APPLICANT: MSD (PTY) LTD
APPROVED PROFESSIONAL INFORMATION
Duplicate Product Name: POSACONAZOLE TABLET 100 mg-MSD

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

POSACONAZOLE Tablet 100 mg-MSD

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg posaconazole.

For the full list of excipients, see section 6.1.

POSACONAZOLE Tablet 100 mg-MSD is sugar free.

3. PHARMACEUTICAL FORM

POSACONAZOLE Tablet 100 mg-MSD: Yellow coated capsule shaped tablets, debossed with “100” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

POSACONAZOLE Tablet 100 mg-MSD is indicated for use in the

treatment of the following fungal infections in patients 13 years of age or

older:

- Oesophageal candidiasis or candidemia in patients with disease that is refractory to other appropriate antifungal agents (amphotericin B, fluconazole or itraconazole). Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.
- Invasive aspergillosis in patients with disease that is refractory to amphotericin B, itraconazole or voriconazole or in patients who are intolerant of these medicinal products. Refractoriness is defined as a progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.
- Fusariosis,, zygomycosis, cryptococcosis, chromoblastomycosis and mycetoma in patients with disease refractory to other therapy, or patients who are intolerant of other therapy.
- Coccidioidomycosis.

POSACONAZOLE Tablet 100 mg-MSD is also indicated for prophylaxis of invasive fungal infections in patients who are at high risk of developing these infections, such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients.

4.2 Posology and method of administration

Non-interchangeability between POSACONAZOLE Tablet 100 mg-MSD and NOXAFIL Oral Suspension

POSACONAZOLE Tablet 100 mg-MSD and NOXAFIL Oral Suspension are not to be used interchangeably due to the difference in the dosing of each formulation.

Therefore, follow the specific dosage recommendation for each of the formulations.

Table 1: Recommended Dose for POSACONAZOLE Tablet 100 mg-MSD according to Indication

Indication	Dose and Duration of therapy
Prophylaxis of Invasive Fungal Infections	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukaemia or myelodysplastic syndromes, prophylaxis with POSACONAZOLE Tablet 100 mg-MSD should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3.
Refractory Invasive Fungal Infections (IFI)/Patients with IFI intolerant to 1st line therapy	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Coccidioidomycosis	

Refractory Oesophageal Candidiasis	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

Increasing the total daily dose of oral suspension above 800 mg does not further enhance the exposure to POSACONAZOLE Tablet 100 mg-MSD.

Use in renal impairment: No dose adjustment is required for renal dysfunction and as POSACONAZOLE Tablet 100 mg-MSD is not significantly renally eliminated, an effect of severe renal insufficiency on the pharmacokinetics of POSACONAZOLE Tablet 100 mg-MSD is not expected and no dose adjustment is recommended

Use in hepatic impairment: There are limited pharmacokinetic data in patients with hepatic insufficiency, but do not suggest that dose adjustment is necessary. In the small number of subjects studied who had hepatic insufficiency, there was an increase in half-life in subjects with decreased in hepatic function.

Use in Paediatrics: Safety and efficacy in adolescents and children

below the age of 13 years have not been established.

Method of Administration

POSACONAZOLE Tablet 100 mg-MSD is intended for oral

administration only.

POSACONAZOLE Tablet 100 mg-MSD can be taken without regard to food. POSACONAZOLE Tablet 100 mg-MSD should be swallowed

whole, and not be divided, crushed, or chewed.

4.3 Contraindications

POSACONAZOLE Tablet 100 mg-MSD is contraindicated in patients with known hypersensitivity to

posaconazole or any component of the product.

Pregnancy and lactation

Although not studied *in vitro* or *in vivo*, co-administration of the CYP3A4

substrates terfenadine, astemizole, cisapride, pimozide, and quinidine

with POSACONAZOLE Tablet 100 mg-MSD are contraindicated since increased plasma concentrations of those drugs can lead to QT

prolongation and occurrences of torsade de pointes.

POSACONAZOLE Tablet 100 mg-MSD may increase the plasma

concentrations of ergot alkaloids which may lead to ergotism. Co-

administration of POSACONAZOLE Tablet 100 mg-MSD and ergot alkaloids is contraindicated.

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolised through CYP3A4 is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis. (see Section 4.5)

4.4 Special warnings and precautions for use

Hypersensitivity: There is no information regarding cross-sensitivity between POSACONAZOLE Tablet 100 mg-MSD and other azole antifungal agents. Caution should be used when prescribing POSACONAZOLE Tablet 100 mg-MSD to patients with hypersensitivity to other azoles.

Hepatic toxicity: In clinical trials, there were infrequent cases of hepatic reactions (e.g. mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis). The elevations in liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalised without drug interruption and rarely required drug discontinuation. Rarely, more severe hepatic reactions including cholestasis or hepatic failure were reported in patients with serious underlying medical conditions (e.g. haematologic malignancy) during treatment with POSACONAZOLE Tablet 100 mg-MSD.

QT prolongation: Some azoles have been associated with prolongation of QT interval. Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval. Nevertheless, POSACONAZOLE Tablet 100 mg-MSD should not be administered with medications that are known to prolong QTc interval and are metabolised through CYP3A4.

Electrolyte disturbances: Especially those involving potassium, magnesium or calcium levels should be monitored and corrected as necessary before and during POSACONAZOLE Tablet 100 mg-MSD therapy.

Vincristine Toxicity: Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion and paralytic ileus. Reserve azole antifungals including posaconazole, for patients receiving a vinca alkaloid including vincristine, who have no alternative antifungal treatment options (see section 4.5).

Venetoclax Toxicity: Concomitant administration of Posaconazole with venetoclax (a CYP3A4 substrate) may increase venetoclax toxicities, including the risk of tumor lysis syndrome (TLS) and neutropenia (see 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction). Refer to the venetoclax prescribing information for detailed guidance.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on POSACONAZOLE Tablet 100 mg-MSD

POSACONAZOLE Tablet 100 mg-MSD is metabolised via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect NOXAFIL plasma concentrations.

Rifabutin (300 mg once a day) decreased the C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration curve) of POSACONAZOLE Tablet 100 mg-MSD by 43 % and 49 % respectively. Concomitant use of POSACONAZOLE Tablet 100 mg-MSD and rifabutin should be avoided.

Phenytoin (200 mg once a day) decreased the C_{max} and AUC of POSACONAZOLE Tablet 100 mg-MSD by 41 % and 50 %, respectively.

Concomitant use of POSACONAZOLE Tablet 100 mg-MSD and phenytoin should be avoided.

H_2 receptor antagonists, proton pump inhibitors (PPIs) and antacids:

POSACONAZOLE Tablet 100 mg-MSD: No clinically relevant effect was observed when POSACONAZOLE Tablet 100 mg-MSD is

used concomitantly with an antacid, H_2 receptor

antagonists and other proton pump inhibitors. No dose adjustments of

POSACONAZOLE Tablet 100 mg-MSD is required when used concomitantly

with these products.

Gastrointestinal Motility Agents:

POSACONAZOLE Tablet 100 mg-MSD: No clinically meaningful effect on

the pharmacokinetics of posaconazole was observed when

POSACONAZOLE Tablet 100 mg-MSD is concomitantly administered with

metoclopramide. No dosage adjustment of POSACONAZOLE Tablet 100 mg-

MSDs is required when given concomitantly with metoclopramide.

Glipizide (10 mg single dose) had no clinically significant effect on

POSACONAZOLE Tablet 100 mg-MSD C_{max} and AUC.

Efavirenz (400 mg once a day) decreased the C_{max} and AUC of

posaconazole by 45 % and 50 %, respectively. Concomitant use of

posaconazole and efavirenz should be avoided.

Fosamprenavir: Combining fosamprenavir with posaconazole may

lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. Repeat dose administration of fosamprenavir (700 mg twice daily x 10 days) decreased the C_{max} and AUC of posaconazole (200 mg oral suspension daily on the 1st day, 200 mg oral suspension twice daily on the 2nd day, then 400 mg oral suspension twice daily x 8 Days) by 21 % and 23 %, respectively.

Effects of POSACONAZOLE Tablet 100 mg-MSD on other medicinal products

POSACONAZOLE Tablet 100 mg-MSD is not metabolised to a clinically significant extent through the cytochrome P450 system.

However, POSACONAZOLE Tablet 100 mg-MSD is an inhibitor of CYP3A4 and thus the plasma levels of drugs that are metabolised through this enzyme pathway may increase when administered with POSACONAZOLE Tablet 100 mg-MSD.

Ergot alkaloids: NOXAFIL may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism. Co-administration of POSACONAZOLE Tablet 100 mg-MSD and ergot alkaloids is contra-indicated. (see section 4.3)

Vinca alkaloids: Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see section 4.4). Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

Ciclosporin: In heart transplant patients on stable doses of ciclosporin, POSACONAZOLE Tablet 100 mg-MSD 200 mg once daily increased ciclosporin concentrations requiring dose reductions. When initiating treatment with POSACONAZOLE Tablet 100 mg-MSD in patients already receiving ciclosporin, the dose of ciclosporin should be reduced (e.g. to about three fourths of the current dose). Thereafter blood levels of ciclosporin should be monitored carefully during co-administration and upon discontinuation of POSACONAZOLE Tablet 100 mg-MSD treatment, the dose of ciclosporin should be adjusted as necessary.

Tacrolimus: POSACONAZOLE Tablet 100 mg-MSD increased C_{max} and AUC of tacrolimus (0,05 mg/kg single dose) by 121 % and 358 % respectively. When initiating POSACONAZOLE Tablet 100 mg-MSD treatment in patients already receiving tacrolimus, the dose of tacrolimus should be reduced (e.g. to about one third of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during co-administration and upon discontinuation of POSACONAZOLE Tablet 100 mg-MSD, and the dose of tacrolimus should be adjusted as necessary.

Sirolimus: Repeat dose administration of oral posaconazole (400 mg oral suspension twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6,7-fold and 8,9-fold,

respectively, in healthy subjects. When initiating therapy in patients already taking sirolimus, the dose of sirolimus should be reduced (e.g. to about 1/10 of the current dose) with frequent monitoring of sirolimus whole blood trough concentrations. Sirolimus concentrations should be performed upon initiation, during co-administration and at discontinuation of POSACONAZOLE Tablet 100 mg-MSD treatment, with sirolimus doses adjusted accordingly.

Rifabutin: NOXAFIL increased the C_{max} and AUC of rifabutin by 31 %

and 72 % respectively. Concomitant use of POSACONAZOLE Tablet 100 mg-MSD and rifabutin

should be avoided unless the benefit to the patient outweighs the risk. If

the drugs are co-administered, careful monitoring of full blood counts and

adverse effects related to increased rifabutin levels (e.g. uveitis) is

recommended.

Midazolam: Repeat dose administration of oral posaconazole (200 mg

oral suspension twice daily for 7 days) increased the C_{max} and AUC of IV

midazolam (0,4 mg single dose) an average of 1,3 and 4,6-fold,

respectively; NOXAFIL 400 mg oral suspension twice daily for 7 days

increased the IV midazolam C_{max} and AUC by 1,6 and 6,2-fold, respectively. Both doses of posaconazole increased C_{max} and AUC of

oral midazolam (2 mg single oral dose) by 2,2 and 4,5-fold, respectively.

In addition, oral NOXAFIL (200 mg or 400 mg oral suspension)

prolonged the mean terminal half-life of midazolam from approximately 3-

4 hours to 8-10 hours during coadministration.

It is recommended that dose adjustments of benzodiazepines

metabolised by CYP3A4 be considered during co-administration

with POSACONAZOLE Tablet 100 mg-MSD.

Zidovudine (AZT), lamivudine (3TC), indinavir: Clinical studies

demonstrated that no clinically significant effects on zidovudine,

lamivudine, indinavir were observed when administered with;

POSACONAZOLE Tablet 100 mg-MSD therefore, no dose adjustments are required for these co-administered drugs.

HIV Protease Inhibitors: As HIV protease inhibitors are CYP3A4

substrates, it is expected that POSACONAZOLE Tablet 100 mg-MSD will increase plasma levels of these antiretroviral medicines.

Repeat dose administration of oral

posaconazole (400 mg oral suspension twice daily for 7 days) increased

the C_{max} and AUC of atazanavir (300 mg once a day for 7 days) an

average of 2,6-fold and 3,7-fold, respectively, in healthy subjects. Repeat

dose administration of NOXAFIL (400 mg oral suspension twice daily for

7 days) increased the C_{max} and AUC of atazanavir to a lesser extent

when administered as a boosted regimen with ritonavir (300 mg

atazanavir plus ritonavir 100 mg once a day for 7 days) with an average

of 1,5-fold and 2,5-fold, respectively, in healthy subjects. Frequent

monitoring for adverse events and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with POSACONAZOLE Tablet 100 mg-MSD.

HMG-CoA reductase inhibitors primarily metabolised through CYP3A4: Repeat dose administration of oral NOXAFIL (50, 100, and 200 mg oral suspension once daily for 13 days) increased the C_{max} and AUC of simvastatin (40 mg single dose) an average of 7,4- to 11,4-fold, and 5,7- to 10,6-fold, respectively. Increased HMG-CoA reductase inhibitor concentrations in plasma can be associated with rhabdomyolysis. Coadministration of posaconazole and HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 is contraindicated. (see section 4.3)

Calcium channel blockers metabolised through CYP3A4:
Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during co-administration with POSACONAZOLE Tablet 100 mg-MSD. Dose adjustment of calcium channel blockers may be required.

Digoxin: Administration of other azoles has been associated with increases in digoxin levels. Therefore, POSACONAZOLE Tablet 100 mg-MSD may increase plasma concentration of digoxin and digoxin levels

need to be monitored when initiating or discontinuing POSACONAZOLE

Tablet 100 mg-MSD treatment.

Venetoclax: Concomitant use of venetoclax (a CYP3A4 substrate) with Posaconazole increases venetoclax Cmax and AUC0-INF, which may increase venetoclax toxicities (see 4.4 Special Warnings and Special Precautions for Use).

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity. POSACONAZOLE Tablet 100 mg-MSD

has been shown to cause skeletal malformations in rats at exposures

lower than those obtained at therapeutic doses in humans. In rabbits

POSACONAZOLE Tablet 100 mg-MSD was embryotoxic at exposures greater than those obtained at

therapeutic doses. The potential risk to humans is unknown. POSACONAZOLE Tablet 100 mg-MSD

should not be used during pregnancy.

Breastfeeding

POSACONAZOLE Tablet 100 mg-MSD is excreted into the milk of lactating rats. The excretion of

POSACONAZOLE Tablet 100 mg-MSD in human breast milk has not been investigated.
POSACONAZOLE Tablet 100 mg-MSD

should not be used by breastfeeding mothers.

4.7 Effects on ability to drive and use machines

Since certain adverse reactions (e.g. dizziness, somnolence, etc.)

have been reported with posaconazole use, which potentially may affect driving/operating machinery, caution needs to be used.

4.8 Undesirable effects

Summary of the safety profile

POSACONAZOLE Tablet 100 mg-MSD: The safety of POSACONAZOLE Tablet 100 mg-MSD has been assessed in 230 patients enrolled in the pivotal clinical study. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of POSACONAZOLE Tablet 100 mg-MSD when given as antifungal prophylaxis. Patients were immunocompromised with underlying conditions including haematological malignancy, neutropenia post-chemotherapy, Graft versus Host Disease (GVHD), and post HSCT. POSACONAZOLE Tablet 100 mg-MSDs therapy was given for a median duration of 28 days. Twenty patients received 200 mg daily dose and 210 patients received 300 mg daily dose (following twice daily dosing on Day 1 in each cohort).

The most frequently reported treatment-related adverse reactions (≥ 5 %) with POSACONAZOLE Tablet 100 mg-MSD (300 mg once daily) were nausea and diarrhoea.

The most frequently reported adverse reaction leading to

discontinuation of POSACONAZOLE Tablet 100 mg-MSD 300 mg once daily was nausea.

In addition, rare cases of torsade de pointes have been reported

in patients taking POSACONAZOLE Tablet 100 mg-MSD.

Treatment-related adverse reactions (TRAEs) reported in

POSACONAZOLE Tablet 100 mg-MSD and NOXAFIL Oral Suspension studies:

The most common treatment-related adverse reactions reported in

POSACONAZOLE Tablet 100 mg-MSD and NOXAFIL Oral Suspension studies across the whole

population of healthy volunteers and patients are shown in **Table 2**.

Table 2: Treatment-related adverse reactions (TRAEs) reported in POSACONAZOLE Tablet 100 mg-MSDs and NOXAFIL Oral Suspension dosed subjects by body system n=2 400. Includes all TRAEs with incidence of 1 % or higher Common (≥ 1/100 to < 1/10)	
Blood and lymphatic system disorders Common	Neutropenia
Metabolism and nutrition disorders Common	Anorexia, electrolyte imbalance, hypokalaemia
Nervous system disorders Common	Dizziness, headache, paraesthesia, somnolence

Gastrointestinal disorders Common	Abdominal pain, diarrhoea, dyspepsia, flatulence, dry mouth, nausea, vomiting, constipation
Heptobiliary disorders Common	Elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, bilirubin)
Skin and subcutaneous tissue disorders Common	Rash, pruritis
General disorders and administration site conditions Common	Asthenia, fatigue, pyrexia (fever)

Post-marketing experience

The following post-marketing adverse experience has been reported:

Endocrine disorders: pseudoaldosteronism

4.9 Overdose

There is no experience with overdosage of POSACONAZOLE Tablet 100 mg-MSD.

POSACONAZOLE Tablet 100 mg-MSD is not removed by haemodialysis.

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.3 Antimicrobial agents - Other

Mechanism of action: Posaconazole is a potent inhibitor of the enzyme lanosterol 14α-demethylase, which catalyses an essential step in ergosterol biosynthesis. Consequently, posaconazole exhibits broad-spectrum antifungal activity against a wide variety of yeasts and moulds including species of *Candida* (including *C. albicans* isolates resistant to fluconazole, voriconazole and itraconazole, *C. krusei and C. glabrata* which are inherently less susceptible to fluconazole, and *C. lusitaniae* which is inherently less susceptible to amphotericin B), *Aspergillus* (including isolates resistant to fluconazole, voriconazole, itraconazole and amphotericin B) and organisms not previously regarded as being susceptible to azoles such as zygomycetes (e.g. species of *Absidia, Mucor, Rhizopus* and *Rhizomucor*). *In vitro* posaconazole exhibited fungicidal activity against species of *Aspergillus*, dimorphic fungi (*Blastomyces dermatitidis, Histoplasma capsulatum, Penicillium marneffei* and *Coccidioides immitis*) and some species of *Candida*.

In animal infection models posaconazole was active against a wide variety of fungal infections caused by moulds or yeasts.

However, there was no consistent correlation between minimum inhibitory concentration and efficacy.

Microbiology: Posaconazole has been shown *in vitro* and in clinical. infections to be active against the following microorganisms: *Aspergillus* species (*A. fumigatus, A. flavus, A. terreus, A. nidulans, A. niger, A. ustus, A. ochraceus*), *Candida* species (*C. albicans, C. glabrata, C. krusei, C. parapsilosis*), *Cryptococcus neoformans, Coccidioides immitus, Fonsecaea pedrosoi, Histoplasma capsulatum, Pseudallescheria boydii* and species of *Alternaria, Exophiala, Fusarium, Ramichloridium, Rhizomucor, Mucor*, and *Rhizopus*

Posaconazole also exhibits *in vitro* activity against the following yeasts and moulds: *Candida dubliniensis, C. famata, C. guilliermondii, C. lusitaniae, C. kefyr, C. rugosa, C. tropicalis, C. zeylanoides, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis, Cryptococcus laurentii, Kluyveromyces marxianus*, *Saccharomyces cerevisiae, Yarrowia lipolytica,* species of *Pichia*, and *Trichosporon, Aspergillus sydowii, Bjerkandera adusta, Blastomyces dermatitidis, Epidermophyton floccosum, Paracoccidioides brasiliensis, Scedosporium apiospermum, Sporothrix schenckii, Wagiella dermatitiditis* and species of *Absidia, Apophysomyces, Bipolaris, Curvularia, Microsporum, Paecilomyces, Penicillium* and *Trichophyton*. However, the safety and

effectiveness of posaconazole in treating clinical infections due to these microorganisms have not been established in clinical trials.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Resistance: *C. albicans* strains resistant to posaconazole could not be generated in the laboratory; spontaneous laboratory *Aspergillus fumigatus* mutants exhibiting a decrease in susceptibility to posaconazole arose at a frequency of $1x10^{-8}$ to $1x10^{-9}$. Clinical isolates of *Candida albicans* and *Aspergillus fumigatus* exhibiting significant decreases in posaconazole susceptibility are rare. In those rare instances where decreased susceptibility was noted, there was no clear correlation

Antifungal medicinal product combinations: When combinations of posaconazole with either amphotericin B or caspofungin were tested *in vitro* and *in vivo* there was little or no antagonism and in some instances there was an additive effect. The clinical significance of these results is

unknown.

5.2 Pharmacokinetic properties

Absorption: Posaconazole tablets are absorbed with a median t_{max} of 4 to 5 hours and exhibit dose proportional pharmacokinetics after single and multiple dosing up to 300 mg.

The absolute availability of the oral tablet is approximately 54 %. Posaconazole tablets can be given once daily after a twice daily dosing on Day 1.

Effect of food on oral absorption in healthy volunteers:

Posaconazole tablets can be taken without regard to food.

Distribution: Posaconazole, after administration of the tablet, has a mean apparent volume of distribution of 394 litre (42 %), ranging between 294-583 litre among the studies in healthy volunteers.

Metabolism: Posaconazole does not have any major circulating metabolites and its concentrations are unlikely to be altered by inhibitors of CYP450 enzymes. Of the circulating metabolites, the majority are glucuronide conjugates of posaconazole with only minor amounts of

oxidative (CYP450 mediated) metabolites observed. The excreted metabolites in urine and faeces account for approximately 17 % of the administered radiolabelled dose.

Excretion: Posaconazole is predominantly eliminated in the faeces (77 % of the radiolabelled dose) with the major component eliminated as parent medicine (66 % of the radiolabelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radiolabelled dose excreted in urine (< 0,2 % of the radiolabelled dose is parent medicine).

Posaconazole tablet is eliminated with a mean half-life ($t_{1/2}$) ranging between 26 and 31 hours and a mean apparent clearance ranging from 7,5 to 11 litre/hr.

Steady-state is attained following 7 to 10 days of multiple-dose administration. The absolute bioavailability of posaconazole in fed mice was 44,2 to 49,2 %.

Summary of the mean pharmacokinetic parameters in patients: The general pharmacokinetic findings across the clinical programme in both healthy volunteers and patients were consistent, in that posaconazole

was slowly absorbed and slowly eliminated with an extensive volume of distribution.

Exposure following multiple administration of posaconazole tablets (200 or 300 mg) once daily was 1,3 times higher in healthy volunteers than in patients.

Pharmacokinetics in special populations

Paediatric: Use of posaconazole tablet in patients 13 to 17 years of age is supported by evidence from adequate and well-controlled studies of posaconazole oral suspension**.**

Gender: The pharmacokinetics of posaconazole is comparable in men and women. No adjustment in the dosage of posaconazole is necessary based on gender.

Geriatric: Of the 230 patients treated with posaconazole tablets, 38 (17 %) were greater than 65 years of age. The pharmacokinetics of posaconazole tablets are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Race: There is insufficient data among different races with posaconazole tablets.

Results from a multiple dose study in healthy volunteers (n=56) indicated that there was only a slight decrease (16 %) in the AUC and C_{max} of posaconazole oral suspension in Black subjects relative to Caucasian subjects, therefore no dose adjustment for race is required.

Weight: Pharmacokinetic modelling for posaconazole suggests that patients weighing greater than 120 kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg.

Renal insufficiency: Following single-dose administration, there was no effect of mild and moderate renal insufficiency (n=18, Cl_{cr} ≥ 20 ml/min/1,73 m^2) on posaconazole pharmacokinetics, therefore no dose adjustment is required. In subjects with severe renal insufficiency (n=6, Cl_{cr} < 20 ml/min/1,73 m^2), the exposure of posaconazole was highly variable (96 % CV) compared to the exposure in other renal groups (< 40 % CV). However, as posaconazole is not significantly renally eliminated, an effect of severe renal insufficiency on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended.

Posaconazole is not removed by haemodialysis.

Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections.

Similar recommendations apply to posaconazole tablets; however, a specific study has not been conducted with posaconazole tablets.

Hepatic insufficiency: In a small number of subjects (n=12) studied with hepatic insufficiency (Child-Pugh class A, B, or C) C_{max} values generally decreased with the severity of hepatic dysfunction (545, 414 and 347 ng/ml for the mild, moderate, and severe groups, respectively), even though the C_{max} values (mean 508 ng/ml) for the normal subjects were consistent with previous trials in healthy volunteers. In addition, an increase in half-life was also associated with a decrease in hepatic function (26,6, 35,3 and 46,1 hours for the mild, moderate, and severe groups, respectively), as all groups had longer half-life values than subjects with normal hepatic function (22,1 hours). Due to the limited pharmacokinetic data in patients with hepatic insufficiency; no recommendation for dose adjustment can be made.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients (Tablets): Hypromellose succinate;

microcrystalline cellulose; hydroxypropyl cellulose; silicone dioxide;

croscarmellose sodium; magnesium stearate; Opadry® II yellow which

consists of polvinyl alcohol, macrogol, titanium dioxide; iron oxide

yellow and talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

POSACONAZOLE Tablet 100 mg-MSD: 24 months

6.4 Special precautions for storage

POSACONAZOLE Tablet 100 mg-MSD: Store at or below 30 °C.

Store out of reach of children.

6.5 Nature and contents of container

POSACONAZOLE Tablet 100 mg-MSD are available in PVC/Aclar/Al blister packs of 30 tablets.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

Halfway House 1685

South Africa

8. REGISTRATION NUMBER

POSACONAZOLE Tablet 100 mg-MSD: 50/20.3/9020.111

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

14 October 2024

CRT-S-CCDS-MK5592-OS-T-042021.