Table 30: Noxafil Oral Suspension Clinical Success, Mycological Eradication, and Relapse Rates in Oropharyngeal Candidiasis

	Noxafil	Fluconazole
Clinical Success at End of Therapy (Day 14)	155/169 (91.7%)	148/160 (92.5%)
Clinical Relapse (4 Weeks after End of Therapy)	45/155 (29.0%)	52/148 (35.1%)
Mycological Eradication (absence of CFU) at End of Therapy (Day 14)	88/169 (52.1%)	80/160 (50.0%)
Mycological Relapse (4 Weeks after End of Treatment)	49/88 (55.6%)	51/80 (63.7%)

Mycologic response rates, using a criterion for success as a posttreatment quantitative culture with ≤20 colony forming units (CFU/mL) were also similar between the two groups (Noxafil 68.0%, fluconazole 68.1%). The clinical significance of this finding is unknown.

14.3 Noxafil Oral Suspension Treatment of Oropharyngeal Candidiasis Refractory to Treatment with Fluconazole or Itraconazole

Noxafil Oral Suspension Study 4 was a noncomparative study of Noxafil oral suspension in HIV-infected subjects with OPC that was refractory to treatment with fluconazole or itraconazole. An episode of OPC was considered refractory if there was failure to improve or worsening of OPC after a standard course of therapy with fluconazole greater than or equal to 100 mg/day for at least 10 consecutive days or itraconazole 200 mg/day for at least 10 consecutive days and treatment with either fluconazole or itraconazole had not been discontinued for more than 14 days prior to treatment with Noxafil. Of the 199 subjects enrolled in this study, 89 subjects met these strict criteria for refractory infection.

Forty-five subjects with refractory OPC were treated with Noxafil oral suspension 400 mg twice daily for 3 days, followed by 400 mg once daily for 25 days with an option for further treatment during a 3-month maintenance period. Following a dosing amendment, a further 44 subjects were treated with posaconazole 400 mg twice daily for 28 days. The efficacy of Noxafil was assessed by the clinical success (cure or improvement) rate after 4 weeks of treatment. The clinical success rate was 74.2% (66/89). The clinical success rates for both the original and the amended dosing regimens were similar (73.3% and 75.0%, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Noxafil Injection

Noxafil injection is available as a clear, colorless to yellow sterile liquid in single-dose Type I glass vials closed with bromobutyl rubber stopper and aluminum seal (NDC 0085-4331-01) containing 300 mg of posaconazole in 16.7 mL of solution (18 mg of posaconazole per mL).

Noxafil Delayed-Release Tablets

Noxafil delayed-release tablets are available as yellow, coated, oblong, debossed with "100" on one side containing 100 mg of posaconazole. Bottles with child-resistant closures of 60 delayed-release tablets (NDC 0085-4324-02).

Noxafil Oral Suspension

Noxafil oral suspension is available as a white, cherry-flavored suspension in 4-ounce (123 mL) amber glass bottles with child-resistant closures (NDC 0085-1328-01) containing 105 mL of suspension (40 mg of posaconazole per mL).

Supplied with each oral suspension bottle is a plastic dosing spoon calibrated for measuring 2.5-mL and 5-mL doses.

Noxafil PowderMix for Delayed-Release Oral Suspension

Noxafil PowderMix for delayed-release oral suspension is supplied as:

- Package A: a kit with 8 child-resistant single-use packets of Noxafil PowderMix for delayed-release oral suspension 300 mg, two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, one mixing liquid bottle, and one bottle adapter for the mixing liquid bottle.
- Package B: a box of six 3 mL (green) and six 10 mL (blue) notched tip syringes.

- Packages A and B are supplied separately.

NDC 0085-2224-02 unit of use carton with 8 packets.
NDC 0085-2224-01 individual packet.

16.2 Storage and Handling

Noxafil Injection

Noxafil injection vial should be stored refrigerated at 2 to 8°C (36 to 46°F). Storage conditions for the diluted solution are presented in another section of the prescribing information *[see Dosage and Administration (2.4)].*

Noxafil Delayed-Release Tablets

Store at 20 to 25°C (68 to 77°F), excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Noxafil Oral Suspension

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]**. DO NOT FREEZE.**

Noxafil PowderMix for Delayed-Release Oral Suspension

Store the entire kit at 20 to25°C (68 to 77°F), excursions permitted to 15 to 30°C (59 to 86°F) in a clean, dry place. Do not open foil packet containing Noxafil PowderMix for delayed-release oral suspension until ready for use. Storage conditions for the reconstituted solution are presented in another section of the prescribing information *[see Dosage and Administration (2.8)].*

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Important Administration Instructions

Noxafil Delayed-Release Tablets

Advise patients to take Noxafil delayed-release tablets with food.

Advise patients that Noxafil delayed-release tablets must be swallowed whole and not divided, crushed, or chewed.

Instruct patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is within 12 hours of the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Noxafil Oral Suspension

Advise patients to take each dose of Noxafil oral suspension during or immediately (i.e., within 20 minutes) following a full meal. In patients who cannot eat a full meal, each dose of Noxafil oral suspension should be administered with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in order to enhance absorption.

Instruct patients that if they miss a dose, they should take it as soon as they remember. However, if it is almost time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Noxafil PowderMix for Delayed-Release Oral Suspension

Instruct parents and/or caregivers that ONLY the provided notched tip syringes can be used to administer Noxafil PowderMix for delayed-release oral suspension to pediatric patients.

Advise patients to take Noxafil PowderMix for delayed-release oral suspension with food.

Drug Interactions

Advise patients to inform their physician immediately if they:

- develop severe diarrhea or vomiting.
- are currently taking drugs that are known to prolong the QTc interval and are metabolized through CYP3A4.

- are currently taking a cyclosporine or tacrolimus, or they notice swelling in an arm or leg or shortness of breath.
- are taking other drugs or before they begin taking other drugs as certain drugs can decrease or increase the plasma concentrations of posaconazole.

Serious and Potentially Serious Adverse Reactions

Advise patients to inform their physician immediately if they:

- notice a change in heart rate or heart rhythm or have a heart condition or circulatory disease. Noxafil can be administered with caution to patients with potentially proarrhythmic conditions.
- are pregnant, plan to become pregnant, or are nursing.
- have liver disease or develop itching, nausea or vomiting, their eyes or skin turn yellow, they feel more tired than usual or feel like they have the flu.
- have ever had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole, or voriconazole.

Hereditary Fructose Intolerance (HFI)

Inform patients and caregivers that Noxafil PowderMix for delayed -release oral suspension contains sorbitol and can be life-threatening when administered to patients with hereditary fructose intolerance (HFI) *[see Warnings and Precautions (5.8)]*. Inquire for symptoms of sorbitol/ fructose and/or sucrose intolerance before administration.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

uspi-mk5592-mf-2105r044

Patient Information
Noxafil® (**NOX**-a-fil)
(posaconazole) injection
Noxafil® (**NOX**-a-fil)
(posaconazole) delayed-release tablets
Noxafil® (**NOX**-a-fil)
(posaconazole) oral suspension
Noxafil® (**NOX**-a-fil) PowderMix
(posaconazole) for delayed-release oral suspension

What is Noxafil and Noxafil PowderMix?

Noxafil (which refers to injection, delayed-release tablets, and oral suspension) and Noxafil PowderMix (for delayed-release oral suspension) are prescription medicines used in adults and children 2 years of age and older to help prevent fungal infections that can spread throughout your body (invasive fungal infections). These infections are caused by fungi called *Aspergillus* or *Candida*. Noxafil and Noxafil PowderMix are used in people who have an increased chance of getting these infections due to a weak immune system. These include people who have had a hematopoietic stem cell transplantation (bone marrow transplant) with graft versus host disease or those with a low white blood cell count due to chemotherapy for blood cancers (hematologic malignancy)

Noxafil oral suspension is also used to treat a fungal infection called “thrush” caused by *Candida* in your mouth or throat area. Noxafil oral suspension can be used as the first treatment for thrush, or as another treatment for thrush after itraconazole or fluconazole treatment has not worked.

Noxafil oral suspension is for adults and children 13 years of age and older.

It is not known if Noxafil or Noxafil PowderMix are safe and effective in children under 2 years of age.

Who should not take Noxafil or Noxafil PowderMix?

Do not take Noxafil or Noxafil PowderMix if you:

- are allergic to posaconazole, any of the ingredients in Noxafil or Noxafil PowderMix, or other azole antifungal medicines. See the end of this leaflet for a complete list of ingredients in Noxafil and Noxafil PowderMix.
- are taking any of the following medicines:
  - sirolimus
  - pimozide
  - quinidine
  - certain statin medicines that lower cholesterol (atorvastatin, lovastatin, simvastatin)
  - ergot alkaloids (ergotamine, dihydroergotamine)
  - are taking Noxafil PowderMix for delayed-release oral suspension and have hereditary fructose intolerance.

Ask your healthcare provider or pharmacist if you are not sure if you are taking any of these medicines.
Do not start taking a new medicine without talking to your healthcare provider or pharmacist.

What should I tell my healthcare provider before taking Noxafil or Noxafil PowderMix?

Before you take Noxafil or Noxafil PowderMix, tell your healthcare provider if you:

- are taking certain medicines that lower your immune system like cyclosporine or tacrolimus.
- are taking certain drugs for HIV infection, such as ritonavir, atazanavir, efavirenz, or fosamprenavir. Efavirenz and fosamprenavir can cause a decrease in the Noxafil levels in your body. Efavirenz and fosamprenavir should not be taken with Noxafil or Noxafil PowderMix.
- are taking midazolam, a hypnotic and sedative medicine.
- are taking vincristine, vinblastine and other “vinca alkaloids” (medicines used to treat cancer).
- have or had liver problems.
- have or had kidney problems.
- have or had an abnormal heart rate or rhythm, heart problems, or blood circulation problems.
- are pregnant or plan to become pregnant. It is not known if Noxafil will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Noxafil passes into your breast milk. You and your healthcare provider should decide if you will take Noxafil or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Noxafil and Noxafil PowderMix can affect the way other medicines work, and other medicines can affect the way Noxafil and Noxafil PowderMix work, and can cause serious side effects.
Especially tell your healthcare provider if you take:

- rifabutin or phenytoin. If you are taking these medicines, you should not take Noxafil delayed-release tablets, Noxafil oral suspension, or Noxafil PowderMix for delayed-release oral suspension.
- cimetidine or esomeprazole. If you are taking these medicines, you should not take Noxafil oral suspension.

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them with you to show your healthcare provider or pharmacist when you get a new medicine.

How will I take Noxafil or Noxafil PowderMix?

- **Do not switch between Noxafil oral suspension and Noxafil delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension**.
- Take Noxafil or Noxafil PowderMix exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much Noxafil or Noxafil PowderMix to take and when to take it.
- Take Noxafil or Noxafil PowderMix for as long as your healthcare provider tells you to take it.
- If you take too much Noxafil or Noxafil PowderMix, call your healthcare provider or go to the nearest hospital emergency room right away.
- Noxafil injection is usually given over 30 to 90 minutes through a plastic tube placed in your vein.
- **Noxafil delayed-release tablets:**
  - Take Noxafil delayed-release tablets with food.
  - Take Noxafil delayed-release tablets whole. Do not break, crush, or chew Noxafil delayed-release tablets before swallowing. If you cannot swallow Noxafil delayed-release tablets whole, tell your healthcare provider. You may need a different medicine.
  - If you miss a dose, take it as soon as you remember and then take your next scheduled dose at its regular time. If it is within 12 hours of your next dose, do not take the missed dose. Skip the missed dose and go back to your regular schedule. Do not double your next dose or take more than your prescribed dose.
- **Noxafil oral suspension:**
  - Shake Noxafil oral suspension well before use.
  - Take each dose of Noxafil oral suspension during or within 20 minutes after a full meal. If you cannot eat a full meal, take each dose of Noxafil oral suspension with a liquid nutritional supplement or an acidic carbonated beverage, like ginger ale.
  - A measured dosing spoon comes with your Noxafil oral suspension and is marked for doses of **2.5 mL** and **5 mL**. **See Figure A.**

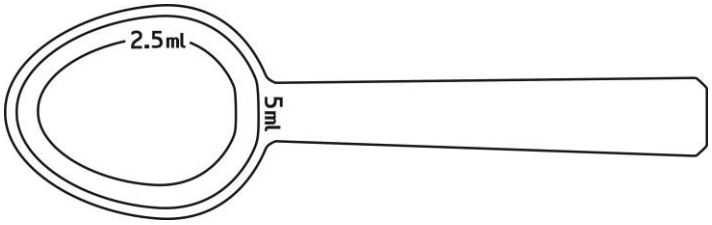

Figure A

  - Rinse the spoon with water after each dose of Noxafil oral suspension and before you store it away.
  - If you miss a dose, take it as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take a double dose to make up for the missed dose.
- **Noxafil PowderMix for delayed-release oral suspension:**
  - Before giving the first dose of Noxafil PowderMix for delayed-release oral suspension, **read the Instructions for Use booklet that comes with Noxafil PowderMix for delayed-release oral suspension** for information about the correct way to mix and give a dose of Noxafil PowderMix for delayed-release oral suspension to your child. **Keep the booklet and follow it each time you prepare the medicine. Bring this booklet to your child's appointments.**
  - If you have questions about how to mix or give Noxafil PowderMix, talk with your doctor or pharmacist.
  - Only use the mixing liquid that comes with the kit to prepare Noxafil PowderMix.
  - Once mixed, measure the prescribed dose with notched tip syringe provided with the kit. **Only use the notched tip syringes that come with the kit to prepare and administer the medicine.**
  - **Give the dose within 1 hour of mixing the suspension. Give with food.**
  - **If your child does not take all of the prescribed dose or spits some of it out, call your doctor to find out**

what to do.

Follow the instructions from your healthcare provider on how much Noxafil or Noxafil PowderMix you should take and when to take it.

What are the possible side effects of Noxafil or Noxafil PowderMix?

Noxafil or Noxafil PowderMix may cause serious side effects, including:

- **drug interactions with cyclosporine or tacrolimus.** If you take Noxafil or Noxafil PowderMix with cyclosporine or tacrolimus, your blood levels of cyclosporine or tacrolimus may increase. Serious side effects can happen in your kidney or brain if you have high levels of cyclosporine or tacrolimus in your blood. Your healthcare provider should do blood tests to check your levels of cyclosporine or tacrolimus if you are taking these medicines while taking Noxafil or Noxafil PowderMix. Tell your healthcare provider right away if you have swelling in your arm or leg or shortness of breath.
- **problems with the electrical system of your heart (arrhythmias and QTc prolongation).** Certain medicines used to treat fungus called azoles, including posaconazole, the active ingredient in Noxafil and Noxafil PowderMix, may cause heart rhythm problems. People who have certain heart problems or who take certain medicines have a higher chance for this problem. Tell your healthcare provider right away if your heartbeat becomes fast or irregular.
- **liver problems.** Some people who also have other serious medical problems may have severe liver problems that may lead to death, especially if you take certain doses of Noxafil or Noxafil PowderMix. Your healthcare provider should do blood tests to check your liver while you are taking Noxafil or Noxafil PowderMix. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - itchy skin
  - nausea or vomiting
  - yellowing of your eyes
  - feeling very tired
  - flu-like symptoms
- **increased amounts of midazolam in your blood.** If you take Noxafil or Noxafil PowderMix with midazolam, Noxafil or Noxafil PowderMix increases the amount of midazolam in your blood. This can make your sleepiness last longer. Your healthcare provider should check you closely for side effects if you take midazolam with Noxafil or Noxafil PowderMix.

The most common side effects of Noxafil in adults include:

- diarrhea
- nausea
- fever
- vomiting
- headache
- coughing
- low potassium levels in the blood

The most common side effects of Noxafil injection and Noxafil PowderMix in children include:

- fever
- fever with low white blood cell count (febrile neutropenia)
- vomiting
- redness and sores of the lining of the mouth, lips, throat, stomach, and genitals (mucositis or stomatitis)
- itching
- high blood pressure
- low potassium levels in the blood

If you take Noxafil delayed-release tablets, Noxafil oral suspension, or Noxafil Powdermix for delayed-release oral suspension, tell your healthcare provider right away if you have diarrhea or vomiting.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Noxafil or Noxafil PowderMix. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Noxafil or Noxafil PowderMix?

Noxafil injection

- Store Noxafil injection refrigerated at 36°F to 46°F (2°C to 8°C).

Noxafil delayed-release tablets

- Store Noxafil delayed-release tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Noxafil oral suspension

- Store Noxafil oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).

- Do **not** freeze Noxafil oral suspension

Noxafil PowderMix for delayed-release oral suspension

- Store the entire kit at room temperature between 68°F to 77°F (20°C to 25°C) in a clean, dry place.
- Do not open the foil packet until ready for use.

Safely throw away medicine that is out of date or no longer needed.

Keep Noxafil and Noxafil PowderMix and all medicines out of the reach of children.

General information about the safe and effective use of Noxafil and Noxafil PowderMix.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Noxafil or Noxafil PowderMix for a condition for which it was not prescribed. Do not give Noxafil or Noxafil PowderMix to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about Noxafil or Noxafil PowderMix that is written for health professionals.

What are the ingredients in Noxafil and Noxafil PowderMix?

Active ingredient: posaconazole

Inactive ingredients:

Noxafil injection: Betadex Sulfobutyl Ether Sodium (SBECD), edetate sodium, hydrochloric acid, sodium hydroxide, and water for injection.

Noxafil delayed-release tablets: hypromellose acetate succinate, microcrystalline cellulose, hydroxypropylcellulose, silicon dioxide, croscarmellose sodium, magnesium stearate, and Opadry® II Yellow (consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350, titanium dioxide, talc, and iron oxide yellow)

Noxafil oral suspension: polysorbate 80, simethicone, sodium benzoate, sodium citrate dihydrate, citric acid monohydrate, glycerin, xanthan gum, liquid glucose, titanium dioxide, artificial cherry flavor, and purified water

Noxafil PowderMix for delayed-release oral suspension: hypromellose acetate succinate. The mixing liquid contains: anhydrous citric acid, antifoam Af emulsion, berry citrus sweet flavor, carboxymethylcellulose sodium, carrageenan calcium sulfate trisodium phosphate, glycerin, methylparaben, microcrystalline cellulose, potassium sorbate, propylparaben, purified water, sodium citrate, sodium phosphate monobasic monohydrate, sodium saccharin, sorbitol solution and xanthan gum.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

usppi-mk5592-mf-2105r019

For more information, go to www.noxafil.com or call 1-800-672-6372.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 05/2021