Applicant: MSD (Pty) Ltd Public
APPROVED PROFESSIONAL INFORMATION
NOXAFIL Tablet and 40 mg/mL Oral Suspension

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

NOXAFIL® Tablet 100 mg

NOXAFIL® 40 mg/mL Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg posaconazole.

NOXAFIL Tablets are sugar free.

Each mL of oral suspension contains 40 mg posaconazole.

Preservative: Sodium benzoate 0,2 % *m/v*

NOXAFIL Suspension contains approximately 1,75 g of glucose per 5 mL of suspension.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

NOXAFIL Tablets: Yellow coated capsule shaped tablets, debossed with “100” on one side.

NOXAFIL Oral Suspension: A white cherry flavoured oral suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NOXAFIL Tablets and Oral Suspension are 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.

NOXAFIL Tablets and Oral Suspension are 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.

NOXAFIL Oral Suspension is also indicated for use in the treatment of the following fungal infections in patients 13 years of age or older:

- Oropharyngeal candidiasis, including in patients with disease that is refractory to itraconazole and fluconazole. 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.

4.2 Posology and method of administration

Non-interchangeability between NOXAFIL Tablets and NOXAFIL Oral Suspension

NOXAFIL Tablets and 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 Noxafil Tablets 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 NOXAFIL 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.

Table 2: Recommended Dose for Noxafil Oral Suspension According to Indication

Indication	**Dose and Duration of Therapy**
Refractory Invasive Fungal Infections (IFI)/Intolerant Patients with IFI	400 mg (10 mL) twice a day. In patients who cannot tolerate a meal or a nutritional supplement, NOXAFIL should be administered at a dose of 200 mg (5 mL) four times a day. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression and clinical response.

Coccidioidomycosis	400 mg (10 mL) twice a day. In patients who cannot tolerate a meal or nutritional supplement, NOXAFIL should be administered a dose of 200 mg (5 mL) four times a day. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression and clinical response.
Oropharyngeal Candidiasis	Loading dose of 200 mg (5 mL) once a day on the first day, then 100 mg (2,5 mL) once a day for 13 days.
Refractory Oropharyngeal or Oesophageal Candidiasis	400 mg (10 mL) twice a day. Duration of the therapy should be based on the severity of the patient's underlying disease and clinical response.
Prophylaxis of Invasive Fungal Infections	200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.

Increasing the total daily dose of oral suspension above 800 mg does not further enhance the exposure to NOXAFIL.

Use in renal impairment: No dose adjustment is required for renal dysfunction and as NOXAFIL is not significantly renally eliminated, an effect of severe renal insufficiency on the pharmacokinetics of NOXAFIL 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

NOXAFIL Tablets and Oral Suspension are intended for oral administration only.

NOXAFIL Tablets can be taken without regard to food. NOXAFIL Tablets should be swallowed whole, and not be divided, crushed or chewed.

Shake NOXAFIL Oral Suspension well before use.

This medicine should not be used after 4 weeks after first opening.

NOXAFIL Oral Suspension **must** be administered with a meal, or with 240 mL of a nutritional supplement.

4.3 Contraindications

NOXAFIL 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 NOXAFIL are contraindicated since increased plasma concentrations of those drugs can lead to QT prolongation and occurrences of torsade de pointes.

NOXAFIL may increase the plasma concentrations of ergot alkaloids which may lead to ergotism. Co-administration of NOXAFIL and ergot alkaloids is contraindicated.

Co-administration 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 NOXAFIL and other azole antifungal agents. Caution should be used when prescribing NOXAFIL 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 NOXAFIL.

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, NOXAFIL 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 NOXAFIL 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 tumour 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.

Glucose: NOXAFIL Oral Suspension contains approximately 1,75 g of glucose per 5 mL of suspension. Patients with rare glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The interactions described in the following subsections apply to posaconazole tablets and oral suspension unless otherwise specified.

Effects of other medicinal products on NOXAFIL Tablets and Oral Suspension

NOXAFIL 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 NOXAFIL by 43 % and 49 % respectively. Concomitant use of NOXAFIL and rifabutin should be avoided.

Phenytoin (200 mg once a day) decreased the C_{max} and AUC of NOXAFIL by 41 % and 50 %, respectively. Concomitant use of NOXAFIL and phenytoin should be avoided.

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

NOXAFIL Tablets: No clinically relevant effect was observed when NOXAFIL Tablets are used concomitantly with an antacid, H_2 receptor antagonists and other proton pump inhibitors. No

dose adjustments of NOXAFIL Tablets is required when used concomitantly with these products.

NOXAFIL Oral Suspension: Plasma concentrations (C_{max} and AUC) were reduced by 39 % when NOXAFIL Oral Suspension was administered with cimetidine (400 mg twice a day) due to reduced absorption possibly secondary to a decrease in gastric acid production. Co-administration of NOXAFIL Oral Suspension with H_2 receptor antagonists should be avoided if possible.

Similarly, administration of 400 mg NOXAFIL Oral Suspension with esomeprazole (40 mg daily) decreased mean C_{max} and AUC by 46 % and 32 %, respectively, compared to dosing with 400 mg posaconazole alone. Co-administration of NOXAFIL Oral Suspension with proton pump inhibitors should be avoided if possible.

Gastrointestinal Motility Agents

NOXAFIL Tablets: No clinically meaningful effect on the pharmacokinetics of posaconazole was observed when NOXAFIL Tablets were concomitantly administered with metoclopramide. No dosage adjustment of NOXAFIL Tablets is required when given concomitantly with metoclopramide.

NOXAFIL Oral Suspension: Metoclopramide, when given with NOXAFIL Oral Suspension, decreases posaconazole plasma concentrations. If metoclopramide is concomitantly

administered with NOXAFIL Oral Suspension, it is recommended to closely monitor for breakthrough fungal infections.

Loperamide does not affect posaconazole plasma concentrations. No dosage adjustment of NOXAFIL Oral Suspension is required when loperamide and posaconazole are used concomitantly.

Glipizide (10 mg single dose) had no clinically significant effect on NOXAFIL 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 NOXAFIL Tablets and Oral Suspension on other medicinal products

NOXAFIL is not metabolised to a clinically significant extent through the cytochrome P450 system. However, NOXAFIL is an inhibitor of CYP3A4 and thus the plasma levels of drugs that are metabolised through this enzyme pathway may increase when administered with NOXAFIL.

Ergot alkaloids: NOXAFIL may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism. Co-administration of NOXAFIL and ergot alkaloids is contraindicated (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, NOXAFIL 200 mg once daily increased ciclosporin concentrations requiring dose reductions. When initiating treatment with NOXAFIL 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 NOXAFIL treatment, the dose of ciclosporin should be adjusted as necessary.

Tacrolimus: NOXAFIL increased C_{max} and AUC of tacrolimus (0,05 mg/kg single dose) by 121 % and 358 % respectively. When initiating NOXAFIL 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 NOXAFIL, 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 NOXAFIL treatment, with sirolimus doses adjusted accordingly.

Rifabutin: NOXAFIL increased the C_{max} and AUC of rifabutin by 31 % and 72 % respectively. Concomitant use of NOXAFIL 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 to 4 hours to 8 to 10 hours during co-administration.

It is recommended that dose adjustments of benzodiazepines metabolised by CYP3A4 be considered during co-administration with NOXAFIL.

Zidovudine (AZT), lamivudine (3TC), indinavir: Clinical studies demonstrated that no clinically significant effects on zidovudine, lamivudine, indinavir were observed when administered with NOXAFIL; 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 NOXAFIL 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 NOXAFIL.

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.

Co-administration of posaconazole and HMG-CoA reductase inhibitors primarily metabolised 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 NOXAFIL. Dose adjustment of calcium channel blockers may be required.

Digoxin: Administration of other azoles has been associated with increases in digoxin levels. Therefore, NOXAFIL may increase plasma concentration of digoxin and digoxin levels need to be monitored when initiating or discontinuing NOXAFIL treatment.

Venetoclax: Concomitant use of venetoclax (a CYP3A4 substrate) with Posaconazole increases venetoclax C_{max} and $AUC_{0\text{-}INF}$, 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. NOXAFIL has been shown to cause skeletal malformations in rats at exposures lower than those obtained at therapeutic doses in humans. In rabbits NOXAFIL was embryotoxic at exposures greater than those obtained at therapeutic doses. The potential risk to humans is unknown. NOXAFIL should not be used during pregnancy.

Breastfeeding

NOXAFIL is excreted into the milk of lactating rats. The excretion of NOXAFIL in human breast milk has not been investigated. NOXAFIL 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

NOXAFIL Tablets: The safety of NOXAFIL Tablets has been assessed in 230 patients enrolled in the pivotal clinical study. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of NOXAFIL Tablets 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. NOXAFIL Tablets 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 NOXAFIL Tablets (300 mg once daily) were nausea and diarrhoea.

The most frequently reported adverse reaction leading to discontinuation of NOXAFIL Tablets 300 mg once daily was nausea.

NOXAFIL Oral Suspension: The safety of NOXAFIL Oral Suspension has been assessed in 2 400 patients and healthy volunteers enrolled in clinical trials and from post-marketing experience, 172 patients received NOXAFIL therapy for ≥ 6 months, 58 of these received NOXAFIL therapy for ≥ 12 months.

Treatment related serious adverse events reported 428 patients with invasive fungal infections (1 % each) included altered concentration of other medicinal products, increased hepatic enzymes, nausea, rash and vomiting. Treatment-related serious adverse events reported in 605 patients treated with NOXAFIL Oral Suspension for prophylaxis (1 % each) included bilirubinaemia, increased hepatic enzymes, hepatocellular damage, nausea and vomiting.

Uncommon and rare treatment related medically significant adverse events reported during clinical trials with NOXAFIL Oral Suspension have included adrenal insufficiency (causality not confirmed), pancreatitis, allergic and/or hypersensitivity reactions.

In addition, rare cases of torsade de pointes have been reported in patients taking NOXAFIL.

In addition, rare cases of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura have been reported primarily among patients who have been receiving concomitant ciclosporin or tacrolimus with NOXAFIL oral suspension for management of transplant rejection or graft vs. host disease.

Treatment-related adverse reactions (TRAEs) reported in NOXAFIL Tablets and Oral Suspension studies:

The most common treatment-related adverse reactions reported in NOXAFIL Tablets and Oral Suspension studies across the whole population of healthy volunteers and patients are shown in Table 3.

Table 3: Treatment-related adverse reactions (TRAEs) reported in NOXAFIL Tablets and 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
Hepatobiliary 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 NOXAFIL Tablets.

During the clinical trials, some patients received NOXAFIL Oral Suspension up to 1 600 mg/day with no adverse events noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg NOXAFIL oral suspension twice a day for 3 days. No adverse events were noted by the investigator.

NOXAFIL 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.

Posaconazole oral suspension is absorbed with a median t_{max} of 3 hours (patients) and 5 hours (healthy volunteers). The pharmacokinetics of posaconazole oral suspension is linear following single and multiple dose administration of up to 800 mg. No further increases in exposure were observed when doses above 800 mg were administered to patients and healthy volunteers. There is no effect of altered pH on the absorption of posaconazole.

Dividing the total posaconazole oral suspension daily dose (800 mg) as 400 mg twice a day results in a 184 % higher exposure relative to once-a-day administration in patients.

Effect of food on oral absorption in healthy volunteers

Posaconazole tablets can be taken without regard to food.

The AUC of posaconazole oral suspension is about 2,6 times greater when administered with a non-fat meal or nutritional supplement (14 g fat) and 4 times greater when administered with a high-fat meal (approximately 50 g fat) relative to the fasted state. Posaconazole oral suspension should be administered with food or a nutritional supplement.

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

Posaconazole oral suspension has a large apparent volume of distribution (1 774 litre) suggesting extensive penetration into the peripheral tissues. Posaconazole is highly protein bound (> 98,0 %), predominantly to serum albumin.

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 radio-labelled dose.

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

Posaconazole oral suspension is slowly eliminated with a mean half-life ($t_{½}$) of 35 hours (range 20 to 66 hours) and a total body clearance (Cl/F) of 32 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.

The exposure to posaconazole following administration of 400 mg oral suspension twice a day was approximately 3 times higher in healthy volunteers than in patients, without additional safety findings at higher concentrations.

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.

Following administration of 800 mg per day of posaconazole oral suspension as a divided dose for treatment of invasive fungal infections, mean trough plasma concentrations from 12 patients, 8 to 17 years of age (776 ng/mL) were similar to concentrations from 194 patients, 18 to 64 years of age (817 ng/mL). No pharmacokinetic data are available from paediatric patients < 8 years of age. Similarly, in the prophylaxis studies, the mean steady-state posaconazole average concentration (C_{av}) was comparable among 10 adolescents (13 to 17 years of age) to C_{av} achieved in adults (≥ 18 years of age).

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 > 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.

An increase in C_{max} (26 %) and AUC (29 %) was observed in elderly subjects (24 subjects ≥ 65 years of age) receiving the posaconazole oral suspension relative to younger subjects (24 subjects, 18 to 45 years of age). However, in a population pharmacokinetic analysis (Study 1899) age did not influence the pharmacokinetics of posaconazole oral suspension. Further in clinical efficacy trials, the safety profile of posaconazole oral suspension between the young and elderly patients was similar. Therefore, no dose adjustment is required for age.

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 polyvinyl alcohol; macrogol; titanium dioxide; iron oxide yellow and talc.

Inactive ingredients (Oral Suspension): artificial cherry flavour; citric acid monohydrate; glycerol; liquid glucose; polysorbate 80; purified water; simeticone; sodium benzoate; sodium citrate dihydrate; titanium dioxide and xanthan gum.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

NOXAFIL Tablets 100 mg: 24 months

NOXAFIL 40 mg/mL Oral Suspension: 24 months

6.4 Special precautions for storage

NOXAFIL Tablets 100 mg: Store at or below 30 °C.

NOXAFIL 40 mg/mL Oral Suspension: Store at or below 30 °C. Do not freeze. Store in the original container. Protect from light. Keep the container tightly closed.

6.5 Nature and contents of container

NOXAFIL Tablets 100 mg are available in PVC/Aclar/Al blister packs of 24 or 96 tablets.

Not all pack sizes may be marketed.

NOXAFIL Oral Suspension is packed into a 123 mL (Ph. Eur. Type IV) amber glass bottle with a 22 mm screw-neck finish, containing a label claim product fill of 105 mL. The bottle is closed with a 22 mm white, two-piece, child resistant, polypropylene closure having an F-422 multi-layer laminated liner with a product contact surface made of high-density polyethylene and with a 5 mL dosing spoon added.

7 HOLDER OF CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

Halfway House

1685

South Africa

8 REGISTRATION NUMBERS

NOXAFIL Tablet 100 mg: 50/20.3/1111

NOXAFIL 40 mg/mL Oral Suspension: 41/20.3/0719

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

NOXAFIL Tablet 100 mg: 28 September 2021

NOXAFIL 40 mg/mL Oral Suspension: 04 June 2010

10 DATE OF REVISION OF THE TEXT

14 October 2024