Public

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NOXAFIL® 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 300 mg of posaconazole.

Each mL contains 18 mg of posaconazole.

Excipients with known effect:

Each vial contains 462 mg (20 mmol) of sodium.

Each vial contains 6,680 mg of cyclodextrin (as Betadex Sulfobutyl Ether Sodium [SBECD]).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NOXAFIL concentrate for solution for infusion is indicated for prophylaxis of invasive fungal infections, including both yeasts and moulds, in patients, 18 years of age and older, who are at high risk of developing these infections, such as patients with prolonged neutropenia or hematopoietic stem cell transplant (HSCT) recipients.
NOXAFIL concentrate for solution for infusion is indicated for use in the treatment of the following fungal infections in patients 18 years of age or older:

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B, itraconazole or voriconazole, or in patients who are intolerant of these medicine. 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.

- Candidaemia in patients with disease that is refractory to amphotericin B, fluconazole or itraconazole, or in patients who are intolerant of these medicines. Refractoriness is defined as progression of infection or failure to improve after a minimum treatment period (persistent fungaemia: 3 days; non-fungaemic infections: 7 days.

- Fusariosis, zygomycosis, cryptococcosis, chromoblastomycosis, and mycetoma in patients with disease refractory to other therapy, or patients who are intolerant of other therapy.

- Coccidioidomycosis. In patients with disease that is refractory to amphotericin B, fluconazole or itraconazole, or in patients who are intolerant of these medicines.

4.2 Posology and method of administration

Treatment should be initiated by a medical practitioner experienced in the management of fungal infections or in the supportive care in the high-risk patients for which posaconazole is indicated as prophylaxis.

Posology

NOXAFIL is also available for oral administration (NOXAFIL 100 mg gastro-resistant tablets and 40 mg/mL oral suspension). A switch to oral administration is recommended as soon as the patients' condition allows (see section 4.4).

Table 1: Recommended Dose According to Indication

Indication	Dose and Duration of therapy
Prophylaxis of Invasive Fungal Infections	Loading dose of 300 mg NOXAFIL twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS), 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 NOXAFIL twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Coccidioidomycosis	

Special populations

Renal impairment: In patients with moderate or severe renal impairment (eGFR < 50 mL/min/1,73m^2), accumulation of the intravenous vehicle, Betadex Sulfobutyl Ether Sodium (SBECD), is expected to occur. Oral formulations of NOXAFIL should be used in these patients unless an assessment of the benefit/risk to the patient justifies the use of NOXAFIL concentrate for solution for infusion. Serum creatinine levels should be closely monitored in these patients (see section 4.4).

Use in hepatic impairment: There are limited pharmacokinetic data in patients with hepatic impairment; therefore, no recommendation for dose adjustment can be made. In the small number of subjects studied who had hepatic impairment (including Child-Pugh C classification of chronic liver disease), there was an increase in half-life with a decrease in hepatic function.

Use in paediatrics: The safety and effectiveness of NOXAFIL concentrate for solution for infusion in adolescents and children below the age of 18 years of age has not been established. The use of NOXAFIL concentrate for solution for infusion to patients under 18 years of age is not recommended.

Method of administration

NOXAFIL concentrate for solution for infusion requires dilution (see section 6.6) prior to administration. NOXAFIL should be administered via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous (IV) infusion over approximately 90 minutes (see sections 4.2, 4.4, and 4.8). NOXAFIL concentrate for solution for infusion should not be given by bolus administration.

If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes to reduce the likelihood of infusion site reactions (see section 4.8).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ergot alkaloids (see section 4.5).

Co-administration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, or quinidine since this may result in increased plasma concentrations of these medicines, leading to QTc prolongation and occurrences of Torsade's de pointes (see sections 4.4 and 4.5).

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

Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Hypersensitivity: There is no information regarding cross-sensitivity between NOXAFIL and other azole antifungal medicines. 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 interruption of the medicine and rarely required medicine 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.

Renal Impairment: In patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) < 50 mL/min/1,73m^2), receiving the NOXAFIL concentrate for solution for infusion, accumulation of the intravenous vehicle, Betadex Sulfobutyl Ether Sodium (SBECD), is expected to occur. NOXAFIL concentrate for solution for infusion should be used with caution in patients with moderate or severe renal impairment (eGFR < 50 mL/min/1,73m^2), when an assessment of the benefit/risk to the patient justifies the use of NOXAFIL concentrate for solution for infusion. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to NOXAFIL oral suspension therapy. Due to the variability in exposure, patients with renal impairment should be monitored closely for breakthrough fungal infections.

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 CYP3A4substrate) may increase venetoclax toxicities, including the risk of tumour lysis syndrome (TLS) and neutropenia (see section 4.5. Refer to the venetoclax prescribing information for detailed guidance.

Midazolam and other benzodiazepines metabolised by CYP3A4: Due to the risk of prolonged sedation and possible respiratory depression co-administration of posaconazole with any benzodiazepines metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) should only be considered if clearly necessary. Dose adjustment of benzodiazepines metabolised by CYP3A4 should be considered (see section 4.5)

4.5 Interaction with other medicines and other forms of interaction

The following information was derived from data with NOXAFIL oral suspension or early tablet formulation. All drug interactions with NOXAFIL oral suspension described below, are considered relevant to NOXAFIL concentrate for solution for infusion as well.

Effects of other medicines on NOXAFIL:

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.

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 on other medicines:

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 medicines 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 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 200 mg oral suspension once daily increased ciclosporin concentrations requiring dose reductions. When initiating treatment with posaconazole 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 treatment, and 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 NOXAFIL (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 medicines 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 NOXAFIL (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 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 medicines.

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 NOXAFIL (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 medicines 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 AUC0-INF, which may increase venetoclax toxicities (see section 4.4).

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

Posaconazole Concentrate for Solution for Infusion Safety:

In initial studies of healthy volunteers, administration of a single dose of NOXAFIL infused over 30 minutes via a peripheral venous catheter was well tolerated. However, multiple doses of NOXAFIL administered via a peripheral venous catheter were associated with thrombophlebitis (60 % incidence). Therefore, in subsequent studies, NOXAFIL concentrate for solution for infusion was administered via central venous catheter. If a central venous catheter was not readily available, patients could receive a single infusion over 30 minutes via a peripheral venous catheter.

The safety of NOXAFIL concentrate for solution for infusion has been assessed in 268 patients in a clinical trial. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of NOXAFIL concentrate for solution for infusion when given as antifungal prophylaxis (Study 5520). Patients were immunocompromised with underlying conditions including haematological malignancy, neutropenia post-chemotherapy, GVHD, and post

HSCT. This patient population was 55 % male, had a mean age of 51 years (range 18-82 years, 19 % of patients were ≥65 years of age), and were 95 % White and 8 % Hispanic. Ten patients received a single dose of 200 mg NOXAFIL concentrate for solution for infusion, 21 patients received 200 mg daily dose for a median of 14 days, and 237 patients received 300 mg daily dose for a median of 9 days.

Treatment-related Adverse Reactions (TRAEs) Reported in Posaconazole Concentrate for Solution for Infusion Studies:

The most common treatment-related adverse reactions (TRAEs) for NOXAFIL concentrate for solution for infusion (300 mg dose) are shown in Table 2.

The most frequently reported TRAEs for patients treated with in the 300-mg dose group (combined IV and oral phase data) in P05520), treated with posaconazole concentrate for solution for infusion in the clinical database with n=237 were diarrhoea (9 %), nausea (8 %), rash (6 %), hypokalaemia (5 %), and vomiting (5 %). The most frequently reported adverse reactions leading to discontinuation of posaconazole concentrate for solution for infusion 300 mg once daily were rash (2 %) and pulmonary mycosis (2 %)

Table 2: Treatment-related Adverse Reactions (TRAEs) Reported in Posaconazole Concentrate for Solution for Infusion by Body System Includes all TRAEs with incidence of 1% or higher Common (>1/100, <1/10)	
Blood and lymphatic system disorders Common	febrile neutropenia

Gastrointestinal disorders Common	abdominal pain, anorectal discomfort, constipation, diarrhoea, dyspepsia, nausea, vomiting,dry mouth, flatulence
General disorders and administration site conditions Common	chest discomfort, chills, infusion site pain, infusion site thrombosis, mucosal inflammation, peripheral oedema, asthenia, fatigue, pyrexia (fever)
Hepatobiliary disorders Common	cholestasis, elevated liver function tests (including AST, ALT, alkaline phosphate, GGT, and bilirubin)
Infections and infestations Common	pulmonary mycosis
Investigations Common	electrocardiogram QT prolonged
Metabolism and nutrition disorders Common	Anorexia, decreased appetite, fluid overload, electrolyte imbalance (including hypokalaemia, hypomagnesaemia, hypophosphataemia)
Nervous system disorders Common	dizziness, dysgeusia, headache, paraesthesia, somnolence

Renal and urinary disorders Common	Acute renal failure
Skin and subcutaneous tissue disorders Common	petechiae, pruritus, rash
Vascular disorders Common	hypertension, orthostatic hypotension

Post-marketing experience

The following post-marketing adverse experience has been reported:

Endocrine Disorders: pseudoaldosteronism

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no experience with overdosage of NOXAFIL concentrate for solution for infusion.

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.

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.

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.

Posaconazole exhibits broad-spectrum antifungal activity against some yeasts and moulds not generally responsive to azoles, or resistant to other azoles:

- 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),
- *C. lusitaniae* (which is inherently less susceptible to amphotericin B),
- *Aspergillus* (including isolates resistant to fluconazole, voriconazole, itraconazole and amphotericin B),
- organisms not previously regarded as being susceptible to azoles such as the 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, Coccidioides immitis),
- 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.

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 between decreased susceptibility and clinical failure. Clinical success has been observed in patients infected with organisms resistant to other azoles; consistent with these observations posaconazole was active *in vitro* against many *Aspergillus* and *Candida* strains that developed resistance to other azoles and/ or amphotericin B. Breakpoints for posaconazole have not been established for any fungi.

Antifungal medicine 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

Posaconazole concentrate for solution for infusion exhibits dose proportional pharmacokinetics after single and multiple dosing in the therapeutic dose range (200-300 mg).

Distribution: Following administration of 300 mg posaconazole concentrate for solution for infusion over 90 minutes, mean peak plasma concentration at the end of infusion was 3280 ng/mL (74 % CV). Posaconazole has a distribution volume of 261 L, indicating extravascular distribution. Posaconazole is highly bound to human plasma proteins (>98%), predominantly to albumin.

Metabolism: Posaconazole primarily circulates as the parent compound in plasma and does not have any major circulating metabolites. 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 of posaconazole oral suspension. Posaconazole is primarily 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 posaconazole plasma concentrations.

Excretion: Posaconazole after administration of 300 mg of posaconazole concentrate for solution for infusion is slowly eliminated with a mean half-life (t½) of 27 hours and mean

total body clearance (CL) of 7,3 L/h. Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (once daily after twice daily loading dose at Day 1).
After administration of 14C-posaconazole as oral suspension, radioactivity was predominantly recovered in the faeces (77 % of the radio-labelled dose) with the major component being parent compound (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 compound). Data obtained with the oral suspension are considered applicable for concentrate for solution for infusion.
The total cumulative excretion should not change after posaconazole concentrate for solution for infusion administration, but excretion in urine may be slightly higher.

Special populations

Paediatric: The safety and effectiveness of NOXAFIL concentrate for solution for infusion in adolescents and children below the age of 18 years of age has not been established.

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 8-17 years of age (776 ng/mL) were similar to concentrations from 194 patients 18-64 years of age (817 ng/mL). No pharmacokinetic data are available from paediatric patients less than 8 years of age. Similarly, in the prophylaxis studies, the mean steady-state posaconazole average concentration (Cav) was comparable among ten adolescents (13-17 years of age) to Cav achieved in adults (≥ 18 years of age).

Elderly: Of the 279 patients treated with posaconazole concentrate for solution for infusion, 52 (19%) were greater than 65 years of age. The pharmacokinetics of

posaconazole concentrate for solution for infusion are comparable in young and elderly subjects. No overall differences in safety were observed between the elderly patients and younger patients; therefore, no dosage adjustment is recommended for NOXAFIL concentrate for solution for infusion in elderly 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 18–45 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.

Gender: The pharmacokinetics of posaconazole concentration for solution for infusion are comparable in men and women. The pharmacokinetics of posaconazole are comparable in men and women. No adjustment in the dosage of NOXAFIL is necessary based on gender.

Race: There is insufficient data among different races with posaconazole concentrate for solution for infusion. 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.

Public

Renal impairment: NOXAFIL concentrate for solution for infusion should be used with caution in patients with moderate or severe renal impairment (eGFR < 50 mL/min/1,73m^2), when an assessment of the benefit/risk to the patient justifies the use of NOXAFIL injection. In patients with moderate or severe renal impairment (eGFR <50 mL/min1,73m^2), receiving the NOXAFIL concentrate for solution for infusion, accumulation of the intravenous vehicle, SBECD, is expected to occur. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral NOXAFIL therapy (see 4.2 and 4.4).

Posaconazole is not removed by haemodialysis.

A specific study in patients with renal impairment has not been conducted with posaconazole concentrate for solution for infusion. Following single-dose administration of posaconazole oral suspension, there was no effect of mild and moderate renal impairment (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 impairment (n=6, Cl cr < 20 mL/min/1,73 m^2), the AUC of posaconazole was highly variable [> 96 % CV (coefficient of variance)] compared to other renal groups [< 40 % CV]. However, as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended. Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see 4.2).

Hepatic impairment: In a small number of subjects (n=12) studied with hepatic impairment (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 impairment, no recommendation for dose adjustment can be made.

Similar recommendations apply to posaconazole concentrate for solution for infusion; however, a specific study has not been conducted with posaconazole concentrate for solution for infusion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex Sulfobutyl Ether Sodium (SBECD)

Disodium edetate

Hydrochloric acid [for pH adjustment]

Sodium hydroxide [for pH adjustment]

Water for injections

6.2 Incompatibilities

NOXAFIL must not be diluted with:

Lactated Ringer’s solution
5 % dextrose with Lactated Ringer’s solution
4,2 % sodium bicarbonate

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf-life

36 months
From a microbiological point of view, once admixed, the product should be used immediately.

If not used immediately, the solution can be stored up to 24 hours refrigerated 2°C-8°C.
This medicinal product is for single use only.

6.4 Special precautions for storage

Store in a refrigerator at 2°C-8°C.

6.5 Nature and contents of container

Type I tubing glass vial sealed with a closed with bromobutyl rubber stopper and capped with a flip-off seal.

Pack size: 1 vial (20 mL)

6.6 Special precautions for disposal and other handling

Administration instructions for NOXAFIL concentrate for solution for infusion

- Equilibrate the refrigerated vial of NOXAFIL to room temperature.
- Aseptically transfer 16,7 mL of posaconazole to an intravenous bag (or bottle) containing a compatible admixture diluent (see below for list of diluents) using the volume ranging from 150 mL to 283 mL depending on the final concentration to be achieved (not less than 1 mg/mL and not greater than 2 mg/mL).
- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous infusion over approximately 90 minutes. NOXAFIL concentrate for solution for infusion should not be given by bolus administration.
- If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter with a volume to achieve a dilution of approximately 2 mg/mL. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes**. Note: In clinical trials, multiple peripheral infusions given through the same vein resulted in infusion site reactions (see section 4.8).**
- NOXAFIL is for single use.

The following medicinal products can be infused at the same time through the same intravenous line (or cannula) as NOXAFIL concentrate for solution for infusion:

Amikacin sulphate
Caspofungin
Ciprofloxacin
Daptomycin
Dobutamine hydrochloride
Famotidine
Filgrastim
Gentamicin sulphate
Hydromorphone hydrochloride

Levofloxacin
Lorazepam
Meropenem
Micafungin
Morphine sulphate
Norepinephrine bitartrate
Potassium chloride
Vancomycin hydrochloride

Any products not listed in the table above should not be co-administered with NOXAFIL through the same intravenous line (or cannula).

NOXAFIL concentrate for solution for infusion should be inspected visually for particulate matter prior to administration. The solution of NOXAFIL ranges from colourless to pale yellow. Variations of colour within this range do not affect the quality of the product.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

Halfway House 1685

South Africa

8. REGISTRATION NUMBER

56/20.3/0975

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 September 2024

10. DATE OF REVISION OF THE TEXT