PRODUCT NAME
DAKTARIN® *ORAL GEL* 2%

DOSAGE FORMS AND STRENGTHS
White, homogeneous gel for oral use. Each gram contains 20mg of the active substance miconazole.
For excipients, see *List of Excipients*.

CLINICAL INFORMATION
Indications
Treatment of candidosis of the oropharyngeal cavity in adults and pediatric patients 4 months and older (see *Contraindications* and *Warnings and Precautions*).

Dosage and Administration
Oral Gel
5 mL (one measuring spoonful) of gel is equivalent to 124 mg miconazole.

Oropharyngeal candidosis
Infants: 4-24 months: 1.25 mL (1/4 measuring spoon) of gel, applied four times a day after meal. Each dose is to be divided into smaller portions and the gel should be applied to the affected area(s) with a clean finger. The gel is not to be swallowed immediately, but kept in the mouth as long as possible.

Adults and children 2 years of age and older: 2.5 mL (1/2 measuring spoon) of gel, applied four times a day after meals. The gel is not to be swallowed immediately, but kept in the mouth as long as possible.

Continue the treatment for at least a week after the symptoms have disappeared.
For oral candidosis, dental prostheses are to be removed at night and brushed with the gel.

Contraindications
DAKTARIN® Oral Gel is contraindicated in the following situations:

- In patients with hypersensitivity to miconazole, or to any of the excipients, or other imidazole derivatives.
- In infants less than 4 months of age or in those whose swallowing reflex is not yet sufficiently developed.
- In patients with liver dysfunction.
- Use in combination with the following drugs that are subject to metabolism by CYP3A4: (See *Interactions*)
  - 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.
- Use of miconazole oral gel in combination with the following drug that is subject to metabolism by CYP2C9 (See *Interactions*):
  - Warfarin

Warnings and Precautions

It is advisable to monitor miconazole and phenytoin levels, if these 2 drugs are used concomitantly.

In patients using certain oral hypoglycemics such as sulfonylureas, an enhanced therapeutic effect leading to hypoglycemia may occur during concomitant treatment with miconazole and appropriate measures must be considered (See *Interactions*).

It is important to take into consideration the variability of the maturation of the swallowing function in infants, especially when giving DAKTARIN® 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 breast-feeding woman for administration to an infant.

Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with DAKTARIN® (see *Adverse Reactions*). If a reaction suggesting hypersensitivity 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® (see *Adverse Reactions*). It is recommended that patients be informed about the signs of serious skin reactions, and that use of DAKTARIN® be discontinued at the first appearance of skin rash.

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 the plasma levels:

- Drugs subject to metabolism by CYP2C9 (see *Warnings and Precautions*):
  - Oral anticoagulants such as warfarin
  - Oral hypoglycemics such as sulfonylureas
  - 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.

Interactions

Pregnancy

At clinically relevant exposures, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of DAKTARIN® during pregnancy unless the benefit of therapy to the patient is considered to outweigh the risks to the fetus.

Breast-feeding

There are no data available on the excretion of miconazole in human milk; therefore caution should be exercised when prescribing DAKTARIN® to nursing women (see *Warnings and Precautions*).

Effects on Ability to Drive and Use Machines

DAKTARIN® does not affect alertness or driving ability.

Adverse Reactions

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 Table 1.

Table 1: 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 Table 2.

Table 2: Adverse Reactions Reported by Pediatric Patients in a Randomized, 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

Post-marketing experience

In Table 3, adverse reactions are presented by frequency category based on spontaneous reporting rates.

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

Table 3. Adverse Reactions Identified During Post-marketing Experience with DAKTARIN® by Frequency Category Estimated from Spontaneous Reporting Rates	
Immune System Disorders	
Very rare	Anaphylactic reaction, Hypersensitivity
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Choking (see *Contraindications)*
Gastrointestinal Disorders	
Very rare	Diarrhea, Stomatitis, Tongue discoloration
Hepatobiliary Disorders	
Very rare	Hepatitis
Skin and Subcutaneous Tissue Disorders	
Very rare	Angioedema, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Urticaria, Rash, Acute generalized exanthematous pustulosis, Drug reaction with eosinophilia and systemic symptoms

Overdose
Symptoms and signs
In the event of accidental overdose, vomiting and diarrhea may occur.

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

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Anti-infectives and antiseptics for local oral treatment and Imidazole derivatives, ATC Code: A01AB09 and A07AC01

Mechanism of action
Miconazole possesses an antifungal activity against the common dermatophytes and yeasts.

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

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
The absorbed portion of miconazole is largely metabolized; less than 1% of an administered dose is excreted unchanged in the urine. About 50% of an oral dose may be excreted in the feces partly metabolized and partly unchanged.

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

Special populations
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.

NON-CLINICAL INFORMATION
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.

PHARMACEUTICAL INFORMATION
List of Excipients
Alcohol
Cocoa flavor
Glycerol
Orange flavor
Pregelatinized potato starch
Polysorbate
Purified water
Sodium saccharin

Incompatibilities
None known.

Shelf Life
Refer to Expiry on Outer Carton

Storage Conditions
Store between 15 and 30^{o}C.
Keep out of the sight and reach of children.

Nature and Contents of Container
DAKTARIN® is supplied as a 2% oral gel.
The gel comes in tubes of 15g.

Instructions for Use and Handling
To open the tube, unscrew the cap and pierce the seal of the tube using the pin on the top of the cap.

BATCH RELEASER
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LAST DATE OF REVISION OF TEXT
31 August 2017 (CCDS 23 November 2016)