Summary of Product Characteristics

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1.0 Name of the medicinal product

Ketoconazole Tablets USP 200 mg

2.0 Qualitative and Quantitative Composition

Each uncoated Tablet contains:

Ketoconazole USP 200mg

For the full list of excipients, see section 6.1

3. Pharmaceutical Form

Tablets (uncoated)

White to off white, round, flat, uncoated tablets with beveled edges and having a score line on one side.

4. Clinical particulars

4.1 Therapeutic Indications

Ketoconazole tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole tablets should not be used for fungal meningitis because it penetrates poorly into the cerebral-spinal fluid.

Ketoconazole tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.

4.2 Posology and Method of administration

Posology

Adults

The recommended starting dose of ketoconazole tablets is a single daily administration of 200 mg (one tablet). If clinical responsiveness is insufficient within the expected time, the dose of ketoconazole tablets may be increased to 400 mg (two tablets) once daily.

Children

Children weighing from 15 to 30 kg: half a tablet (100 mg) once daily with a meal.

Children weighing more than 30 kg: same as for adults.

Method of administration:

Oral: Ketoconazole should be taken during meals for maximal absorption.

4.3 Contraindications

Drug Interactions

Coadministration of a number of CYP3A4 substrates such as dofetilide, quinidine cisapride and pimozide is contraindicated with ketoconazole tablets. Coadministration with ketoconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious adverse reaction may occur. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and sometimes resulting in life-threatening ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia.

Additionally, the following other drugs are contraindicated with ketoconazole tablets: methadone, disopyramide, dronedarone, ergot alkaloids such as dihydroergotamine, ergometrine, ergotamine, methylergometrine, irinotecan, lurasidone, oral midazolam, alprazolam, triazolam, felodipine, nisoldipine, ranolazine, tolvaptan, eplerenone, lovastatin, simvastatin and colchicine.

Enhanced Sedation

Coadministration of ketoconazole tablets with oral midazolam, oral triazolam or alprazolam has resulted in elevated plasma concentrations of these drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. Concomitant administration of ketoconazole tablets with oral triazolam, oral midazolam or alprazolam is contraindicated.

Myopathy

Coadministration of CYP3A4 metabolized HMG-CoA reductase inhibitors such as simvastatin, and lovastatin is contraindicated with ketoconazole tablets.

Ergotism

Concomitant administration of ergot alkaloids such as dihydroergotamine and ergotamine with ketoconazole tablets is contraindicated.

Liver Disease

The use of ketoconazole tablets is contraindicated in patients with acute or chronic liver disease.

Hypersensitivity

Ketoconazole tablets USP, 200 mg is contraindicated in patients who have shown hypersensitivity to the drug**.**

4.4 Special warnings and special precautions for use

General

Ketoconazole tablets have been demonstrated to lower serum testosterone. Once therapy with ketoconazole tablets has been discontinued, serum testosterone levels return to baseline values. Testosterone levels are impaired with doses of 800 mg per day and abolished by 1600 mg per day. Clinical manifestations of decreased testosterone concentrations may include gynecomastia, impotence and oligospermia.

Information for Patients

Patients should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate biochemical testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, abdominal pain, jaundice, dark urine or pale stools

4.5 Interaction with other medicinal products and other forms of interaction.

Drug Class	Contraindicated	Not Recommended	Use with Caution	Comments
	Under no circumstances should the drug be co administered with ketoconazole tablets, and up to one week after discontinuation of treatment with ketoconazole.	Under no circumstances should the drug be co administered with ketoconazole tablets, and up to one week after discontinuation of treatment with ketoconazole.	Under no circumstances should the drug be co administered with ketoconazole tablets, and up to one week after discontinuation of treatment with ketoconazole.	
Alpha Blockers		Tamsulosin		
Analgesics	methadone		alfentanil, buprenorphine IV and sublingual, fentanyl, oxycodone, sufentanil	Methadone: The potential increase in plasma concentrations of methadone when coadministered with ketoconazole tablets may increase the risk of serious cardiovascular events including QT prolongation and torsade de pointes, or respiratory or CNS depression. Fentanyl: The potential increase in plasma concentrations of fentanyl when coadministered with ketoconazole tablets may increase the risk of potentially fatal respiratory depression. Sufentanil: No human pharmacokinetic data of an interaction with ketoconazole are available. In vitro data suggest that sufentanil is metabolized by

				CYP3A4 and so potentially increased sufentanil plasma concentrations would be expected when coadministered with ketoconazole tablets.
Antiarrhythmics	disopyramide, dofetilide, dronedarone, quinidine		digoxin	Disopyramide, dofetilide, dronedarone, quinidine: The potential increase in plasma concentrations of these drugs when coadministered with ketoconazole may increase the risk of serious cardiovascular events including QT prolongation. Digoxin: Rare cases of elevated plasma concentrations of digoxin have been reported. It is not clear whether this was due to the combination of therapy. It is, therefore, advisable to monitor digoxin concentrations in patients receiving ketoconazole.
Antibacterials		rifabutin	telithromycin	Rifabutin Telithromycin: A multiple- dose interaction study with ketoconazole showed that Cmax of telithromycin was increased by 51% and AUC by 95%.
Anticoagulants and Antiplatelet Drugs		rivaroxaban	cilostazol, coumarins, dabigatran	Cilostazol: Concomitant administration of single doses of cilostazol 100 mg and ketoconazole 400 mg approximately doubled cilostazol concentrations and altered (increase/decrease) the concentrations of the active metabolites of cilostazol. Coumarins: Ketoconazole may enhance the anticoagulant effect of coumarin-like drugs, thus the anticoagulant effect should be carefully titrated and monitored. Dabigatran: In patients with moderate renal impairment (CrCL 50 mL/min to $\leq$ 80 mL/min), consider reducing the dose of dabigatran to 75 mg twice daily when it is coadministered with ketoconazole.

Antidiabetics		repaglinide, saxagliptin		
Antihelmintics and Antiprotozoals		praziquantel		
Antivirals			indinavir, maraviroc, saquinavir	
Beta Blockers			nadolol	
Diuretics	eplerenone			The potential increase in plasma concentrations of eplerenone when coadministered with ketoconazole tablets may increase the risk of hyperkalemia and hypotension.
Gastrointestinal Drugs	cisapride		aprepitant	Cisapride: Oral ketoconazole potently inhibits the metabolism of cisapride resulting in a mean eight-fold increase in AUC of cisapride, which can lead to serious cardiovascular events including QT prolongation.
Lipid Regulating Drugs	lovastatin, simvastatin		atorvastatin	The potential increase in plasma concentrations of atorvastatin, lovastatin and simvastatin when coadministered with ketoconazole tablets may increase the risk of skeletal muscle toxicity, including rhabdomyolysis
Urological Drugs			fesoterodine, sildenafil, solifenacin, tadalafil, tolterodine, vardenafil	Vardenafil: A single dose of 5 mg of vardenafil should not be exceeded when coadministered with ketoconazole.

Antidiabetics		repaglinide, saxagliptin		

4.6 Pregnancy and lactation

Pregnancy:

Teratogenic effects

Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day (2 times the maximum recommended human dose, based on body surface area

comparisons). However, these effects may be related to maternal toxicity, evidence of which also was seen at this and higher dose levels.

There are no adequate and well controlled studies in pregnant women. Ketoconazole tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No teratogenic Effects

Ketoconazole has also been found to be embryotoxic in the rat when given in the diet at doses higher than 80 mg/kg during the first trimester of gestation.

In addition, dystocia (difficult labor) was noted in rats administered oral ketoconazole during the third trimester of gestation. This occurred when ketoconazole was administered at doses higher than 10 mg/kg (about one fourth the maximum human dose, based on body surface area comparison).

Nursing Mothers

Ketoconazole has been shown to be excreted in the milk. Mothers who are under treatment with ketoconazole tablets should not breast feed.

Pediatric Use

Ketoconazole tablets have not been systematically studied in children of any age, and essentially no information is available on children under 2 years. Ketoconazole tablets should not be used in pediatric patients unless the potential benefit outweighs the risks.

Lactation:

Since ketoconazole is excreted in the milk, mothers who are under treatment should not breast-feed whilst being treated with ketoconazol tablets.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

The safety of ketoconazole 2% shampoo was evaluated in 2890 subjects who participated in 22 clinical trials. Ketoconazole 2% shampoo was administered topically to the scalp and/or skin. Based on pooled safety data from these clinical trials, there were no ADRs reported with an incidence >1%.

The following table displays ADRs that have been reported with the use of Ketoconazole 2% Shampoo from either clinical trial or postmarketing experiences.

The displayed 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)

Not known (cannot be estimated form the available clinical trial data).

System Organ Class	Adverse Drug Reactions		
	Frequency Category		
	Uncommon (>1/1,000 to <1/100)	**Rare** (>1/10,000 and <1/1,000)	**Not Known**
Immune System disorders		Hypersensitvity	
Nervous System Disorders		Dysgeusia	
Infections and Infestations	Folliculitis		
Eye Disorders	Increased lacrimation	Eye irritation	
Skin and Subcutaneous Tissue Disorders	Alopecia Dry skin Hair texture abnormal Rash Skin burning sensation	Acne Dermatitis contact Skin disorder Skin exfoliation	Angioedema Urticaria Hair colour changes
General Disorders and Administration Site Conditions	Application site erythema Application site irritation Application site pruritus Application site reaction	Application site hypersensitivity Application site pustules	

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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

In the event of acute accidental overdose, treatment consists of supportive and symptomatic measures. Within the first hour after ingestion, activated charcoal may be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Azole Antifungals

As an antifungal, ketoconazole is structurally similar to imidazole, and interferes with the fungal synthesis of ergosterol, a constituent of fungal cell membranes, as well as certain enzymes. As with all

azole antifungal agents, ketoconazole works principally by inhibiting the enzyme cytochrome P450 14α-demethylase (CYP51A1).[29] This enzyme participates in the sterol biosynthesis pathway that leads from lanosterol to ergosterol. Lower doses of fluconazole and itraconazole are required to kill fungi compared to ketoconazole, as they have been found to have a greater affinity for fungal cell membranes.

Resistance to ketoconazole has been observed in a number of clinical fungal isolates, including Candida albicans. Experimentally, resistance usually arises as a result of mutations in the sterol biosynthesis pathway. Defects in the sterol 5-6 desaturase enzyme reduce the toxic effects of azole inhibition of the 14-alpha demethylation step. Multidrug-resistance (MDR) genes can also play a role in reducing cellular levels of the drug. As azole antifungals all act at the same point in the sterol pathway, resistant isolates are normally cross-resistant to all members of the azole family

5.2 Pharmacokinetics:

Absorption

Ketoconazole is a weak dibasic agent and thus requires acidity for dissolution and absorption.

Mean peak plasma concentrations of approximately 3.5 mcg/mL are reached within 1 to 2 hours, following oral administration of a single 200 mg dose taken with a meal. Oral bioavailability is maximal when the tablets are taken with a meal.

Absorption of ketoconazole tablets is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as acid neutralizing medicines (e.g. aluminum hydroxide) and gastric acid secretion suppressors (e.g. H2-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases. (See Section PRECAUTIONS: DRUG INTERACTIONS.) Absorption of ketoconazole under fasted conditions in these subjects is increased when ketoconazole tablets are administered with an acidic beverage (such as non-diet cola). After pretreatment with omeprazole, a proton pump inhibitor, the bioavailability of a single 200 mg dose of ketoconazole under fasted conditions was decreased to 17% of the bioavailability of ketoconazole administered alone. When ketoconazole was administered with non-diet cola after pretreatment with omeprazole, the bioavailability was 65% of that after administration of ketoconazole alone.

Distribution

In vitro, the plasma protein binding is about 99% mainly to the albumin fraction.

Ketoconazole is widely distributed into tissues; however, only a negligible proportion reaches the cerebrospinal fluid.

Metabolism

Following absorption from the gastrointestinal tract, ketoconazole tablets are converted into several inactive metabolites. In vitro studies have shown that CYP3A4 is the major enzyme involved in the

metabolism of ketoconazole. The major identified metabolic pathways are oxidation and degradation of the imidazole and piperazine rings, by hepatic microsomal enzymes. In addition, oxidative O-dealkylation and aromatic hydroxylation does occur. Ketoconazole has not been demonstrated to induce its own metabolism.

Elimination

Elimination from plasma is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Approximately 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged drug. The major route of excretion is through the bile into the intestinal tract with about 57% being excreted in the feces.

5.3 Preclinical safety data

None stated.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, Microcrystalline Cellulose, maize Starch, Sodium Methyl Paraben, Sodium Propyl Paraben, Purified Talc, Magnesium Stearate, Colloidal Anhydrous Silica, Sodium Starch Glycolate, Croscarmellose Sodium

6.2 Incompatibilities

None reported

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place. Protect from light.

6.5 Nature and contents of container

10×10's Blister

6.6 Instructions for use and handling and disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance

with local requirements.

7.0 MARKETING AUTHORISATION HOLDER

Medicamen Biotech Limited

SP-1192 A&B, PHASE - IV,

Industrial Area, Bhiwadi - 301 019

Distt. Alwar, Rajasthan,

India.

8.0 NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

Registration No 08436/06661/NMR/2018

9.0 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Approval date 01-03-2023

10.0 Date of revision of the text

July 2023