SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Daktazol (Miconazole 2% oral gel)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of Daktazol oral gel contains 20 mg of miconazole.

Excipient (S) with known effect:

- This product contains Methyl paraben and Propyl paraben, which may cause allergic reactions (possibly delayed).
- This product contains Propylene glycol, If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Oral gel

White Opaque fluid Homogeneous gel with orange odor and taste.

4. CLINICAL PARTICULARS

4.1. *THERAPEUTIC INDICATIONS*

Oral treatment of candidosis of the oropharynx.

Daktazol Oral Gel is for use in adults, children and infants 4 months and older.

4.2. *POSOLOGY AND METHOD OF ADMINISTRATION*

For oral administration.
Oropharyngeal candidosis
Infants: 4-24 months: 1.25 mL 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: 2.5 mL 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.

4.3. *CONTRAINDICATIONS*

Known hypersensitivity to miconazole, 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.

In patients with liver dysfunction.
Coadministration of the following drugs that are subject to metabolism by CYP3A4. (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 SPECIAL 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 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction and section 4.8 Undesirable effects).If the concomitant use of Daktazol Oral Gel with an oral anticoagulant such as warfarin is planned, caution should be excercised and the anticoagulant effect must be carefully monitored and titrated (see section 4.5).

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 Daktazol and with other miconazole formulations (see section 4.8). If a reaction suggesting hypersensitivity or irritation should occur, the treatment should be discontinued.

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

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 should not be applied to the back of the throat.Each dose should 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.

It is important to take into consideration the variability of the maturation of the swallowing function in infants, especially when giving miconazole 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.

Serious skin reactions (e.g. Toxic epidermal necrolysis and Stevens-Johnson syndrome) have been reported in patients receiving Daktazol Oral Gel (see section 4.8). It is recommended that patients be informed about the signs of serious skin reactions, and that use of Daktazol Oral Gel be discontinued at the first appearance of skin rash.
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
This medicine contains 0.00785 g of alcohol (ethanol) in each 1 g which is equivalent to 0.00785 mg/mg (0.785 % w/w). The amount in 1 g 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.

Orange flavour and cocoa flavour
This medicinal product contains orange flavour (containing: citral, citronellol, linalool, geraniol, d-limonene) and cocoa flavour (containing: benzyl alcohol, benzyl benzoate) that may cause allergic reactions.
This medicinal product contains 0.000000017 mg of benzyl benzoate in each single maximum dose for an adult (10 ml of oral gel). Benzyl benzoate may cause mild local irritation.

Benzyl alcohol

Medicinal product contains 0.0000000285 mg of benzyl alcohol in each single maximum dose for an adult (10 ml of oral gel). Benzyl alcohol may cause allergic reactions.

Administration of benzyl alcohol is associated with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children.

Pregnant or breastfeeding women should ask doctor for advice before taking this medicine. This is because large amounts of benzyl alcohol can build-up in their body and may cause side effects (called “metabolic acidosis”).

Patients with a kidney disease should ask doctor for advice before taking this medicine. This is because large amounts of benzyl alcohol can build-up in their body and may cause side effects (called “metabolic acidosis”). High volumes of benzyl alcohol should be administrated with caution and only if necessary, especially in patients with kidney impairment because of the risk of accumulation of toxicity (metabolic acidosis).
Benzyl alcohol may cause mild local irritation.

4.5. *INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS*

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;

- 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

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

Drugs subject to metabolism by CYP2C9 9 (see Section 4.4 Special warnings and precautions for use);

- Oral anticoagulants such as warfarin
- 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, busulfan 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 animals, miconazole has shown no teratogenic effects but is foetotoxic at high oral doses. The significance of this to man is unknown. However, as with other imidazoles, Daktazol Oral Gel should be avoided in pregnant women if possible. The potential hazards should be balanced against the possible benefits.

It is not known whether miconazole is excreted in human milk. Caution should be exercised when prescribing Daktazol Oral Gel to nursing mothers.

4.7. *EFFECTS ON ABILITY TO DRIVE AND USE MACHINES*

Daktazol should not affect alertness or driving ability.

4.8. *UNDESIRABLE EFFECTS*

The safety of miconazole 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 Miconazole Oral Gel and provided safety data.

Based on the pooled safety data from these 5 clinical trials (adult and paediatric), the most commonly reported (≥ 1% incidence) ADRs were nausea (6.3%), product taste abnormal (3.6%), vomiting (3.6%), oral discomfort (2.7%), regurgitation (1.8%), and dry mouth (1.8%). Dysgeusia was reported in 0.9% of patients.

Adult Patients

Based on the pooled safety data from the 4 clinical trials in adults, common adverse reactions 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 adverse reactions in children are expected to be similar to that in adults.

Description of selected adverse reactions

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

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

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: Adverse Drug Reactions in Patients Treated with MICONAZOLE Oral Gel or Tablets

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, Angioedema, 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		

4.9. **Reporting of side effects**

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. By reporting side affects you can help provide more information on the safety of this medicine.

You can report side effects through contacting us to our address:
Jerusalem Pharmaceuticals Co. Ltd
Al-Bireh - Ramallah - Palestine
P.O. Box: 3570
Tel. +970-597867777 or +970-2-2406550
Fax: +970-2-2403246
E-mail: qppv@jepharm.ps
www.jepharm.ps :Internet Home Page

:on-line reporting form at the following link fill the to ministry of health directly or
https://www.pharmacy.moh.ps/index/Form/Language/ar

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 Daktazol an appropriate method of gastic emptying may be used, if considered necessary

5. PHARMACOLOGICAL PROPERTIES

5.5. *PHARMACODYNAMICS PROPERTIES* d

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.
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. Plasma concentrations of miconazole are moderately reduced (approximately 50%) during hemodialysis. About 50% of an oral dose may be excreted in the faeces partly metabolized and partly unchanged.

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

Edetate disodium
Methylparaben sodium
Propylparaben sodium
Saccharin sodium
Propylene glycol
Glycerine
Orange oil
Carbopol
Triethanolamine
Purified water.

6.2. INCOMPATIBILITIES

Not applicable .

6.3. SHELF-LIFE

4 years.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C

6.5. NATURE AND CONTENT OF CONTAINER

1 Laminated Aluminum tube containing 40 g of gel / box

6.6. INSTRUCTIONS FOR USE AND HANDLING, AND DISPOSAL

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Jerusalem Pharmaceuticals Co.LTD
Al-Bireh, Ramallah, West Bank, Palestine.
P.O. Box 3570
Tel : 0097022406550 / Fax: 0097022403246

8. MARKETING AUTHORIZATION NUMBER

08874/NMR/2021

9. DATE OF FIRST AUTHORIZATION

April 5, 2023

10. DATE OF REVISION

12/07/2023