

# DATA SHEET

## 1. PRODUCT NAME

DAKTARIN® Oral Gel

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains 20 mg of miconazole. The other ingredients are glycerol, purified water, pregelatinised potato starch, ethanol, polysorbate 20, sodium saccharin, orange flavour, and cocoa flavour. For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

A white, homogenous, orange-flavoured oral gel.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

DAKTARIN® oral gel is indicated for the treatment of clinically significant oral and gastrointestinal candidiasis.

### 4.2 Dose and method of administration

Dose:

Infants: For infants 6-24 months, one quarter ( $\frac{1}{4}$ ) of a measuring spoon\* of gel four times daily, or 20 mg/kg/day is recommended.

Children (2 years of age and older) and Adults: Half ( $\frac{1}{2}$ ) a measuring spoon\* of gel four times daily.

\* 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.

### Method of administration:

DAKTARIN® oral gel should be placed on the tongue and kept in 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 prosthesis it is recommended that DAKTARIN® oral gel be applied directly to the dentures in the evening and left on overnight. The treatment should be continued for at least one week after the symptoms have disappeared and generally until all clinical and mycological laboratory tests no longer indicate that active fungal infection is present.

### 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-administrating of the following drugs that are subject to metabolism by CYP3A4 (see **Interactions**):

- Substrates known to prolong the QT-interval eg. Astemizole, bepridil, cisapride, dofetilide, halofantrine, mizolastine, pimoziide, 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**):
  - Warfarin

#### 4.4 Special warnings and precautions for use

##### Co-administration with certain medicines

If the concomitant use of DAKTARIN® oral gel and anticoagulants such as warfarin is envisaged, the anticoagulant effect should be carefully monitored and titrated (see **Interactions**).

It is advisable to monitor miconazole and phenytoin levels, if these two drugs 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**).

##### Serious drug reactions

Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with DAKTARIN® Oral Gel. If a reaction suggesting sensitivity should occur, the 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. It is recommended that patients be informed about the signs of serious skin reactions, and that use of DAKTARIN Oral Gel be discontinued at the first appearance of skin rash.

##### Paediatric population

It is important to take into consideration the variability of the maturation of the swallowing function in infants, especially when giving DAKTARIN® Oral Gel to infants between the ages of 4-6 months. The lower age limit should be increased to 5-6 months of age for infants who are pre-term, or infants exhibiting slow neuromuscular development.

Particularly in infants and young children (aged 4 months – 2 years) caution is required, to ensure that the gel does not obstruct the throat. Hence, the gel is not to be applied to the back of the throat. Each dose is to be divided into smaller portions and applied into the mouth with a clean finger. Observe the patient for possible choking. Also due to the risk of choking, the gel must not be applied to the nipple of a breastfeeding woman for administration to an infant.

#### 4.5 Interaction with other medicines and other forms of interaction

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, pimoziide, 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 **Warnings and Precautions**):
  - Oral anticoagulants such as warfarin. Patients taking coumarin anticoagulants who are given DAKTARIN® oral gel should be monitored for anticoagulant effect and the dosage of the coumarin derivative adjusted, if necessary.
  - Oral hypoglycemics such as sulfonylureas. Miconazole can potentiate the effect of oral hypoglycaemics so that a reduction of their dosage may be needed.
  - Miconazole slows the metabolism of phenytoin and cyclosporine, tacrolimus and sirolimus. The dosage of these medicines may need to be reduced in patients using DAKTARIN® oral gel.
- Other drugs subject to metabolism by CYP3A4:
  - HIV protease inhibitors such as saquinavir: In vitro inhibition of the metabolism of saquinavir has been demonstrated. Therefore, the dosage may need to be reduced in patients receiving DAKTARIN® oral gel. However, clinically relevant interactions between oral miconazole and indinavir and ritonavir are not expected.
  - Certain antineoplastic agents such as vinca alkaloids, busulfan and docetaxel. Miconazole, when administered orally, may inhibit the metabolism of vinca alkaloids, busulfan and docetaxel resulting in elevation of plasma concentration. Dosage adjustment may be required in these instances.
  - Certain calcium channel blockers such as dihydropyridines and verapamil. There is the potential for increased plasma concentrations of these drugs when administered concomitantly with oral miconazole. Dosage adjustments may be required in these instances.
  - Certain immunosuppressive agents: cyclosporine, tacrolimus, sirolimus (rapamycin)
  - Others: alfentanil, alprazolam, brotizolam, buspirone, carbamazepine, cilostazol, disopyramide, ebastine, methylprednisolone, midazolam IV, reboxetine, rifabutin, sildenafil, and trimetrexate. Miconazole, when administered orally, may alter the metabolism of these drugs resulting in elevation of plasma concentration. Dosage adjustment may be required in these instances.
- Antagonism between miconazole and amphotericin B has been reported *in vitro* and *in vivo*. In studies miconazole and amphotericin combination were also shown to be antagonistic in antifungal activity against *Candida albicans*.

#### 4.6 Fertility, pregnancy and lactation

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

There are no data available on the excretion of miconazole in human milk; therefore caution should be exercised when breastfeeding women are using DAKTARIN Oral Gel.

#### 4.7 Effects on ability to drive and use machines

DAKTARIN® Oral Gel does not affect alertness or driving ability.

#### 4.8 Undesirable effects

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

<b>System Organ Class</b> Preferred Term	DAKTARIN® Oral Gel % (N=88)
<b>Nervous System Disorders</b>	
Dysgeusia	1.1
<b>Gastrointestinal Disorders</b>	
Dry Mouth	2.3
Nausea	4.5
Oral discomfort	3.4
Vomiting	1.1
<b>General Disorders and Administration Site Conditions</b>	
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 Randomised, Active-Controlled, Open Label Clinical Trial of DAKTARIN® Oral Gel

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

## Postmarketing Experience

Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience DAKTARIN® Oral Gel are presented below. The adverse drug reactions are presented by system/organ class, and are ranked by frequency, using the following convention:

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 reactions.

### Respiratory, thoracic and mediastinal disorders

Vary rare Choking (see Contraindications).

### Gastrointestinal system disorders

Very rare Nausea, vomiting and diarrhoea, anorexia, stomatitis, tongue discoloration

### Hepatobiliary disorders

Very rare Hepatitis.

### Skin and subcutaneous disorders

Very rare Angioedema, Lyell syndrome (Toxic Epidermal Necrolysis), Stevens Johnson syndrome, urticaria, rash, acute generalized exanthematous pustulosis, Drug reaction with eosinophilia and systemic symptoms

## 4.9 Overdose

### Treatment

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

In the event of accidental ingestion of large quantities of DAKTARIN® Oral Gel, an appropriate method of gastric emptying may be used, if considered necessary.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

Miconazole inhibits the biosynthesis of ergosterol in fungi and changes the composition of other lipid components in the membrane, resulting in fungal cell necrosis.

### 5.2 Pharmacokinetic properties

#### Absorption:

The oral bioavailability is low (25-30%) because there is little absorption of miconazole from the intestinal tract.

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%).

### Elimination:

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 half-life of plasma miconazole is 20 to 25 hours in most patients.

### Renal Impairment:

The elimination half-life of miconazole is similar in renally impaired patients. Plasma concentrations of miconazole are moderately reduced (approximately 50%) during hemodialysis.

## **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**

Alcohol  
Cocoa flavor  
Glycerol  
Orange flavor  
Pregelatinized potato starch  
Polysorbate  
Purified water  
Sodium saccharin

### **6.2 Incompatibilities**

None known

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Store below 30°C.

### **6.5 Nature and contents of container**

DAKTARIN® Oral Gel is supplied in 40 g tubes with a measuring spoon.

### **6.6 Special precautions for disposal**

No special requirements for disposal. Any unused medicine or water material should be disposed of in accordance with local requirements.

## **7. MEDICINE SCHEDULE**

Restricted Medicine

## **8. SPONSOR**

Johnson & Johnson (New Zealand) Limited

507 Mt Wellington Highway

Mt Wellington

Auckland 1060

## **9 DATE OF FIRST APPROVAL**

27 November 1980.

## **10 DATE OF REVISION OF THE TEXT**

21 March 2017