

Package leaflet: Information for the user

Noxafil® 300 mg concentrate for solution for infusion posaconazole

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Noxafil is and what it is used for
2. What you need to know before you use Noxafil
3. How to use Noxafil
4. Possible side effects
5. How to store Noxafil
6. Contents of the pack and other information

1. What Noxafil is and what it is used for

Noxafil contains a medicine called posaconazole. This belongs to a group of medicines called “antifungals”. Noxafil is used to prevent and treat many different fungal infections.

Noxafil works by killing or stopping the growth of some types of fungi that can cause infections.

Noxafil can be used in adults to treat the following types of fungal infections when other antifungal medicines have not worked or you have had to stop taking them:

- infections caused by fungi of the *Aspergillus* family that have not improved during treatment with the anti-fungal medicines amphotericin B or itraconazole or when these medicines have had to be stopped;
- infections caused by fungi of the *Fusarium* family that have not improved during treatment with amphotericin B or when amphotericin B has had to be stopped;
- infections caused by fungi that cause the conditions known as “chromoblastomycosis” and “mycetoma” that have not improved during treatment with itraconazole or when itraconazole has had to be stopped;
- infections caused by a fungus called *Coccidioides*. that have not improved during treatment with one or more of amphotericin B, itraconazole or fluconazole or when these medicines have had to be stopped.

Noxafil can also be used to prevent fungal infections in adults who are at high risk of getting a fungal infection, such as:

- patients who have a weak immune system due to having chemotherapy for “acute myelogenous leukemia” (AML) or “myelodysplastic syndromes” (MDS)
- patients having “high-dose immunosuppressive therapy” after “hematopoietic stem cell transplant” (HSCT).

2. What you need to know before you use Noxafil

Do not use Noxafil if:

- you are allergic to posaconazole or any of the other ingredients of this medicine (listed in section 6).
- you are taking: terfenadine, astemizole, cisapride, pimozide, halofantrine, quinidine, any medicines that contain “ergot alkaloids” such as ergotamine or dihydroergotamine, or a “statin” such as simvastatin, atorvastatin or lovastatin.

Do not use Noxafil if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Noxafil.

See “Other medicines and Noxafil” below for information on other medicines which may interact with Noxafil.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Noxafil if you:

- have had an allergic reaction to another antifungal medicine such as ketoconazole, fluconazole, itraconazole or voriconazole.
- have or have ever had liver problems. You may need to have blood tests while you are taking Noxafil.
- have an abnormal heart rhythm tracing (ECG) that shows a problem called long QTc interval
- have a weakness of the heart muscle or heart failure
- have a very slow heartbeat
- have heart rhythm disturbance
- have any problem with potassium, magnesium or calcium levels in your blood
- are taking vincristine, vinblastine and other “vinca alkaloids” (medicines used to treat cancer).

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before using Noxafil.

Children

Noxafil should not be used in children (17 years of age and younger).

Other medicines and Noxafil

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Noxafil if you are taking any of the following:

- terfenadine (used to treat allergies)
- astemizole (used to treat allergies)
- cisapride (used to treat stomach problems)
- pimozide (used to treat symptoms of Tourette's disorder)
- halofantrine (used to treat malaria)
- quinidine (used to treat abnormal heart rhythms).

Noxafil can increase the amount of these medicines in the blood which may lead to very serious changes to your heart rhythm:

- any medicines that contain “ergot alkaloids” such as ergotamine or dihydroergotamine used to treat migraines. Noxafil can increase the amount of these medicines in the blood which may lead to a severe decrease in blood flow to your fingers or toes and could cause damage to them.
- a “statin” such as simvastatin, atorvastatin or lovastatin used to treat high cholesterol.

Do not take Noxafil if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Noxafil.

Other medicines

Look at the list of medicines given above that must not be taken while you are taking Noxafil. In addition to the medicines named above there are other medicines that carry a risk of rhythm problems that may be greater when they are taken with posaconazole. Please make sure you tell your doctor about all the medicines you are taking (prescribed or non-prescribed).

Certain medicines may increase the risk of side effects of Noxafil by increasing the amount of Noxafil in the blood.

The following medicines may decrease the effectiveness of Noxafil by decreasing the amount of Noxafil in the blood:

- rifabutin and rifampicin (used to treat certain infections). If you are already taking rifabutin, you will need a blood test and you will need to look out for some possible side effects of rifabutin.
- some medicines used to treat or prevent fits including: phenytoin, carbamazepine, phenobarbital or primidone.
- efavirenz and fosamprenavir used to treat HIV infection.

Noxafil may possibly increase the risk of side effects of some other medicines by increasing the amount of these medicines in the blood. These medicines include:

- vincristine, vinblastine and other “vinca alkaloids” (used to treat cancer)
- ciclosporin (used during or after transplant surgery)
- tacrolimus and sirolimus (used during or after transplant surgery)
- rifabutin (used to treat certain infections)
- medicines used to treat HIV called protease inhibitors (including lopinavir and atazanavir, which are given with ritonavir)
- midazolam, triazolam, alprazolam or other “benzodiazepines” (used as sedatives or muscle relaxants)
- diltiazem, verapamil, nifedipine, nisoldipine or other “calcium channel blockers” (used to treat high blood pressure)
- digoxin (used to treat heart failure)
- Glipizide or other “sulfonylureas” (used to treat high blood sugar)

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Noxafil.

Pregnancy and breast-feeding

Tell your doctor if you are or think you are pregnant before you start to take Noxafil.

Do not use Noxafil if you are pregnant unless you are told to by your doctor.

If you are a woman who could become pregnant you should use effective contraception while you are using Noxafil. If you become pregnant while you are using Noxafil, contact your doctor straight away.

Do not breast-feed while using Noxafil. This is because small amounts may pass into breast milk.

Driving and using machines

You may feel dizzy, sleepy, or have blurred vision while taking Noxafil, which may affect your ability to drive or use tools or machines. If this happens, do not drive or use any tools or machines and contact your doctor.

Noxafil contains sodium

This medicinal product contains 462 mg (20 mmol) sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

3. How to use Noxafil

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 300 mg twice a day on the first day, then 300 mg once a day, thereafter.

Noxafil concentrate for solution for infusion will be diluted to the correct concentration by your pharmacist or nurse.

Noxafil concentrate for solution for infusion will always be prepared and given to you by a healthcare professional.

You will be given Noxafil:

- through a plastic tube placed in your vein (intravenous infusion)
- usually over 90 minutes

The length of treatment may depend on the type of infection that you have or the length of time your immune system is not working properly and may be individually adapted for you by your doctor. Do not adapt your dose yourself before consulting your doctor or change your treatment regimen.

If a dose of Noxafil has been forgotten

As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However, tell your doctor or pharmacist if you think that a dose has been forgotten.

When Noxafil treatment is stopped by your doctor you should not experience any effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Tell your doctor, pharmacist or nurse straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- nausea or vomit (feeling or being sick), diarrhoea,
- signs of liver problems, these include yellowing of your skin or whites of the eyes, unusually dark urine or pale faeces, feeling sick for no reason, stomach problems, loss of appetite or unusual tiredness or weakness, an increase in liver enzymes shown up in blood tests
- allergic reaction

Other side effects

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common: the following may affect up to 1 in 10 people

- a change in the salt level in your blood shown in blood tests signs include feeling confused or weak
- abnormal skin sensations, such as numbness, tingling, itching, creeping, pricking, or burning
- swelling, redness, and tenderness along the vein in which Noxafil was given
- headache
- low potassium levels – shown up in blood tests
- low magnesium levels – shown up in blood tests
- high blood pressure
- loss of appetite, stomach pain or upset stomach, passing wind, dry mouth, changes in your taste
- heartburn (a burning sensation in the chest rising up to the throat)

- low levels of “neutrophils” a type of white blood cell (neutropenia) – this can make you more likely to get infections and be shown up in blood tests
- fever
- feeling weak, dizzy, tired, or sleepy
- rash
- itching
- constipation
- rectal discomfort

Uncommon: the following may affect up to 1 in 100 people

- anaemia- signs include headaches, feeling tired or dizzy, being short of breath or looking pale and a low level of haemoglobin shown up in blood tests
- low level of platelets (thrombocytopenia) shown in blood tests – this may lead to bleeding
- low level of “leukocytes” a type of white blood cell (leukopenia) shown in blood tests – this can make you more likely to get infections
- high level of “eosinophils” a type of white blood cell (eosinophilia) – this can happen if you have inflammation
- inflammation of the blood vessels
- heart rhythm problems
- fits (convulsions)
- nerve damage (neuropathy)
- abnormal heart rhythm – shown up on a heart trace (ECG), palpitations, slow or fast heartbeat, high or low blood pressure
- low blood pressure
- inflammation of the pancreas (pancreatitis) – this may cause severe stomach pain
- oxygen supply to the spleen is interrupted (splenic infarction) - this may cause severe stomach pain
- severe kidney problems – signs include passing more or less urine that is a different colour than usual
- high blood levels of creatinine – shown in blood tests
- cough, hiccups
- nose bleeds
- severe sharp chest pain when breathing in (pleuritic pain)
- swelling of lymph glands (lymphadenopathy)
- reduced feeling of sensitivity especially on the skin
- tremor
- high or low blood sugar levels
- blurred vision, sensitivity to light
- hair loss (alopecia)
- mouth ulcers
- shivering, feeling generally unwell
- pain, back or neck pain, pain in arms or legs
- water retention (oedema)
- menstrual problems (abnormal vaginal bleeding)
- inability to sleep (insomnia)
- being completely or partially unable to talk
- swelling of the mouth
- abnormal dreams, or difficulty sleeping
- problems with co-ordination or balance
- mucosal inflammation
- stuffy nose
- difficulty breathing
- chest discomfort
- feeling bloated

- mild to severe nausea, vomiting, cramps and diarrhoea, usually caused by a virus, stomach pain
- belching
- feeling jittery
- inflammation or pain at injection site

Rare: the following may affect up to 1 in 1,000 people

- pneumonia – signs include feeling short of breath and producing discoloured phlegm
- high blood pressure in the blood vessels in the lungs (pulmonary hypertension) this can cause serious damage to your lungs and heart
- blood problems such as unusual blood clotting or prolonged bleeding
- severe allergic reactions, including widespread blistering rash and skin peeling
- mental problems such as hearing voices or seeing things that are not there
- fainting
- having problems thinking or talking, having jerking movements, especially in your hands that you cannot control
- stroke – signs include pain, weakness, numbness, or tingling in the limbs
- having a blind or dark spot in your field of vision
- heart failure or heart attack which could lead to the heart stopping beating and death, heart rhythm problems, with sudden death
- blood clots in your legs (deep vein thrombosis) – signs include intense pain or swelling of the legs
- blood clots in your lungs (pulmonary embolism) – signs include feeling short of breath or pain while breathing
- bleeding into your stomach or gut – signs include vomiting blood or passing blood in your stool
- a blockage in your gut (intestinal obstruction) especially in the “ileum”. The blockage will prevent the contents of your intestine from passing through to the lower bowel signs include feeling bloated, vomiting, severe constipation, loss of appetite, and cramps
- “haemolytic uraemic syndrome” when red blood cells breakup (hemolysis) which may happen with or without kidney failure
- “pancytopenia” low level of all blood cells (red and white blood cells and platelets) shown in blood tests
- large purple discolourations on the skin (thrombotic thrombocytopenic purpura)
- swelling of the face or tongue
- depression
- double vision
- breast pain
- adrenal glands not working properly – this may cause weakness, tiredness, loss of appetite, skin discolouration
- pituitary gland not working properly – this may cause low blood levels of some hormones that affect the function of the male or female sex organs
- hearing problems

Some patients have also reported feeling confused after using Noxafil, the frequency of this is not known.

Tell your doctor, pharmacist or nurse if you notice any of the side effects listed above.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom: Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

Ireland: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie

5. How to store Noxafil

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C–8°C).
- Once prepared, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours at 2°C-8°C (in a refrigerator). This medicinal product is for single use only and any unused solution should be discarded.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Noxafil contains

The active substance is posaconazole. Each vial contains 300 mg of posaconazole.

The other ingredients are: Betadex Sulfobutyl Ether Sodium (SBECD), disodium edetate, hydrochloric acid (concentrated), sodium hydroxide, water for injections.

What Noxafil looks like and contents of the pack

Noxafil concentrate for solution for infusion is a clear, colourless to yellow liquid. Variations of colour within this range do not affect the quality of the product.

This medicine is available in a single use glass vial closed with bromobutyl rubber stopper and aluminium seal.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer

SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

Ireland

Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfo_ireland@merck.com

United Kingdom

Merck Sharp & Dohme Limited
Tel: +44 (0) 1992 467272

This leaflet was last revised in April 2017.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

© Merck Sharp & Dohme Limited, 2017. All rights reserved.

PIL.NOX.IV.17.UK.5091.II-048

The following information is intended for healthcare professionals only:

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 sulfate
Caspofungin
Ciprofloxacin
Daptomycin
Dobutamine hydrochloride
Famotidine
Filgrastim
Gentamicin sulfate
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 coadministered with Noxafil through the same intravenous line (or cannula).

The infusion solution 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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 below:

5 % dextrose in water
0.9 % sodium chloride
0.45 % sodium chloride
5 % dextrose and 0.45 % sodium chloride
5 % dextrose and 0.9 % sodium chloride
5 % dextrose and 20 mEq KCl

© Merck Sharp & Dohme Limited, 2017. All rights reserved.

PIL.NOX.IV.17.UK.5091.II-048