PRODUCT INFORMATION- DAKTARIN ORAL GEL

1 NAME OF THE MEDICINE

Miconazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DAKTARIN® Oral Gel contains miconazole base 2% - white homogenous gel with orange taste. It also contains glycerol, purified - water, pregelatinised potato starch, ethanol, polysorbate 20, saccharin sodium, cocoa flavour, orange flavour.

3 PHARMACEUTICAL FORM

A white, microcrystalline powder, practically insoluble in water and slightly soluble in polyethoxylated castor oil (Cremophor EL) (1%) and ethanol (10%).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DAKTARIN® Oral Gel is indicated for the treatment of clinically significant oral candidiasis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children 2 years of age and older

Half (½) a measuring spoon* of gel four times a day.

Infants (6-24 months)

One quarter (¼) of a measuring spoon* of gel four times a day is recommended.

* A measuring spoon (5 mL) is provided with the gel. One spoonful contains approximately 124 mg of miconazole. All spoonful dose volumes should be administered with this spoon.

DAKTARIN® Oral Gel should be dropped on the tongue and kept in the mouth for as long as possible before swallowing. When treating infants and younger children it is recommended that the measured dose of gel be given in several portions in the front of the mouth. Avoid dosing to the back of the throat to prevent obstruction. With oral thrush in elderly patients, where a contributing cause is the dental prostheses, it is recommended that in addition to application to the mouth, DAKTARIN® Oral Gel be applied directly to the dentures in the evening, left on overnight, and washed off before the dentures are put back in the morning.

Generally treatment should be continued until all clinical and mycological laboratory tests no longer indicate that active fungal infection is present. It is recommended that treatment should continue for at least a week after the symptoms have disappeared.

4.3 CONTRAINDICATIONS

DAKTARIN® Oral Gel is contraindicated in the following situations:

•In patients with a known hypersensitivity to miconazole or to any of the other ingredients of the gel or other imidazole derivatives.

•In infants less than 6 months of age or in those whose swallowing reflex is not yet sufficiently developed.

•In patients with liver dysfunction.

•Co-administration of the following drugs that are subject to metabolism by CYP3A4 (see Interactions with other drugs):

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

•Use of miconazole oral gel in combination with the following drug that is subject to metabolism by CYP2C9 (see Interactions):

- Coumarin anticoagulants such as warfarin

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Administration of DAKTARIN® Oral Gel has been shown to induce mild side effects (see Adverse Effects) but no haematological or biochemical abnormalities have been reported.

Prolonged use of miconazole may result in superinfection from non-susceptible organisms. If superinfection occurs, the sensitivity of the organism should be determined to decide the most appropriate therapy.

Miconazole is systemically absorbed and is known to inhibit CYP2C9 and CYP3A4 (see Pharmacokinetic) which can lead to prolonged effects of warfarin. Bleeding events, some with fatal outcomes, have been reported with concurrent use of miconazole oral gel and warfarin (see Contraindications

It is advisable to monitor miconazole and phenytoin levels, if they are used concomitantly.

In patients using certain oral hypoglycaemic such as sulfonylureas, an enhanced therapeutic effect leading to hypoglycaemia may occur during concomitant treatment with miconazole and appropriate measures should be considered (see Interactions with other medicines)

Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with DAKTARIN® Oral Gel (see Adverse Effects). If a reaction suggesting sensitivity should occur, treatment should be discontinued.

Serious skin reactions (e.g Toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported in patients receiving DAKTARIN® Oral Gel (see Adverse Effects). It is recommended that patients be informed about the signs of serious skin reactions, and that the use of DAKTARIN® Oral Gel be discontinued at the first appearance of skin rash.

Use in the elderly

No data available.

Paediatric use

DAKTARIN® Oral Gel may be used in children and infants over the age of 6 months suffering from oral candidiasis. Caution is required when administering DAKTARIN® Oral Gel to infants and younger children, to ensure the throat does not become obstructed by the gel (see Dosage and Administration).

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

When using any concomitant medication, consult the corresponding label for information on the route of metabolism. Miconazole can inhibit the metabolism of drugs metabolized 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 co-administration of the following drugs that are subject to metabolism by CYP3A4 (see Contraindications):

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

Miconazole oral gel is contraindicated with the co-administration of the following drug that is subject to metabolism by CYP2C9 (see Contraindications):

- Warfarin

When co-administered with oral miconazole, the following drugs must be used with caution because of a possible increase or prolongation of the therapeutic outcome and/or adverse effects. If necessary, reduce their dosage and, where appropriate, monitor plasma levels:

- Drugs subject to metabolism by CYP2C9 (see Precautions):
- Oral hypoglycemics such as sulfonylureas (CYP2C9)
- 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: cyclosporine, tacrolimus, sirolimus (rapamycin)
- Others: alfentanil, alprazolam, brotizolam, buspirone, carbamazepine, cilostasol, disopyramide, ebastine, methylprednisolone, midazolam IV, reboxetine, rifabutin, sildenafil, and trimetrexate.

Antagonism between miconazole and amphotericin B has been reported in vitro and in vivo. In this study miconazole and amphotericin combination were shown to be antagonistic in antifungal activity against Candida albicans.

4.6 FERTILITY, PREGNANCY AND LACTATION

Use in pregnancy – Pregnancy Category A

Although there is no evidence that miconazole is embryotoxic or teratogenic in animals, potential hazards of prescribing DAKTARIN® Oral Gel during pregnancy should always be weighed against the expected therapeutic benefits.

Use in lactation

There is no information whether miconazole or its metabolites are excreted in breast milk. Therefore, miconazole is not recommended for nursing mothers unless its use is considered essential or alternative-feeding arrangements can be made for the baby.

Effects on fertility

No data available

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

DAKTARIN® does not affect the alertness. However, it may affect the ability to focus the eyes. Patients should be warned not to drive or operate machinery if affected.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In a randomized, active-controlled, open-labelled trial of 47 paediatric patients, 0-10.7 years of age with oral candidiasis due to various predisposing conditions, efficacy and safety of DAKTARIN Oral Gel were compared to nystatin suspension. The adverse drug reactions reported for ≥ 1% of patients in either treatment group are presented in Table 1. Patients were examined daily, and treatment was continued for 3 days after symptoms had disappeared.

Table 1: Adverse Drug Reactions Reported for ≥ 1% of Patients in Either Treatment Group in a Randomized, Active-controlled, Open-label Clinical Trial of

DAKTARIN®System/Organ Class Adverse Drug Reaction	DAKTARIN oral gel (n=23) %	Nystatin suspension (n=24) %
Overall adverse reactions	34.8	8.3
Gastrointestinal Disorder		
Nausea	3 (13%)	1 (4.3%)
Regurgitation of food	2 (8.7%)	1 (4.3%)
Vomiting	3 (13%)	---

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of miconazole based on the comprehensive assessment of the available adverse event information. A causal relationship with miconazole cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of DAKTARIN® Oral Gel was evaluated in 88 adult patients with oral candidiasis or oral mycoses who participated in one randomized, active-controlled, double-blind clinical trial and three open-label clinical trials. These patients took at least one dose of DAKTARIN® Oral Gel and provided safety data.

Adverse reactions reported by DAKTARIN® Oral Gel-treated adult patients in the four clinical trials are shown in the following table.

Adverse Reactions Reported by Adult Patients in Four Clinical Trials of DAKTARIN® Oral Gel

System Organ Class Preferred Term	DAKTARIN Oral Gel % (N=88)
Nervous System Disorders	
Dysgeusia	1.1
Gastrointestinal Disorders	
Dry Mouth	2.3

Nausea	4.5
Oral discomfort	3.4
Vomiting	1.1
General Disorders and Administration Site Conditions	
Product taste abnormal	4.5

The safety of DAKTARIN® Oral Gel was evaluated in 23 pediatric patients with oral candidiasis who participated in one randomized, active-controlled, open-label clinical trial in pediatric patients aged ≤ 1 month to 10.7 years. These patients took at least one dose of DAKTARIN® Oral Gel and provided safety data.

Adverse reactions reported for DAKTARIN® Oral Gel-treated pediatric patients in the one clinical trial are presented in the following table.

Adverse Reactions Reported by Pediatric Patients in a Ramdomised, Active-Controlled, Open Label Clinical Trial of DAKTARIN® Oral Gel

System Organ Class Preferred Term	DAKTARIN® Oral Gel % (N=23)
Gastrointestinal Disorders	
Nausea	13.0
Regurgitation	8.7
Vomiting	13.0

<u>Postmarketing Data</u>

Additional adverse drug reactions first identified during postmarketing experience with Daktarin Oral GelBecause these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Therefore, the frequencies are provided according to the following convention (3,4):

Very Common :	≥ 1/10
Common:	≥ 1/100 and < 1/10
Uncommon:	≥ 1/1000 and < 1/100
Rare:	≥ 1/10000 and < 1/1000
Very rare:	≥ 1/10000, including isolated reports

The frequency 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 oedema and anaphylactic reaction, Hypersensitivity
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Choking (see Contraindications).
Gastrointestinal Disorders	
Very rare	Nausea, vomiting and diarrhea, anorexia, Stomatatis, Tongue discoloration
Hepatobiliary Disorders	
Very rare	Hepatitis
Skin and Subcutaneous Tissue Disorders	
Very rare	Angiodema, Lyell syndrome (Toxic epidermal necrolysis), Stevens-Johnson syndrome, Urticaria, Rash, Acute generalised exanthematous pustulosis, Drug reaction with eosinophilia and systemic symptoms.
General disorders	
Very rare	Malaise, chills and difficulty in accommodation

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at: https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In the event of accidental dosage, vomiting and diarrhoea may occur. Accidental ingestion of large quantities of DAKTARIN® may have clinically relevant implications for patients concomitantly using medication metabolised by cytochrome P450 subsystems 3A4 and/or 2C9 (see Interactions with other drugs).

Treatment of overdose is symptomatic and supportive. A specific antidote is not available. For the latest treatment advice, contact the Poisons Information Centre on 131126 in Australia or 0800 764 766 in New Zealand..

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Miconazole has shown fungistatic activity, in vitro, against a number of fungi.

Miconazole appears to act on the fungal cell wall membranes inducing permeability changes, which alter the ionic macromolecular composition of the affected cells by the inhibition of the ergosterol biosynthesis in fungi. The result is fungal cell necrosis.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

DAKTARIN® Oral Gel has a low bioavailability in man (25-30%) compared with intravenous administration because of the limited absorption of miconazole from the gastrointestinal tract.

Miconazole is systemically absorbed after administration as the oral gel. Administration of 60 mg dose of DAKTARIN® Oral Gel results in peak plasma concentrations of 31-49 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%).

Excretion

The absorbed portion of DAKTARIN® Oral Gel is largely metabolized; less than 1% of the administered dose is excreted unchanged in the urine. The terminal plasma half-life is 20-25 hours in most patients. The elimination half-life of miconazole is similar in any renally impaired patient. Plasma concentrations of miconazole are moderately reduced (approximately 50%) during hemodialysis.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. Refer to section 4.5: Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

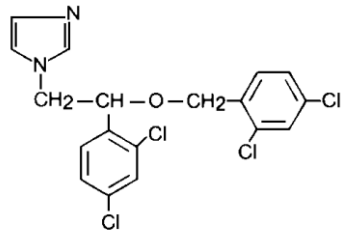
DAKTARIN® Oral Gel supplied in 15 g and 40 g tubes each with a measuring spoon.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical Name: Miconazole, 1-(2(2,4-dichlorophenyl)-2-(2,4-dichlorophenyl)methoxy]ethyl)-1H-imidazole, is a synthetic 1-phenethyl-imidazole derivative

Chemical formula: C18H14Cl4N2O

MW: 416.14

CAS number CAS-22916-47-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Pharmacy Medicine (S3)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

August 1991

10 DATE OF REVISION

July 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatted product information