PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

This medicine is marketed upon physician's prescription only

NOXAFIL® Suspension
40 mg/mL
Oral Suspension

Each mL of suspension contains:
Posaconazole 40 mg
For a list of inactive ingredients please refer to section 6. See also section 2.7 "Important information about some of the ingredients of the medicine".

Read all of this leaflet carefully before you start using this medicine.
- This leaflet contains consice information about **NOXAFIL**. If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their medical condition seems similar to yours.
- **NOXAFIL** suspension is intended for use in adults (18 years of age and older).

1. WHAT NOXAFIL IS INTENDED FOR?
NOXAFIL is used to prevent and treat different types of fungal infections.
NOXAFIL is used to treat the following types of fungal infections in adults when other antifungal medicines have not worked or you have had to stop taking them:
- Infections caused by fungi of the *Aspergillus* family and are resistant to treatment with amphotericin B or itraconazole or when the patient cannot receive these medicines;
- Infections caused by fungi of the *Fusarium* family and are resistant to treatment with amphotericin B or when the patient cannot receive this medicine;
- Infections caused by fungi that cause the conditions known as "chromoblastomycosis" and "mycetoma" and are resistant to treatment with itraconazole or when the patient cannot receive this medicine;
- Infections caused by a fungus called *Coccidioides* that are resistant to treatment with amphotericin B, itraconazole or fluconazole or when the patient cannot receive these medicines;
- Infections in the mouth or throat area (known as "thrush") caused by fungi called *Candida*, which were not previously treated.
- Fungal infection called Zygomycosis, in patients intolerant of or with disease that is refractory to alternative therapy.

NOXAFIL can also be used to prevent fungal infections in adults who are at high risk of getting a fungul infection, such as:
- patients whose immune system may be weakened due to chemotherapy for "acute myelogenous leukaemia" (AML) or "myelodysplastic syndromes" (MDS)
- patients having "high-dose immunosuppressive therapy" after "hematopoietic stem cell transplant" (HSCT).

Therapeutic group:
- Posaconazole belongs to a group of medicines called "antifungals".
- This medicine works by killing or stopping the growth of some types of fungi that can cause infections.

2. BEFORE YOU TAKE NOXAFIL
2.1 Do not take NOXAFIL if:

- you are allergic (hypersensitive) 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 medicine from the statin family such as simvastatin, atorvastatin or lovastatin.
- you have just started taking venetoclax or your venetoclax dose is being slowly increased for treatment of chronic lymphocytic leukaemia (CLL).

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**.

See section **2.3** “**Interactions with other medicines**” below for more information including information on other medicines which may interact with **NOXAFIL**.

2.2 Special warnings concerning use of NOXAFIL
Before taking NOXAFIL, tell your doctor if:
- you have had an allergic reaction to another antifungal medicine such as ketoconazole, fluconazole, itraconazole or voriconazole.
- you have or have ever had liver problems. You may need to have blood tests while you are taking this medicine.
- you develop severe diarrhoea or vomiting, as these conditions may limit the effectiveness of this medicine.
- you have an abnormal heart rhythm tracing (ECG) that shows a problem called long QTc interval
- you have a weakness of the heart muscle or heart failure
- you have a very slow heartbeat
- you have heart rhythm disturbance
- you have any problem with potassium, magnesium or calcium levels in your blood.
- you are taking vincristine, vinblastine and other “vinca alkaloids” (medicines used to treat cancer).
- you are taking venetoclax (a medicine used to treat cancer).

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

If you develop severe diarrhoea or vomiting (being sick) while taking **NOXAFIL**, talk to your doctor or the pharmacist straight away, as this may stop it from working properly. See section 4 for more information.

2.3 Interactions with other medicines
If you are taking, have recently taken or might take other medicines, including non-prescription medicines and nutritional supplements, you should inform the attending doctor or pharmacist.

Do not take NOXAFIL if you are taking any of the following medicines:
- terfenadine (used to treat allergies)
- astemizole (used to treat allergies)
- cisapride (used to treat stomach problems)
- pimozide (used to treat symptoms of Tourette's and mental illness)
- 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 medicine of the statin family such as simvastatin, atorvastatin or lovastatin used to treat high levels of cholesterol.
- venetoclax when used at the start of the treatment of a type of cancer, chronic lymphocytic leukaemia (CLL).

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 this medicine.

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 **NOXAFIL**. 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 caused by **NOXAFIL** due to 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 taking rifabutin, you will need a blood test and you will need to look out for some possible side effects of rifabutin.
- phenytoin, carbamazepine, phenobarbital or primidone (used to treat or prevent fits).
- efavirenz and fosamprenavir used to treat HIV infection.
- medicines used to decrease stomach acid such as cimetidine and ranitidine or omeprazole and similar medicines that are called proton pump inhibitors.

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)
- venetoclax (used to treat cancer)
- ciclosporin (used among others to prevent transplant rejection)
- tacrolimus and sirolimus (used to prevent transplant rejection)
- 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).
- all-trans retinoic acid (ATRA), also called tretinoin (used to treat certain blood cancers).

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

2.4 Taking NOXAFIL with food and drink

To improve absorption of posaconazole, whenever possible it should be taken during or immediately after food or a nutritional drink (see section 3 “**How should you use**

NOXAFIL?"). There is no information on the effect of alcohol on posaconazole.

2.5 Pregnancy and breast-feeding
Tell your doctor if you are or think you are pregnant before you start to take **NOXAFIL**.
Do not take **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 taking this medicine.
If you become pregnant while you are taking **NOXAFIL**, contact your doctor straight away.

Do not breast-feed while taking **NOXAFIL**. This is because small amounts of **NOXAFIL** may pass into breast milk.

2.6 Driving and using machines
You may feel dizzy, sleepy, or have blurred vision while taking **NOXAFIL**. These may affect your ability to drive or use tools or machines. If you suffer from these side effects, do not drive or use any tools or machines and contact your doctor.

2.7 Important information about some of the ingredients of the medicine

NOXAFIL contains glucose
NOXAFIL contains approximately 1.75 g of glucose per 5 mL of suspension (350 mg/mL). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

NOXAFIL contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 5 mL of suspension, that is to say essentially 'sodium free.'

NOXAFIL contains sodium benzoate
This medicine contains 10 mg of sodium benzoate per 5 mL of suspension.

NOXAFIL contains benzyl alcohol
This medicine contains up to 1.25 mg of benzyl alcohol per 5 mL of suspension. Benzyl alcohol may cause allergic reactions.

NOXAFIL contains propylene glycol
This medicine contains up to 24.75 mg of propylene glycol per 5 mL of suspension.

3. HOW SHOULD YOU USE NOXAFIL?

Do not switch between taking **NOXAFIL tablets** and **NOXAFIL oral suspension** without talking to your doctor or pharmacist because it may result in a lack of efficacy or an increased risk of adverse reactions.

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Your doctor will monitor your response and condition to determine how long **NOXAFIL** needs to be given and whether any change is needed to your daily dose.
The table below shows the recommended dose and length of treatment which depend on the type of infection that you have 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, without consulting the attending doctor.

Whenever possible you should take posaconazole during or immediately after food or a

nutritional drink.
Shake well before use.

You should always use the measuring spoon to measure the correct amount of the medicine. If a measuring spoon or some other measuring device is not provided with the package, consult the pharmacist. Do not use a household spoon to measure the amount of medicine. Household spoons differ in their size and you may not get the correct dose of the medicine.

Child resistant caps significantly lowered the number of poisonings that are caused by medicines every year. However, if you are having difficulties opening the package, you can ask the pharmacist to remove the safety mechanism of the cap and turn it to a regular and easy-to-open cap.

Indication	**Recommended dose and length of treatment**
Treatment of refractory Fungal Infections (*Invasive aspergillosis, Fusariosis, zygomycosis, Chromoblastomycosis/Mycetoma, Coccidioidomycosis)*	The recommended dose is 200 mg (one 5 mL spoonful) taken four times daily. Alternatively, if recommended by your doctor, you may take 400 mg (two 5 mL spoonfuls) twice a day provided that you are able to take both doses during or after food or a nutritional drink.
First time treatment of Thrush	On the first day of treatment take 200 mg (one 5 mL spoonful) once. After the first day, take 100 mg (2.5 mL) once a day.
Prevention of serious Fungal Infections	Take 200 mg (one 5 mL spoonful) three times a day.

Do not exceed the recommended dose.

If you have accidentally taken a higher dose than you should
If you have taken an overdose of **NOXAFIL**, or if a child has accidentally swallowed the medicine, proceed immediately to a doctor or to a hospital emergency room and bring the package of the medicine with you.

If you forget to take NOXAFIL
If you have missed a dose, take it as soon as you remember and then carry on as before. However, if it is almost time for your next dose, take your dose when it is due. Do not take a double dose to make up for a forgotten dose.

Complete the full course of treatment as instructed by the doctor.
Even if there is an improvement in your health, do not discontinue use of this medicine before consulting your doctor or pharmacist.
Do not take medicines in the dark! Check the label and the dose each time you take your medicine. Wear glasses if you need them.

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

4. SIDE EFFECTS
Like all medicines, **NOXAFIL** can cause side effects, in some users.
Do not be alarmed by reading the list of side effects, you may not suffer from any of them.

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

Common side effects: 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
- 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) – that can be shown up in blood tests. This can make you more likely to get infections
- fever
- feeling weak, dizzy, tired or sleepy
- rash
- itching
- constipation
- rectal discomfort

Uncommon side effects: 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
- 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

<u>Rare side effects: the following may affect up to 1 in 1,000 people</u>
- 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 the 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
- pseudoaldosteronism, which results in high blood pressure with a low potassium level (shown in blood test)

Side effects with unknown frequency: frequency cannot be estimated from the available data
- some patients have also reported feeling confused after taking **NOXAFIL**.

If a side effect appears, if any of the side effects gets serious or if you notice side effects not mentioned in this leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health by using the online form for adverse events reporting which is on the Ministry of Health Homepage: (www.health.gov.il)
or by following the link:
https://sideeffects.health.gov.il/

5. HOW TO STORE NOXAFIL?
- **Avoid poisoning**! This medicine, and all other medicines, must be stored in a safe place out of the sight and reach of children and/or infants, in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use **NOXAFIL** after the expiry date (exp. date) which is stated on the pack. The expiry date refers to the last day of the indicated month.
- **Storage conditions:** Store below 25˚C. Do not freeze. If you have any suspension left in a bottle more than four weeks after it was first opened, you should not use this medicine. Please return the bottle containing any leftover suspension to your pharmacist.
- 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. FURTHER INFORMATION
6.1 In addition to the active ingredient the medicine also contains the following inactive ingredients: liquid glucose (corn syrup), glycerol, polysorbate 80, artificial cherry flavour #13174 containing benzyl alcohol and propylene glycol, titanium dioxide, simethicone, xanthan gum, sodium benzoate, citric acid monohydrate, sodium citrate dihydrate, and purified water.

6.2 What NOXAFIL looks like and contents of the pack
NOXAFIL is a white, cherry flavoured, 105 mL oral suspension packaged in amber glass bottles. A measuring spoon is provided with each bottle for measuring 2.5 and 5 mL doses of the oral suspension.

Marketing Authorization Holder:
Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.B 7121, Petah-Tikva 49170.

Manufacturer:
Merck Sharp & Dohme Corp., One Merck Drive, POB 100, Whitehouse Station, NJ 08889-0100, USA.

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138.37.31627

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