

NAME OF THE MEDICINAL PRODUCT

DAKTARIN *ORAL GEL*- Miconazole 2.0 % gel

DAKTARIN TABLETS- Miconazole 250 mg tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

DAKTARIN Oral Gel: Each gram contains 20 mg of the active substance miconazole.

DAKTARIN Tablets: Each tablet contains 250 mg of the active substance miconazole.

For excipients, see List of Excipients

PHARMACEUTICAL FORM

DAKTARIN Oral Gel: 20 mg/g oral gel: white, homogeneous gel for oral use.

DAKTARIN Tablets: 250 mg buccal tablet: white, circular, flat, bevel-edged tablets for oral use.

CLINICAL PARTICULARS

Therapeutic Indications

Oral Gel

Therapeutic and prophylactic treatment of candidosis of the oropharyngeal cavity and the gastrointestinal tract.

Tablets

Therapeutic and prophylactic treatment of digestive tract mycoses.

Posology And Method Of Administration

Oral Gel

(Provided measuring spoon is equivalent to 124 mg per 5 mL).

Oropharyngeal candidosis

Infants: 6-24 months: 1.25 mL (1/4 measuring spoon) of gel, applied four times a day. Each dose should be divided into smaller portions and the gel should be applied to the affected area(s). The gel should not 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. The gel should not be swallowed immediately, but kept in the mouth as long as possible.

The treatment should be continued for at least a week after the symptoms have disappeared.

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

Gastrointestinal tract candidosis

The gel may be used for infants (≥ 6 months of age), children, and adults who have difficulty swallowing tablets. The dosage is 20 mg per kg body weight per day, administered in 4 divided doses. The daily dose should not exceed 250 mg (10 mL Oral Gel) four times a day.

The treatment should be continued for at least a week after the symptoms have disappeared.

Tablets

Adults: One tablet four times a day.

Children: The dosage should be adjusted to 20 mg per kg body weight per day, administered in 4 divided doses. The daily dose should not exceed 250 mg four times a day.

The treatment should be continued for at least a week after the symptoms have disappeared.

Contraindications

DAKTARIN Oral Gel and Tablets are contraindicated in the following situations:

- In patients with a known hypersensitivity to miconazole or to any of the excipients
- In infants less than 6 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. Interactions with Other Medicinal Products and Other Forms of Interaction)
 - 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.

Special Warnings and Special 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.

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 should be considered (See 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.

Interactions 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 Contraindications):

- 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.

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 effects. If necessary, their dosage should be reduced and, where appropriate, plasma levels monitored:

- Drugs subject to metabolism by CYP2C9 (see Special Warnings and Special Precautions for Use):
 - 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, cilostazol, disopyramide, ebastine, methylprednisolone, midazolam IV, reboxetine, rifabutin, sildenafil, and trimetrexate.

Pregnancy and Lactation

Although there is no evidence that miconazole is embryotoxic or teratogenic in animals, potential hazards of prescribing DAKTARIN 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 prescribing DAKTARIN to nursing women.

Effects on Ability to Drive and Use Machines

DAKTARIN does not affect alertness or driving ability.

Undesirable Effects

Clinical trial data

The safety of DAKTARIN Oral Gel was evaluated in 88 adult patients with oral candidiasis or oral mycoses who participated in one randomised, 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 drug reactions (ADRs) reported by DAKTARIN Oral Gel-treated adult patients in the four clinical trials are shown in Table 1.

Table 1. Adverse Drug 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 paediatric patients with oral candidiasis who participated in one randomised, active-controlled, open-label clinical trial in paediatric patients aged ≤ 1 month to 10.7 years. These patients took at least one dose of DAKTARIN Oral Gel and provided safety data.

Adverse drug reactions reported for DAKTARIN Oral Gel-treated paediatric patients in the one clinical trial are presented in Table 2.

Table 2. Adverse Drug Reactions Reported by Paediatric Patients in a Randomised, 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

Adverse drug reactions first identified during post-marketing experience with DAKTARIN are included in Table 3. In the table, the frequencies are provided according to the following convention:

Very common	$\geq 1/10$
Common	$\geq 1/100$ and $< 1/10$
Uncommon	$\geq 1/1000$ and $< 1/100$
Rare	$\geq 1/10000$ and $< 1/1000$
Very rare	$< 1/10000$, including isolated reports

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

Table 3. Adverse Drug Reactions Identified During Post-Marketing Experience with DAKTARIN by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders

Very rare Anaphylactic reaction, Angioedema, Hypersensitivity

Respiratory, Thoracic and Mediastinal Disorders

Very rare Choking (see Section Contraindications)

Gastrointestinal Disorders

Very rare Diarrhoea, Stomatitis, Tongue discolouration

Hepatobiliary Disorders

Very rare Hepatitis

Skin and Subcutaneous Tissue Disorders

Very rare Toxic epidermal necrolysis, Stevens-Johnson syndrome, Urticaria, Rash

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 gastric emptying may be used, if considered necessary. (See Interactions with Other Medicinal Products and Other Forms of Interaction.)

PHARMACOLOGICAL PROPERTIES

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.

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.

Pharmacokinetic Properties

Absorption:

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

Maximum plasma levels are reached 2 to 4 hours post-dose in most subjects. Peak plasma concentration following a single 1000 mg oral dose was 1160 ng/mL.

Oral Gel: 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.

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.

PHARMACEUTICAL PARTICULARS

List of Excipients

The inactive ingredients of the oral gel are glycerol, purified water, pregelatinized potato starch, alcohol, polysorbate, sodium saccharin, cocoa flavor, orange flavor.

The inactive ingredients of the tablets are sucrose, lactose, maize starch, sodium saccharin, sodium lauryl sulphate, polyvidone, rice starch, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica.

Incompatibilities

None known.

Shelf Life

Observe expiry date on the outer pack.

Special Precautions for Storage

Store between 15 and 30° C.

Keep out of reach of children.

Nature and Contents of Container

DAKTARIN is supplied as 250 mg tablets and 2% oral gel.

The gel comes in tubes of 40 g with a measuring spoon of 5 ml (corresponding with 124 mg miconazole).

Instructions for Use and Handling <and Disposal>

Oral gel: To open the tube unscrew the cap. Then pierce the seal of the tube by means of the pin on the top of the cap.

MANUFACTURED BY

To be provided locally

See outer carton.

DATE OF REVISION OF THE TEXT

March 2010