *warfarin*).
- HIV Protease Inhibitors such as *saquinavir* (used to treat **HIV**).
- Certain antineoplastic agents such as *vinca alkaloids, busulfan* and *docetaxel* (used to treat **cancer**).
- Certain calcium channel blockers such as *dihydropyridines* and *verapamil* (used to treat **hypertension, angina** and **arrhythmias**).
- Certain medicines that act on the **heart and blood vessels** such as cilostazol or disopyramide.
- Certain immunosuppressive agents such as *cyclosporin, tacrolimus, sirolimus (= rapamycin)* (used to treat **autoimmune disorders**).
- *Sulphonylureas* such as chlorpropamide and glibenclamide (medicines for **diabetes** taken by mouth).
- **Other medicines** such as *phenytoin, carbamazepine, buspirone, alfentanil, sildenafil, alprazolam, brotizolam, midazolam (by injection), rifabutin, methylprednisolone, trimetrexate, ebastine* and *reboxetine*.

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, think you are pregnant, planning to become pregnant or breast-feeding.

Special warnings about this medicine

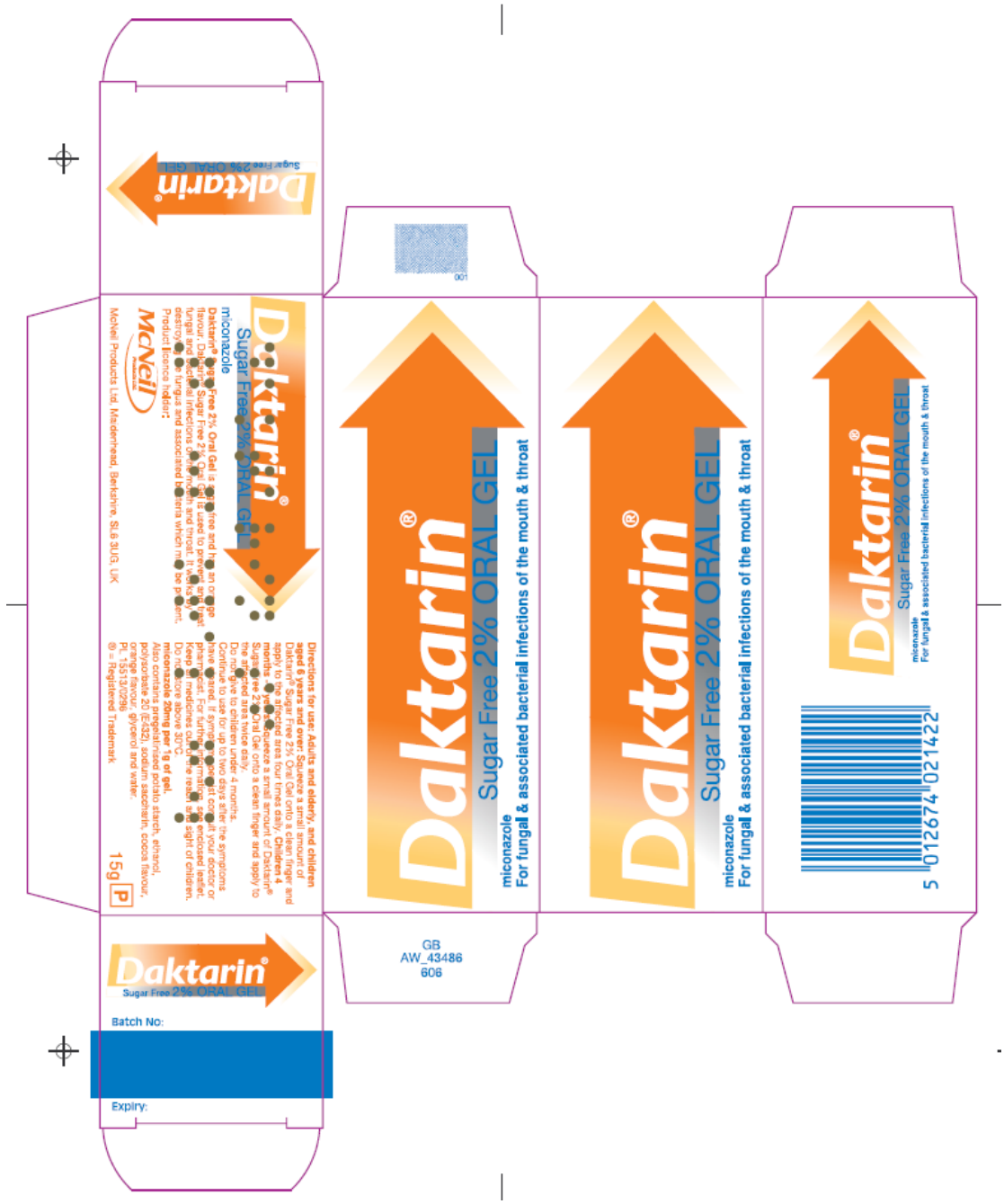
- Daktarin Sugar free 2% Oral Gel is sticky. This ensures that it stays in the mouth for as long as possible. If you are giving the gel to a child or infant, make sure that the gel does not close off the child's or infant's throat as they could choke on it. You should place the gel at the front of the mouth - **never put it at the back of the throat.**
- If the infant is 4 - 6 months old, and is premature or has slow development, check with your doctor before using this medicine.

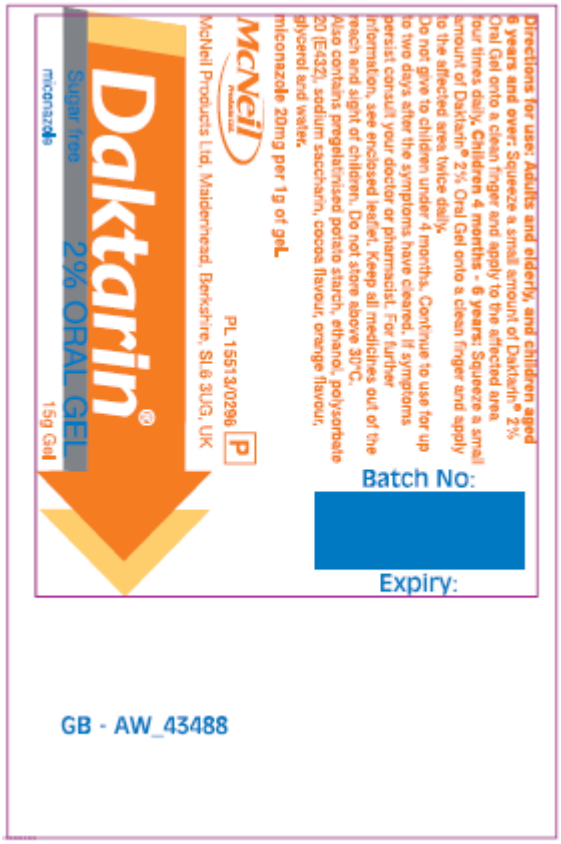
Some of the ingredients can cause problems

- Daktarin Sugar free 2% Oral Gel contains small amounts of ethanol (alcohol), less than 100 mg per dose.

turn over ▶

Labelling


Daktarin®
Sugar Free 2% ORAL GEL
miconazole
For fungal & associated bacterial infections of the mouth & throat
Daktarin®
Sugar Free 2% ORAL GEL
miconazole
For fungal & associated bacterial infections of the mouth & throat
Daktarin®
Sugar Free 2% ORAL GEL
miconazole
For fungal & associated bacterial infections of the mouth & throat
5 012674 021422
GB
AW_43486
606
Daktarin®
Sugar Free 2% ORAL GEL
Batch No:
Expiry:
Daktarin®
Sugar Free 2% ORAL GEL
miconazole
Daktarin® Sugar Free 2% Oral Gel is sugar free and has an orange flavour. Daktarin® Sugar Free 2% Oral Gel is used to prevent and treat fungal and bacterial infections of the mouth and throat. It works by destroying the fungus and associated bacteria which may be present.
Product licence holder:
McNeil Products Ltd, Maidenhead, Berkshire, SL6 3UG, UK
McNeil
Directions for use: Adults and elderly, and children aged 6 years and over: Squeeze a small amount of Daktarin® Sugar Free 2% Oral Gel onto a clean finger and apply to the affected area four times daily. Children 4 months - 6 years: Squeeze a small amount of Daktarin® Sugar Free 2% Oral Gel onto a clean finger and apply to the affected area twice daily.
Do not give to children under 4 months.
Continue to use for up to two days after the symptoms have cleared. If symptoms persist consult your doctor or pharmacist. For further information consult the enclosed leaflet.
Keep all medicines out of the reach and sight of children.
Do not store above 30°C
Active ingredient: miconazole 20mg per 1g of gel.
Also contains: propylene glycol, modified maize starch, ethanol, polysorbate 20 (E432), sodium saccharin, cocoa flavour, orange flavour, glycerol and water.
PL 15513/0296
® = Registered Trademark
15g
P


Directions for use: Adults and elderly, and children aged 6 years and over: Squeeze a small amount of Daktarin® 2% Oral Gel onto a clean finger and apply to the affected area four times daily. Children 4 months - 6 years: Squeeze a small amount of Daktarin® 2% Oral Gel onto a clean finger and apply to the affected area twice daily.
Do not give to children under 4 months. Continue to use for up to two days after the symptoms have cleared. If symptoms persist consult your doctor or pharmacist. For further information, see enclosed leaflet. Keep all medicines out of the reach and sight of children. Do not store above 30°C.
Also contains pregelatinised potato starch, ethanol, polysorbate 20 (E432), sodium saccharin, cocos flavour, orange flavour, glycerol and water.
miconazole 20mg per 1g of geL
PL 15513/0296
P
McNeil Products Ltd, Maidenhead, Berkshire, SL6 3UG, UK
Batch No:
Expiry:
Daktarin®
Sugar free
2% ORAL GEL
miconazole
15g Gel
GB - AW_43488