1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

KETAZOL TABLET

COMPOSITION

Each tablet **KETAZOL TABLET** contains 200 mg of ketoconazole.

Excipients:

Croscarmellose sodium, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, povidone, purified talc, sodium sulphite anhydrous.

Contains sugar: Lactose monohydrate 50,00 mg.

CATEGORY AND CLASS

A.20.2.2 Antimicrobial (Chemotherapeutic) agents: Fungicides.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Ketoconazole is a synthetic imidazole dioxolane derivative, active (*in vitro*) against dermatophytes, yeasts and other pathogenic fungi. *In vitro* ketoconazole is fungicidal and, therefore, suppresses the formation of mycelia. *In vivo*, at therapeutic levels, however, it is primarily fungistatic. Ketoconazole acts in the case of *C. albicans* by inhibiting lanosterol demethylation in the biosynthesis of ergosterol,

resulting in cell membrane defects.

Pharmacokinetic properties

Absorption

Ketoconazole is a weak dibasic substance and thus requires acidity for dissolution and absorption. Mean peak plasma levels of approximately 3, 5 μg/mℓ are reached within 1 to 2 hours following oral administration of a single 200 mg dose taken with a meal.

Distribution

In vitro, the plasma protein binding is about 99 %, mainly to the albumin fraction. Only a negligible proportion of ketoconazole reaches the cerebrospinal fluid.

Metabolism

Following absorption from the gastrointestinal tract, ketoconazole is converted in the liver into several inactive metabolites. The major identified metabolic pathways appear to be oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation. The cytochrome P450 3A4 isoenzyme is involved in the metabolism of ketoconazole (see INTERACTIONS).

Elimination

Plasma elimination is biphasic with a rapid elimination phase with a half-life of 2 hours, followed by a slower elimination phase with a half-life of 8 hours. Concentrations of active ketoconazole in the urine are very low. The major route of excretion is through the bile into the faeces.

INDICATIONS

It is recommended that KETAZOL TABLET should be used only when other effective antifungal therapy is not well tolerated.

KETAZOL TABLET is indicated for the treatment of superficial and deep mycoses:

- Systemic mycotic infections such as systemic candidiasis.
- Chronic and recurrent vaginal candidiasis not responding to topical treatment.
- Serious chronic infections of the skin, hair and nails caused by sensitive dermatophytes e.g. *Trichophyton rubrum*, *T. menagrophytes*; and/or yeasts (dermatomycoses, paronychia, serious chronic mucocutaneous candidiasis etc.).
- When topical treatment is ineffective owing to the involvement of large areas of the skin, or lesions penetrating the deeper dermal layers, nails and hair.
- Serious mycoses of the gastrointestinal tract not responsive to other therapy or when the organism is resistant to other therapy.
- Serious chronic mucocutaneous candidiasis not responsive to other therapy or when the organism is resistant to other therapy.
- Paracoccidioidomycosis.
- Pulmonary, oral and/or disseminated histoplasmosis.
- Coccidioidomycosis.

CONTRAINDICATIONS

KETAZOL TABLET is contraindicated in:

- Patients with hypersensitivity to ketoconazole and/or to any imidazole antifungal medication, or to any of the excipients in KETAZOL TABLET (see COMPOSITION).
- Patients with acute or chronic liver disease and/ or if pre-treatment liver enzyme levels are above 2 times the upper limit of normal (see WARNINGS

AND SPECIAL PRECAUTIONS).

- Children, as safety has not been proven.
- Patients with congenital or documented acquired QTc prolongation.
- Coadministration with eplerenone due to an increased risk of hyperkaleamia and hypotension.
- Coadministration with medicines that may have their plasma concentrations increased and have QT prolonging potential or occurrences of torsades de pointes: methadone, disopyramide, saquinavir (saquinavir/ritonavir 1000/100 mg bid), halofantrine, mizolastine, cisapride, dofetilide, quinidine or pimozide.
- Coadministration with dabigatran due to an increased bleeding risk.
- Coadministration of domperidone is contraindicated since the combination can lead to QTc prolongation.
- Coadministration of triazolam, oral midazolam and alprazolam due to potential for prolonged or increased sedation and respiratory depression.
- Coadministration with ergot alkaloids (e.g. dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) due to an increased risk of ergotism and other serious vasospastic adverse events.
- Coadministration with quetiapine due to an increased risk of toxicity.
- Coadministration with CYP3A4 metabolised HMG-CoA reductase inhibitors, such as simvastatin, atorvastatin and lovastatin, due to an increased risk of skeletal muscle toxicity including rhabdomyolysis.
- Coadministration with telithromycin and clarithromycin in patients with severe renal impairment due to an increased risk of hepatotoxicity and QT interval prolongation.
- Coadministration with felodipine due to an increased risk of oedema and congestive heart failure.

- Coadministration with colchicine in patients with renal impairment due to an increased risk of severe adverse reactions.
- Coadministration with irinotecan due to an alteration of the metabolism of this medicine.
- Coadministration with everolimus, sirolimus (also known as rapamycin) due to an increase of the plasma concentrations of these medicines.
- Coadministration with vardenafil in men older than 75-years due to increased risk of adverse events.
- Coadministration with solifenacin in patients with renal impairment.
- KETAZOL TABLET should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid.
- Pregnancy, as ketoconazole, as contained in KETAZOL TABLET, has been shown to be teratogenic in animals (see PREGNANCY AND LACTATION).
- Breastfeeding mothers (see PREGNANCY AND LACTATION).

The list above is not an inclusive list of compounds that may interact with KETAZOL TABLET and result in potentially life-threatening reactions.

WARNINGS AND SPECIAL PRECAUTIONS

KETAZOL TABLET should be used only when other effective antifungal therapy is not available or tolerated.

Hepatic toxicity

Cases of serious hepatic toxicity, including cases with a fatal outcome or requiring liver transplantation have occurred with the use of KETAZOL TABLET (see SIDE EFFECTS). Some

patients had no obvious risk factors for liver disease. Cases have been reported that occurred within the first month of treatment, including some within the first week.

Liver function monitoring should be considered in all patients receiving treatment with KETAZOL TABLET.

Patients should be instructed to promptly report to their medical practitioner when experiencing signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine. In these patients, treatment should be stopped immediately and liver function testing should be conducted.

In patients with raised liver enzymes, or who have experienced liver toxicity with other medicines, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases particularly close monitoring of liver enzymes is necessary.

A risk-benefit evaluation should be made before ketoconazole, as contained in KETAZOL TABLET, is used in cases of non-life-threatening diseases requiring long treatment periods.

Monitoring of hepatic function.
It is recommended to perform liver function tests prior to

treatment and at frequent intervals during treatment in all patients receiving KETAZOL TABLET.

Factors increasing the risk of hepatitis are: females over 50 years of age, previous long-term treatment with griseofulvin, history of liver disease, known medicine intolerance, long lasting treatment and concomitant use of liver compromising medicines.

Decreased plasma testosterone values which normalise within 24 hours after administration of KETAZOL TABLET may also occur.
Oral dosing with KETAZOL TABLET at 200 mg twice daily for 3 to 7 days can result in an increase of the QTc interval of about 6 to 60 msec at ketoconazole peak plasma levels, about 1 to 4 hours after KETAZOL TABLET administration.

Decreased gastric acidity

Absorption is impaired when the gastric acidity is decreased. In patients also receiving acid neutralising medicines (e.g. aluminium hydroxide) these should be administered at least 2 hours after the intake of KETAZOL TABLET. In patients with achlorhydria such as certain AIDS patients and patients on acid secretion suppressors (e.g. H_2-antagonists, proton pump inhibitors) it is advisable to administer KETAZOL TABLET with a cola beverage.
If acid secretion suppressors are added to or removed from the concomitant medicine then the KETAZOL TABLET dose should be adjusted according to cortisol levels.

Adrenal insufficiency

KETAZOL TABLET may cause adrenal insufficiency by decreasing the body's production of corticosteroids.

KETAZOL TABLET decrease adrenal corticosteroid secretion at doses of 400 mg and higher. The recommended dose of 200 mg to 400 mg daily should not be exceeded.

Serum cortisol levels may decrease and response of cortisol on ACTH may be blunted. The adrenal function should therefore be monitored in patients with adrenal insufficiency or with borderline adrenal function and in patients under prolonged periods of stress (major surgery, intensive care, etc.).

Coexisting inflammatory/ autoimmune disorders

Exacerbation or development of inflammatory/ autoimmune disorders has been described after Cushing's syndrome remission, including after treatment with ketoconazole, as contained in KETAZOL TABLET. Patients with Cushing's syndrome and coexisting inflammatory/autoimmune disorders should be supervised after normalisation of cortisol levels.

QT-prolongation and medicine interactions leading to QT-prolongation

KETAZOL TABLET can prolong the QT interval (see CONTRAINDICATIONS and INTERACTIONS).

An ECG should be performed:

- Prior to the start of KETAZOL TABLET
- Within one week after the beginning of the treatment

- As clinically indicated thereafter.

In case of coadministration of a medicine known to increase QTc interval (see INTERACTIONS), ECG monitoring is recommended.

Effects on ability to drive and use machines

Since adverse reactions such as dizziness have been reported in patients receiving KETAZOL TABLET, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that KETAZOL TABLET does not adversely affect their ability to do so (see SIDE EFFECTS).

Lactose warning:

KETAZOL TABLET contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, or glucose-galactose malabsorption should not take KETAZOL TABLET.

Porphyria:

Safety has not been established.

INTERACTIONS

KETAZOL TABLET has a potential for clinically important medicine interactions.

Oral dosing with ketoconazole at 200 mg twice daily for 3 to 7 days can result in an increase of the QTc interval of about 6 to 60 msec at ketoconazole peak plasma levels, about 1 to 4 hours after KETAZOL TABLET administration.

Medicines affecting the absorption of KETAZOL TABLET:

Medicines affecting gastric acidity impair the absorption of KETAZOL TABLET (see WARNINGS AND SPECIAL PRECAUTIONS).

Medicines affecting the metabolism of KETAZOL TABLET:

- Enzyme-inducing medicines such as rifampicin, rifabutin, carbamazepine, isoniazid, nevirapine, mitotane and phenytoin significantly reduce the bioavailability of KETAZOL TABLET. Use of KETAZOL TABLET with potent enzyme inducers is not recommended.
- Potent inhibitors of CYP3A4 (e.g. antivirals such as ritonavir, ritonavir-boosted darunavir and ritonavir-boosted fosamprenavir) increases the bioavailability of KETAZOL TABLET. Therefore, when it is given concomitantly, a dose reduction of KETAZOL TABLET should be considered and patients should be monitored closely for signs and symptoms of adrenal insufficiency (see CONTRAINDICATIONS).

Effect of KETAZOL TABLET on the metabolism of other medicines:

- KETAZOL TABLET can inhibit the metabolism of medicines metabolised by certain hepatic P450 enzymes, especially of the CYP 3A family. This can result in an increase and/or prolongation of their effects, including side effects.
- KETAZOL TABLET, is an inhibitor of CYP1A2 and does not significantly inhibit CYP 2A6 and 2E1. At clinically relevant concentrations inhibition of CYP2B6, 2C9/C8, 2C19 and 2D6 by ketoconazole cannot be excluded.
- KETAZOL TABLET can inhibit the transport of medicines by P-glycoprotein (P-gp), which may result in an increased plasma concentration of these medicines.
- KETAZOL TABLET inhibits BCRP (Breast Cancer Resistance Protein). There is no risk of interaction with BCRP substrates at the systemic level. However ketoconazole, as contained in KETAZOL TABLET, may be an inhibitor of

BCRP at the intestinal level at clinically relevant concentrations. Considering the rapid absorption of KETAZOL TABLET, intake of BCRP substrates should be postponed for 2 hours after KETAZOL TABLET intake.

Cases have been reported of a disulfiram-like reaction to alcohol, characterised by flushing, peripheral oedema, nausea and headache.

After long term griseofulvin treatment, it is advisable to wait for one month before starting KETAZOL TABLET treatment.

Interactions between ketoconazole, as contained in KETAZOL TABLET, and other medicines are listed in the table below (increase is indicated as "↑", decrease as "↓", and no change as "↔"). The degrees of interaction mentioned below are not absolute values and may be dependent on the dose given i.e. many results are reported following a dose of 200 mg and a stronger interaction may be expected at a higher dose and/or shorter dosing interval. The following list is not an inclusive list of interactions between KETAZOL TABLET and other medicines.

Medicine by therapeutic area	**Expected effect on medicine levels**	**Recommendation for coadministration**
Analgesic opioid		
Methadone	Potential ↑ in plasma concentrations of methadone	Contraindicated due to the increased risk of serious cardiovascular events including QT prolongation and torsade de pointes, or respiratory or CNS depression (see CONTRAINDICATIONS).
Buprenorphine IV and sublingual	Buprenorphine, AUC ↑ 1,5-fold C_{max} ↑1,7-fold	Careful monitoring. The buprenorphine dose should be adjusted.
Alfentanil, fentanyl	Potential ↑ in plasma concentrations	Careful monitoring of adverse effects (respiratory depression,

	of alfentanil and fentanyl	sedation) is recommended. It may be necessary to lower the dose of alfentanil and fentanyl.
Oxycodone	↑ in plasma concentrations of oxycodone.	Careful monitoring. The oxycodone dose may be adjusted.
Antiarrhythmic medicines		
Disopyramide Quinidine	Potential ↑ in plasma concentrations of disopyramide and quinidine	Contraindicated due to the risk of serious cardiovascular events including QT prolongation (see CONTRAINDICATIONS).
Digoxin	Potential ↑ in plasma concentrations of digoxin	Careful monitoring of digoxin levels is recommended.
Anticoagulants and antiplatelet medicines		
Rivaroxaban	Rivaroxaban, AUC ↑ 2,6-fold C_{max} ↑1,7-fold	Not recommended due to an increased bleeding risk.
Warfarin and other coumarin-like medicines	Potential ↑ in plasma concentrations of warfarin	Careful monitoring INR (international normalised ratio) monitoring recommended.
Dabigatran	Dabigatran, AUC ↑ 2,6-fold C_{max} ↑ 2,5-fold	Contraindicated due to an increased bleeding risk (see CONTRAINDICATIONS).
Anticonvulsants		
Carbamazepine Phenytoin	Potential ↑ in plasma concentrations of carbamazepine and phenytoin Potential ↓ in plasma concentrations of ketoconazole, as contained in KETAZOL TABLET is expected. (CYP3A	Not recommended.

	enzyme induction)	
Antidiabetics		
Repaglinide	Repaglinide, AUC ↑ 1,2-fold C_{max} ↑ 1,2-fold	Careful monitoring. Dose adjustment of repaglinide may be required.
Saxagliptin	Saxagliptin, AUC ↑ 2,5-fold C_{max} ↑ 1,6-fold Associated with a decrease in corresponding values for the active metabolite	Careful monitoring. Dose adjustment of saxagliptin may be required.
Anti-infectives		
Rifabutin Rifampicin Isoniazid	Potential ↑ in plasma concentrations of rifabutin. Potential ↓ in plasma concentrations of KETAZOL TABLET is expected. (CYP3A4 enzyme induction)	Not recommended.
Telithromycin Clarithromycin	Telithromycin, AUC ↑ 2-fold C_{max} ↑ 1,5-fold Potential ↑ in plasma concentrations of clarithromycin	Not recommended. Contraindicated in patients with severe renal impairment due to the risk of QT interval prolongation and serious hepatic adverse reactions (see CONTRAINDICATIONS).
Praziquantel	↑ in plasma concentrations of praziquantel	Careful monitoring. Dose adjustment of praziquantel may be required.
Antimigraine medicines		
Ergots alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)	Potential ↑ in plasma concentrations of ergot alkaloids	Contraindicated due to the increased risk of ergotism and other serious vasospastic adverse events (see CONTRAINDICATIONS).

Eletriptan	Eletriptan, AUC ↑ 5,9-fold C_{max} ↑ 2,7-fold	Not recommended.
Antineoplastics		
Sunitinib Dasatinib Lapatinib Nilotinib Erlotinib	Sunitinib, AUC ↑ 1,5-fold C_{max} ↑ 1,5-fold Lapatinib, AUC ↑ 3,6-fold Nilotinib, AUC ↑ 3,0-fold Erlotinib, AUC ↑ 1,9-fold C_{max} ↑ 1,7-fold Dasatinib, ↑ in plasma concentrations of Dasatinib.	Not recommended due to the risk of increased exposure to these medicines and QT prolongation.
Irinotecan	Irinotecan: AUC ↑ 2,1-fold	Contraindicated due to an alteration of the metabolism of this medicinal product (see CONTRAINDICATIONS).
Bortezomib Busulphan Docetaxel Imatinib Cabazitaxel	Bortezomib, AUC ↑ 1,4-fold Imatinib, AUC ↑ 1,4-fold C_{max} ↑ 1,3-fold ↑ in plasma concentrations of docetaxel. Potential ↑ in plasma concentrations of busulphan Cabazitaxel, AUC ↑ 1,3-fold	Careful monitoring. Dose adjustment of each drug may be required.
Paclitaxel	Paclitaxel, No change in plasma concentration were shown with paclitaxel concentrate. No studies were performed with albumin bound nanoparticules.	Careful monitoring. Dose adjustment of paclitaxel may be required.
Vincristine, vinblastine (vinca alkaloids)	Potential ↑ in plasma concentrations	Careful monitoring as it may cause an earlier onset and/or an

	of vinca alkaloids	increased severity of side-effects.
Antipsychotics, Anxiolytics and Hypnotics		
Triazolam Alprazolam Midazolam oral	AUC ↑ C_{max} ↑	Contraindicated due to the risk of potentially prolonged or increased sedation and respiratory depression (see CONTRAINDICATIONS).
Midazolam IV	Midazolam, AUC ↑ 1,6-fold	Careful monitoring. Dose adjustment of midazolam IV may be required.
Pimozide	Potential ↑ in plasma concentrations of pimozide.	Contraindicated due to the risk of serious cardiovascular events including QT prolongation (see CONTRAINDICATIONS).
Buspirone	Potential ↑ in plasma concentrations of buspirone.	Careful monitoring. Dose adjustment of buspirone may be required.
Aripiprazole	Aripiprazole, AUC ↑ 1,6-fold C_{max} ↑ 1,4-fold	Careful monitoring. Aripiprazole dose should be reduced to approximatively one-half of its prescribed dose.
Haloperidol	Potential ↑ in plasma concentrations of haloperidol.	Not recommended due to the increased risk of QT prolongation and extrapyramidal symptoms. It may be necessary to reduce haloperidol dosage.
Quetiapine	Quetiapine, AUC ↑ 6,2-fold C_{max} ↑ 3,4-fold	Contraindicated as it may increase quetiapine-related toxicity (see CONTRAINDICATIONS).
Risperidone	Potential ↑ in AUC of risperidone:	Careful monitoring. Dose adjustment of risperidone may be required.
Antivirals products		
Maraviroc	Maraviroc, AUC ↑ 5-fold C_{max} ↑ 3,4-fold	Careful monitoring. Maraviroc dose should be decreased to 150 mg twice daily.
Saquinavir (saquinavir/ritonavir	Saquinavir, AUC ↔	Contraindicated due to the risk of QT

1000/100 mg bid)	C_{max} ↔ Ketoconazole, as contained in KETAZOL TABLET, AUC ↑ 2,7-fold C_{max} ↑ 1,5-fold (CYP3A4 enzyme inhibition by ritonavir)	prolongation (see CONTRAINDICATIONS).
Indinavir	Indinavir (600 mg TID): AUC = 0,8-fold C_{min} ↑ 1,3-fold (Relative to Indinavir 800 mg TID alone)	Careful monitoring. Dose reduction of Indinavir to 600 mg every 8 hours should be considered.
Nevirapine	Ketoconazole as contained in KETAZOL TABLET, AUC ↓ 0,28-fold C_{max} ↓ 0,56-fold Nevirapine, plasma levels, ↑ 1,15 to 1,28-fold compared to historical controls (CYP3A enzyme induction)	Not recommended
Ritonavir	Ketoconazole, as contained in KETAZOL TABLET, AUC ↑ 3,4-fold C_{max} ↑ 1,6-fold (CYP3A enzyme inhibition)	A dose reduction of KETAZOL TABLET should be considered when coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.
Beta Blockers		
Nadolol	↑ in plasma concentrations of nadolol	Careful monitoring. Dose adjustment of nadolol may be required.
Calcium Channel Blockers		
Felodipine	AUC ↑ C_{max} ↑	Contraindicated due to an increase risk of oedema and congestive

		heart failure (see CONTRAINDICATIONS).
Other dihydropyridines Verapamil	Potential ↑ in plasma concentrations of these medicines	Careful monitoring. Dose adjustment of dihydropyridines and verapamil may be required.
Diuretics		
Eplerenone	Eplerenone, AUC ↑ 5,5-fold	Contraindicated due to the increased risk of hyperkalaemia and hypotension (see CONTRAINDICATIONS).
Gastrointestinal medicines		
Aprepitant	Aprepitant, AUC ↑ 5-fold	Careful monitoring. Dose adjustment of aprepitant may be required
Domperidone	Domperidone, AUC ↑ 3,0 fold C_{max} ↑ 3,0 fold	Not recommended due to an increased risk in QT prolongation.
Immunosuppressants		
Everolimus Sirolimus (rapamycin)	Everolimus, AUC ↑ 15,3-fold C_{max} ↑ 4,1-fold Sirolimus (rapamycin), AUC ↑ 10,9-fold C_{max} ↑ 4,4-fold	Contraindicated due to the large increase in these medicines' concentrations (see CONTRAINDICATIONS).
Temsirolimus Tacrolimus Ciclosporin Budesonide Ciclesonide	Temsirolimus, AUC ↔ C_{max} ↔ Ciclesonide active metabolite, AUC ↑ 3,5-fold Rest of medicines ↑ in plasma concentrations of these medicines	Not recommended unless necessary. Careful monitoring and dose adjustment of these medicines may be required.
Dexamethasone, fluticasone, methylprednisolone	Potential ↑ in plasma concentrations of these medicines	Careful monitoring. Dose adjustment of these medicines may be required.
Lipid Lowering medicines		
Lovastatin, simvastatin,	Potential ↑in	Contraindicated due to

atorvastatin*	plasma concentrations of these medicines	an increased risk of skeletal muscle toxicity, including rhabdomyolysis (see CONTRAINDICATIONS).
Respiratory medicines		
Salmeterol	Salmeterol, AUC ↑ 15-fold C_{max} ↑ 1,4-fold	Not recommended due to an increased risk in QT prolongation.
Urological medicines		
Fesoterodine Tolterodine Solifenacin	Fesoterodine active metabolite, AUC ↑ 2,3-fold C_{max} ↑ 2,0-fold Solifenacin, AUC ↑ 3,0-fold ↑ in plasma concentrations of tolterodine	Not recommended due to an increased risk of QT prolongation. Fesoterodine and solifenacin are contraindicated in patients with renal impairment (see CONTRAINDICATIONS).
Phosphodiesterase (PDE5) inhibitors		
Sildenafil Tadalafil Vardenafil	Tadalafil, AUC ↑ 4-fold C_{max} ↑ 1,2-fold Vardenafil, AUC ↑ 10-fold C_{max} ↑ 4-fold Potential ↑in plasma concentrations of sildenafil	Not recommended due to the increased risk of adverse events. Vardenafil is contraindicated in men older than 75 years old (see CONTRAINDICATION).
Other		
Colchicine	↑ in plasma concentrations of colchicine.	Not recommended due to a potential increase in colchicine-related toxicity. Contraindicated in patients with renal impairment (see CONTRAINDICATION).
Cinacalcet	Cinacalcet, AUC ↑ 2 fold C_{max} ↑ 2 fold	Careful monitoring. Dose adjustment of cinacalcet may be required.
Ebastine	↑ in plasma concentrations of ebastine	Not recommended due to an increased risk in QT prolongation.
Mizolastine Halofantrine	Potential ↑ in plasma	Contraindicated due to the potential for serious

	concentrations of these medicines	cardiovascular events including QT prolongation (see CONTRAINDICATIONS).
*Rosuvastatin is not a CYP 3A4 substrate. Ketoconazole, as contained in KETAZOL TABLET, did not produce any change in rosuvastatin pharmacokinetics, therefore, coadministration of KETAZOL TABLET and rosuvastatin is unlikely to increase the risk of toxicity of rosuvastatin. Other statins that are not CYP3A4 substrates (pravastatin and fluvastatin) can be coadministered with KETAZOL TABLETS.		

PREGNANCY AND LACTATION

The safety of KETAZOL TABLET in pregnancy and lactation has not been established (see CONTRAINDICATIONS).

Pregnancy

No studies are available on its use in pregnant women. Therefore KETAZOL TABLET must not be administered during pregnancy.

Lactation

KETAZOL TABLET, is excreted in the milk, mothers who are under treatment should not breastfeed.

Women of childbearing potential

Women must be provided with comprehensive information on pregnancy prevention when being prescribed KETAZOL TABLET. As a minimum requirement, women of childbearing potential must use an effective method of contraception.

DOSAGE AND DIRECTIONS FOR USE

Chronic and recurrent vaginal candidiasis not responding to topical treatment:

Two tablets (400 mg) once daily with a meal for 5 days.

All other indications:

One tablet (200 mg) once daily with a meal until at least one week after the symptoms have disappeared and until all cultures have become negative. The dose of KETAZOL TABLET may be doubled to two tablets (400 mg) if the clinical response is insufficient after a reasonable period of treatment.

The usual duration of treatment is as follows:

Serious chronic mycoses of the skin and hair: 1 to 2 months.

Systemic candidiasis: 1 to 2 months.

Serious chronic mucocutaneous candidiasis: 6 to 12 months.

Paracoccidioidomycosis and histoplasmosis: 2 to 6 months.

Dermatophytes: 4 weeks.

Note: KETAZOL TABLET should be taken with meals for maximal absorption. Effective absorption depends upon intact gastric activity, hence concomitant administration with medicines that reduce gastric secretion (anticholinergic medicines, antacids and H_2 blockers) should be avoided. When indicated, these medicines should not be taken within two hours after KETAZOL TABLET.

SIDE EFFECTS

Blood and the lymphatic system disorders

Less frequent: Thrombocytopenia

Immune system disorders

Less frequent: Allergic reactions including anaphylactic shock, anaphylactoid reaction, angioedema

Endocrine disorders

Frequent: Adrenal insufficiency

Less frequent: Gynaecomastia

Metabolism and nutrition disorders

Frequency unknown: Alcohol intolerance, anorexia, hyperlipidaemia, increased appetite

Psychiatric disorders

Frequency unknown: Insomnia, nervousness

Nervous system disorders

Less frequent: Headache, dizziness, somnolence

Frequency unknown: Paraesthesia, reversible increase in intracranial pressure (e.g. papilloedema, bulging fontanelles in infants)

Eye disorders

Frequency unknown: Photophobia

Cardiac disorders

Less frequent: QT prolongation

Vascular disorders

Less frequent: Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Epistaxis

Gastrointestinal disorders

Frequent: Nausea and vomiting, abdominal pain, diarrhoea

Frequency unknown: Dyspepsia, constipation, dry mouth, dysgeusia, flatulence, tongue discolouration

Hepato-biliary disorders

Frequent: Abnormal liver function tests

Less frequent: Serious hepatic toxicity, including jaundice, hepatitis, hepatic cirrhosis biopsy-confirmed hepatic necrosis, hepatic failure including cases resulting in transplantation or death (see WARNINGS AND SPECIAL PRECAUTIONS).

Skin and subcutaneous tissue disorders

Frequent: Pruritus, rash

Less frequent: Alopecia, urticaria, acute generalised exanthematous pustulosis

Frequency unknown: Photosensitivity, erythema multiforme, dermatitis, erythema, xeroderma

Musculoskeletal, connective tissue and bone disorders

Frequency unknown: Myalgia, arthralgia

Reproductive system and breast disorders

Less frequent: Impotence, oligospermia

Frequency unknown: Menstrual disorders, azoospermia, erectile dysfunction, gynaecomastia

General disorders and administrative site conditions

Less frequent: Asthenia, fatigue, pyrexia, chills

Frequency unknown: Hot flush, malaise, peripheral oedema

Investigations

Frequent: Increased hepatic enzymes

Less frequent: Decreased platelet count

Frequency unknown: Transient decrease of testosterone concentrations

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

See SIDE EFFECTS.

Treatment

In the event of accidental overdosage, supportive and symptomatic measures should be employed.

Within the first hour after ingestion gastric lavage may be performed. Activated charcoal may be given if considered appropriate.

In the case of signs suggestive of an adrenal insufficiency, in addition to the general measures to eliminate the medicine and reduce its absorption, a 100 mg dose of hydrocortisone should be administered at once, together with saline and glucose infusions. Close surveillance will be necessary: blood pressure and fluid and electrolyte balance should be monitored for a few days.

IDENTIFICATION

A round, white tablet with bevelled edges, bisected on one side.

PRESENTATION

10, 30 and 100 tablets are packed in a polyvinyl chloride/polyvinylidenechloride blister strips. The blister strips are packed into an outer cardboard carton together with a leaflet.

100 tablets are packed in a white polypropylene securitainer with a white low-density polyethylene snap on cap, together with a white foam insert and a silica gel sachet and a leaflet.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 ℃ in a dry place.

Protect from light.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

33/20.2.2/0309

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE

OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THE PACKAGE INSERT

Date on registration certificate: 01 November 2000

Date of the most recent amendment to the professional information as approved by the Authority: 25 April 2020

Namibia: NS2 04/20.2.2/0036

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

ZA_KETATAB_2004_00