

NOXAFIL® 40 mg/mL oral suspension (Posaconazole)
NOXAFIL® 100 mg gastro-resistant tablets (Posaconazole)
NOXAFIL® 300 mg concentrate for solution for infusion (Posaconazole)

PRESCRIBING INFORMATION

Refer to Summary of Product Characteristics (SmPC) before prescribing.

Noxafil oral suspension, gastro-resistant tablets and concentrate for solution for infusion will hence forth be referred as suspension, tablets and infusion.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD (tel: 01992 467272), UK. By clicking the above link you will leave the MSD website and be taken to the MHRA website.

PRESENTATION

Suspension contains 40 mg of posaconazole in each mL and approximately 1.75 g of glucose per 5 mL. **Tablets** contain 100 mg of posaconazole. **Infusion** contains 18 mg of posaconazole in each mL.

USES

Treatment of the following fungal infections in adults: Invasive aspergillosis (where disease is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products); Fusariosis (where disease is refractory to amphotericin B or in patients who are intolerant of amphotericin B); Chromoblastomycosis and mycetoma (where disease is refractory to itraconazole or in patients who are intolerant of itraconazole); Coccidioidomycosis (where disease is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products). 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.

Prophylactic treatment of invasive fungal infections in the following patients:

Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia or myelodysplastic syndromes expected to result in prolonged neutropenia and are at high risk of developing invasive fungal infections; Haematopoietic stem cell transplant recipients who are undergoing high-dose immunosuppressive therapy for

graft versus host disease and are at high risk of developing invasive fungal infections. The **suspension** is also indicated for oropharyngeal candidiasis (as first-line therapy in patients who have severe disease or are immunocompromised, where response to topical therapy is expected to be poor).

DOSAGE AND ADMINISTRATION

The tablet and oral suspension are not to be used interchangeably due to the difference between the two formulations in frequency of dosing, administration with food and plasma concentration achieved. Follow the dosage recommendations for each formulation.

Infusion: requires dilution. Administer via a central venous line by slow intravenous (IV) infusion over approximately 90 minutes. Not to be administered by bolus administration. A switch to oral administration is recommended as soon as the patient's condition allows. **Suspension:** shake well before use, to be administered during or immediately after a meal or nutritional supplement. **Tablets** take with or without food, should be swallowed whole with water. Do not crush, chew or break. Noxafil tablets are the preferred formulation to optimize plasma concentrations and generally provide higher plasma drug exposures than oral suspension.

Table 1. Recommended dose and duration according to indication and formulation

Indication	Infusion	Tablets	Suspension
Refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1 st line therapy	Loading dose of 300 mg b.d. on the first day, then 300 mg o.d.thereafter.	Loading dose of 300 mg (three 100 mg tablets) b.d. on the first day, then 300 mg (three 100 mg tablets) o.d. thereafter. Each dose may be taken without regard to food intake.	200 mg (5mL) q.d.s. Alternatively, patients who can tolerate food or a nutritional supplement may take 400 mg (10 mL) b.d. during/ immediately following a meal or nutritional supplement.
	Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.		
Prophylaxis of invasive fungal infections	Loading dose of 300 mg b.d. on the first day, then 300 mg o.d.thereafter.	Loading dose of 300 mg (three 100 mg tablets) b.d. on the first day, then 300 mg (three 100 mg tablets) o.d. thereafter. Each dose may be taken without regard to food intake.	200 mg (5 mL) t.d.s. during/ immediately after a meal, or nutritional supplement in patients who cannot tolerate food to enhance oral absorption.
	Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with AML or 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 .		
Oropharyngeal candidiasis	Not indicated	Not indicated	Loading dose 200 mg (5 mL) o.d. on the first day, then 100 mg (2.5 mL) o.d. for 13 days, during/ immediately after a meal, or nutritional supplement in patients who cannot tolerate food to enhance oral absorption.

Renal impairment: **Suspension and tablets**, no dose adjustment recommended. **Infusion**, vehicle, Betadex Sulfobutyl Ether Sodium, expected to accumulate in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min). Monitor serum creatinine levels. Oral formulations should be used in these patients unless the benefit/risk justifies use of infusion. **Hepatic impairment:** Exercise caution as potential for higher plasma exposure. **Children and adolescents ≤ 18 years:** Safety and efficacy not established.

CONTRA-INDICATIONS

Hypersensitivity. Co-administration with ergot alkaloids; the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine or the HMG-CoA reductase inhibitors simvastatin, lovastatin and atorvastatin.

PRECAUTIONS

Use caution in patients with hypersensitivity to other azoles. Use with caution in hepatic impaired patients, plasma levels may be higher. Evaluate LFTs at start and during therapy. In event of abnormal LFT, monitor for more severe hepatic injury. Consider discontinuation if signs and symptoms are consistent with development of liver disease. Monitor patients with severe renal impairment on infusion for breakthrough fungal infections. Some azoles have been associated with QTc interval prolongation. Do not administer with medicinal products that are substrates for CYP3A4 and are known to prolong QTc interval. Administer with caution in patients with pro-arrhythmic conditions and/or on medicinal products known to prolong QTc interval. Monitor and correct electrolyte disturbances before and during therapy. Caution advised, where posaconazole is administered peripherally, infusion time of 30 minutes may increase

C_{max} . Monitor patients with severe diarrhoea or vomiting for breakthrough fungal infections.

Monitor patients receiving posaconazole infusion for signs and symptoms of thromboembolic events. Plasma levels may increase over time with infusion or tablets.

Posaconazole is an inhibitor of CYP3A4. Only use with benzodiazepines metabolised by CYP3A4 when clearly necessary and reserve for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options. Posaconazole may increase plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Posaconazole plasma concentrations may be significantly lowered with rifamycin antibacterials, certain anticonvulsants and efavirenz. Concomitant use of these drugs with posaconazole should be avoided unless the benefit outweighs the risk (see Drug Interactions).

Suspension: Patients with glucose-galactose malabsorption should not use the suspension as it contains 1.75 g of glucose per 5 mL. **Infusion:** Infusion contains 462 mg of sodium in each vial.

DRUG INTERACTIONS

If co-administered with fosamprenavir, monitor for breakthrough fungal infections. Concomitant use of efavirenz, rifabutin, phenytoin and similar inducers (e.g. rifampicin, carbamazepine, phenobarbital, primidone) should be avoided unless benefit outweighs risk. If co-administered with rifabutin, monitor for adverse reactions related to increased rifabutin levels and full blood counts. Co-administration with vinca alkaloids (e.g. vincristine and vinblastine) should be avoided unless there is no alternative antifungal treatment. If unavoidable, consider vinca alkaloid dose reduction. Co-administration with sirolimus is not recommended. If unavoidable greatly reduce sirolimus dose when starting posaconazole and monitor blood levels of sirolimus frequently. If co-administered with ciclosporin or tacrolimus, reduce the dose of these drugs when starting posaconazole and monitor blood levels. If co-administered with HIV protease inhibitors monitor for adverse reactions and toxicity. Monitor glucose levels in diabetic patients on sulfonylureas. Co-administration of posaconazole with benzodiazepines metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) should only be considered if clearly necessary and if co-administered,

benzodiazepines dose adjustment should be considered. Dose adjustment may also be necessary with other CYP3A4 substrates including calcium channel blockers, and digoxin. **Suspension:** co-administration with H_2 -receptor antagonists and proton pump inhibitors should be avoided if possible. Absorption is significantly increased by food.

PREGNANCY AND LACTATION

Women of childbearing potential must use effective contraception. Posaconazole must not be used during pregnancy unless the benefit outweighs the risk. Breast-feeding must be stopped on initiation of treatment.

SIDE EFFECTS – Refer to Summary of Product Characteristics for complete information on side effects.

The safety profile for **tablets** and **suspension** is similar. The most frequently reported serious adverse reactions included nausea, vomiting, diarrhoea, pyrexia and increased bilirubin. **Infusion** The most frequently reported adverse reaction during IV dosing was diarrhoea. Plasma exposure resulting from the tablet and infusion formulation was higher than observed with the suspension. A higher incidence of adverse reactions cannot be ruled out.

During post-marketing surveillance severe hepatic injury with fatal outcome has been reported.

Adverse reactions are listed under headings of frequency using the following categories: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known.

Very common and common undesirable effects: *Very common:* nausea. *Common:* neutropenia; electrolyte imbalance, hypokalaemia; hypomagnesaemia; decreased appetite; anorexia; paresthesia; dizziness; somnolence; headache; dysgeusia; hypertension; vomiting; abdominal pain; diarrhoea; dyspepsia; dry mouth; flatulence; constipation; anorectal discomfort; raised liver function tests; rash; pruritis; pyrexia; asthenia; fatigue. **Serious Undesirable Effects:** *Uncommon:* splenic infarction; allergic reaction; hyperglycaemia; hypoglycaemia; long QT syndrome; electrocardiogram abnormal; palpitations; bradycardia; supraventricular extrasystoles; tachycardia; hypotension; vasculitis; pancreatitis, enteritis, gastroesophageal reflux disease; hepatitis, hepatomegaly; hepatic toxicity; cholestasis; acute renal failure; renal failure; oedema. *Rare:*

coagulopathy; haemorrhage; hypersensitivity reaction; cerebrovascular accident; encephalopathy, peripheral neuropathy; torsade de pointes; sudden death; ventricular tachycardia; cardio-respiratory arrest; cardiac failure; myocardial infarction; pulmonary embolism; deep vein thrombosis; gastrointestinal haemorrhage; hepatic failure; hepatitis cholestatic; hepatosplenomegaly; liver tenderness; Stevens Johnson syndrome; tongue oedema; face oedema.

PACKAGE QUANTITIES AND BASIC NHS COST

Noxafil 40 mg/mL oral suspension
105 mL Bottle £491.20

Noxafil 100 mg gastro –resistant tablets
24 Tablets (2 x 12) £596.96
96 Tablets (8 x 12) £2,387.85

Noxafil 300 mg concentrate for solution for infusion
1 Glass vial £211.00

Marketing Authorisation numbers

Noxafil 40 mg/mL oral suspension
EU/1/05/320/001

Noxafil 100 mg gastro – resistant tablets
24 Tablets (2 x 12) EU/1/05/320/002
96 Tablets (8 x 12) EU/1/05/320/003

Noxafil 300 mg concentrate for solution for infusion
1 x Glass vial EU/1/05/320/004

Marketing Authorisation holder

Merck Sharp & Dohme Limited,
Hertford Road, Hoddesdon, Hertfordshire
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Legal Category: POM

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