Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Daktarin 20 mg/g Oral Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 124 mg of miconazole.
Each gram contains 20 mg miconazole.

Excipients with known effect
Ethanol 7.85 mg/g
0.17 mg/g orange flavour containing allergens (citral, citronellol, d-limonene, geraniol, linalool)
0.46 mg/g cocoa flavour containing allergens (benzyl benzoate and benzyl alcohol).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral gel.
White homogeneous gel having an orange taste.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of superficial fungal (e.g. *Candida*) infections of the oral cavity and gastro-intestinal tract in adults and paediatric patients 4 months and older.

4.2 Posology and method of administration

For oral administration.

Oropharyngeal candidosis

1 measuring spoon (provided) is equivalent to 124 mg miconazole per 5 mL gel.

Infants: 4-24 months: 1.25ml (1/4 measuring spoon) of gel, applied four times a day after meals. Each dose should be divided into smaller portions and the gel should be applied to the affected area(s) with a clean finger. The gel should not be applied to the back of the throat due to possible choking. 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: 2.5ml (1/2 measuring spoon) of gel, applied four times a day after meals. 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 (≥4 months of age), children and adults who have difficulty swallowing tablets. The dosage is 20mg per kg body weight per day, administered in four individual doses. The daily dose should not exceed 250mg (10ml oral gel) four times a day. The treatment should be continued for at least a week after the symptoms have disappeared.

4.3 Contraindications

Hypersensitivity to the active substance, other imidazole derivatives or to any of the excipients listed in Section 6.1.

In infants less than 4 months of age or in those whose swallowing reflex is not yet sufficiently developed (see section 4.4).

Co-administration with warfarin is contraindicated except when oral miconazole gel is specifically prescribed and used under medical supervision with close monitoring of INR (see section 4.4, 4.5 and 4.8)In patients with liver dysfunction.

Coadministration of the following drugs that are subject to metabolism by CYP3A4 or CYP2C9: (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

Miconazole is systemically absorbed and is known to inhibit CYP2C9 and CYP3A4 (see Section 5.2 Pharmacokinetic Properties) 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 Section 4.3 Contraindications, Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction and Section 4.8 Undesirable effects).

The label (outer carton and tube) will state: WARNING: Do not use if you are taking warfarin unless Daktarin is prescribed by your doctor.

If the concomitant use of Daktarin and an oral anticoagulant such as warfarin is planned, the anticoagulant effect must be carefully monitored and titrated.

Patients should be advised that if they experience unexpected bleeding or bruising, nosebleeds, coughing up blood, blood in the urine, black tarry stools or coffee ground vomit, to stop treatment with miconazole and seek medical advice.

Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with miconazole formulations. If a reaction suggesting hypersensitivity or irritation 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 (see *Adverse Reactions*). 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.

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 must be considered (See Section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction).

It is important to take into consideration the variability of the maturation of the swallowing reflex 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

Choking in infants and young children.

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 and 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.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose (2.5 ml), that is to say essentially 'sodium-free'.

This medicinal product contains 7.85 mg of ethanol in each gram of oral gel. The amount in each dose (2.5 ml) is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.
This medicinal product contains orange flavour with allergens (citral, citronellol, d-limonene, geraniol and linalool) and cocoa flavour with allergens (benzyl benzoate and benzyl alcohol) which may cause allergic reactions.

4.5 Interaction with other medicinal products 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 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 and CYP2C9 (See Section 4.3 Contraindications);

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

Co-administration with warfarin is contraindicated except when oral miconazole gel is specifically prescribed and used under medical supervision with close monitoring of INR (see section 4.3, 4.4, and 4.8)

When coadministered 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 events. If necessary, reduce their dosage and, where appropriate, monitor plasma levels:

Drugs subject to metabolism by CYP2C9 (see Section 4.4 Special Warnings and Precautions for Use);
· 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, bulsulfan and docetaxel
· Certain calcium channel blockers such as dihydropyridines and verapamil
· Certain immunosuppressive agents: cyclosporin, tacrolimus, sirolimus (rapamycin)
· Others: carbamazepine, cilostazol, disopyramide, buspirone, alfentanil, sildenafil, alprazolam, brotizolam, midazolam IV, rifabutin, methylprednisolone, trimetrexate, ebastine and reboxetine.

4.6 Fertility, pregnancy and lactation

In animal studies, miconazole has not shown teratogenic effects, but is foetotoxic at high oral doses. The significance of this in relation to man is not known.

Safety in human pregnancy has not been established and the drug should not be used in pregnant women unless considered absolutely essential by the physician. The potential hazards should be balanced against the possible benefits.

It is not known whether miconazole or its metabolites are excreted in human milk. Caution should be exercised when prescribing Daktarin Oral Gel to nursing mothers.

4.7 Effects on ability to drive and use machines

Daktarin Oral Gel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Increases in INR and bleeding events such as epistaxis, contusion, haematuria, melaena, haematemesis, haematoma and haemorrhages have been reported in patieints treated with oral anticoagulants such as warfarin in association with miconazole oral gel (see sections 4.3, 4.4 and 4.5). Some events had fatal outcomes.

The safety of DAKTARIN Oral Gel was evaluated in 111 patients with oral candidiasis or oral mycoses who participated in 5 clinical trials. Of these 111 patients, 88 were adults with oral candidiasis or oral mycoses who participated in 1 randomised, active-controlled, double-blind clinical trial and 3 open-label clinical trials. The other 23 patients were paediatric patients with oral candidiasis who participated in 1 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.

Adult Patients
Based on the pooled safety data from the 4 clinical trials in adults, common ADRs reported included nausea (4.5%), product taste abnormal (4.5%), oral discomfort (3.4%), dry mouth (2.3%), dysgeusia (1.1%), and vomiting (1.1%).

Paediatric Patients
In the 1 paediatric clinical trial, the frequency of nausea (13.0%) and vomiting (13.0%) was very common, and regurgitation (8.7%) was common. As identified through post-marketing experience, choking may occur in infants and young children (See Section 4.3 Contraindications and Section 4.4 Special Warnings and Special Precautions). The frequency, type, and severity of other ADRs in children are expected to be similar to that in adults.
The frequency categories use the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available clinical trial data).

Table A includes all identified ADRs, including those that that have been reported from post-marketing experience.

Table A: Adverse Drug Reactions in Patients Treated with DAKTARIN Oral Gel

System Organ Class	**Adverse Drug Reactions**		
	Frequency Category		
	Common (≥1/100 to < 1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Not Known**
Immune System Disorders			Anaphylactic reaction, Hypersensitivity
Nervous System Disorders		Dysgeusia	
Respiratory, Thoracic and Mediastinal Disorders			Choking
Gastrointestinal Disorders	Dry mouth, Nausea, Oral discomfort, Vomiting, Regurgitation		Diarrhoea, Stomatitis, Tongue discolouration
Hepatobiliary Disorders			Hepatitis

Skin and Subcutaneous Tissue Disorders			Angioedema, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Urticaria, Rash. Acute generalised exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms
General Disorders and Administration Site Conditions	Product taste abnormal		

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, website: www.hpra.ie.

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.

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 (*Staphylococcus* and *Streptococcus* spp).

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 (based on 19 patients with renal impairment). Plasma concentrations of miconazole are moderately reduced (approximately 50%) during hemodialysis.

5.3 Preclinical safety data

Preclinical data reveal no specific hazard for humans based on conventional studies in animals of local irritation, single and repeated dose toxicity, genotoxicity, and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised potato starch
Ethanol
Polysorbate 20 (E432)
Sodium saccharin
Cocoa flavour (containing benzyl alcohol, benzyl benzoate and ethanol)
Orange flavour (containing citral, citronellol, linalool, geraniol and d-limonene)
Glycerol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

An aluminium collapsible membrane tube with polypropylene screw cap containing 30 g or 40 g gel.

A 5 ml polypropylene spoon, marked with ¼ and ½ spoon graduations (1.25 & 2.5 ml) is provided.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Johnson & Johnson (Ireland) Limited
Airton Road
Tallaght
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0330/048/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 July 1979

Date of last renewal: 10 July 2009

10 DATE OF REVISION OF THE TEXT

July 2023