CLINICAL UPDATE

Brand Name	Noxafil®
Generic Name	posaconazole
Drug Manufacturer	Merck Sharp & Dohme LLC

Clinical Update

TYPE OF CLINICAL UPDATE

New Formulation and Indication

FDA APPROVAL DATE

January 20, 2022

LAUNCH DATE

November 4, 2022

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

Type 5 - New Formulation or New Manufacturer; New Drug Application (NDA): 214770

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Noxafil® is indicated for the prophylaxis of invasive Aspergillus and Candida infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graftversus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

Noxafil® PowderMix for delayed-release oral suspension: pediatric patients 2 years of age and older who weigh 40 kg or less.

MECHANISMS OF ACTION

Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane. This may be responsible for the antifungal activity of posaconazole.

DOSAGE FORM(S) AND STRENGTH(S)

- Noxafil® Powder Mix for delayed-release oral suspension: 300 mg

DOSE & ADMINISTRATION

- Administer with food
- Administration with alcohol is not recommended
- To ensure delivery of the correct dose, ONLY the provided notched tip syringes must be used for preparation and administration. The design of the notched tip syringe prevents aggregation of the suspension during preparation and administration
- The recommended dosing for Noxafil PowderMix in pediatric patients is based on weight.

Weight (kg)	Loading Dose (volume)	Maintenance Dose (volume)
10 to less than 12	90 mg twice daily on the first day	90 mg once daily
12 to less than 17	120 mg twice daily on the first day	120 mg once daily
17 to less than 21	150 mg twice daily on the first day	150 mg once daily
21 to less than 26	180 mg twice daily on the first day	180 mg once daily
26 to less than 36	210 mg twice daily on the first day	210 mg once daily
36 to 40	240 mg twice daily on the first day	240 mg once daily

EFFICACY

Prophylaxis of Aspergillus and Candida Infections with Noxafil® Oral Suspension

Two randomized, controlled studies were conducted using Noxafil® as prophylaxis for the prevention of invasive fungal infections (IFIs) among patients at high risk due to severely compromised immune systems.

The first study (Noxafil® Oral Suspension Study 1) was a randomized, double-blind trial that compared Noxafil® oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD). Efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (patients may have met more than one of these criteria). This assessed all patients while on study therapy plus 7 days and at 16 weeks post-randomization. The mean duration of therapy was comparable between the 2 treatment groups (80 days, Noxafil® oral suspension; 77 days, fluconazole).

Table 1: Results from Blinded Clinical Study in Prophylaxis of IFI in All Randomized Patients with Hematopoietic Stem Cell Transplant (HSCT) and Graft-vs.-Host Disease (GVHD): Noxafil® Oral Suspension Study 1.

	Posaconazole n=301	Fluconazole n=299
On therapy plus 7 days		
Clinical Failure*	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
(*Aspergillus*)	3 (1%)	17 (6%)
(*Candida*)	1 (<1%)	3 (1%)
(Other)	3 (1%)	2 (1%)
All Deaths	22 (7%)	24 (8%)
Proven/probable fungal infection prior to death	2 (<1%)	6 (2%)
SAF †	27 (9%)	25 (8%)

Through 16 weeks		
Clinical Failure*,‡	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(*Aspergillus*)	7 (2%)	21 (7%)
(*Candida*)	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths	58 (19%)	59 (20%)
Proven/probable fungal infection prior to death	10 (3%)	16 (5%)
SAF †	26 (9%)	30 (10%)
Event free lost to follow -up §	24 (8%)	30 (10%)

* Patients m ay have met more than one criterion defining failure.

† Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >4 consecutive days).

‡ 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%).

§ Patients who are lost to follow -up (not observed for 112 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

The second study (Noxafil® Oral Suspension Study 2) was a randomized, open-label study that compared Noxafil® oral suspension (200 mg 3 times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS. As in Noxafil® Oral Suspension Study 1, efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (Patients might have met more than one of these criteria). This study assessed patients while on treatment plus 7 days and 100 days postrandomization. The mean duration of therapy was comparable between the 2 treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole).

Table 2: Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and Prolonged Neutropenia: Noxafil® Oral Suspension Study 2.

	Posaconazole n=304	Fluconazole/Itraconazole n=298
On therapy plus 7 days		
Clinical Failure*,†	82 (27%)	126 (42%)
Failure due to:		
Proven/Probable IFI	7 (2%)	25 (8%)
(*Aspergillus*)	2 (1%)	20 (7%)
(*Candida*)	3 (1%)	2 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	17 (6%)	25 (8%)
Proven/probable fungal infection prior to death	1 (<1%)	2 (1%)
SAF ‡	67 (22%)	98 (33%)
Through 100 days post randomization		
Clinical Failure †	158 (52%)	191 (64%)

Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(*Aspergillus*)	2 (1%)	26 (9%)
(*Candida*)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	44 (14%)	64 (21%)
Proven/probable fungal infection prior to death	2 (1%)	16 (5%)
SAF ‡	98 (32%)	125 (42%)
E vent free lost to follow -up §	34 (11%)	24 (8%)

* 95% confidence interval (posaconazole-fluconazole/itraconazole) = (-22.9%, -7.8%).

† Patients m ay have met more than one criterion defining failure.

‡ Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >3 consecutive days).

§ Patients who are lost to follow -up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

In summary, 2 clinical studies of prophylaxis were conducted with the Noxafil® oral suspension. As seen in the accompanying tables (Tables 1 and 2), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Noxafil® Oral Suspension Study 1 (Table 1), the clinical failure rate of posaconazole (33%) was similar to fluconazole (37%), (95% CI for the difference posaconazole–comparator -11.5% to 3.7%) while in Noxafil® Oral Suspension Study 2 (Table 33) clinical failure was lower for patients treated with posaconazole (27%) when compared to patients treated with fluconazole or itraconazole (42%), (95% CI for the difference posaconazole–comparator -22.9% to - 7.8%).

All-cause mortality was similar at 16 weeks for both treatment arms in Noxafil® Oral Suspension Study 1 [POS 58/301 (19%) vs. FLU 59/299 (20%)]; all-cause mortality was lower at 100 days for Noxafil®-treated patients in Noxafil® Oral Suspension Study 2 [POS 44/304 (14%) vs. FLU/ITZ 64/298 (21%)]. Both studies demonstrated fewer breakthrough infections caused by Aspergillus species in patients receiving Noxafil® prophylaxis when compared to patients receiving fluconazole or itraconazole.

Treatment of Oropharyngeal Candidiasis with Noxafil® Oral Suspension.

Noxafil® Oral Suspension Study 3 was a randomized, controlled, evaluator-blinded study in HIV-infected patients with oropharyngeal candidiasis. Patients were treated with Noxafil® or fluconazole oral suspension (both Noxafil® and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

Clinical and mycological outcomes were assessed after 14 days of treatment and at 4 weeks after the end of treatment. Patients who received at least 1 dose of study medication and had a positive oral swish culture of Candida species at baseline were included in the analyses. The majority of the subjects had C. albicans as the baseline pathogen. 41 Clinical success at Day 14 (complete or partial resolution of all ulcers and/or plaques and symptoms) and clinical relapse rates (recurrence of signs or symptoms after initial cure or improvement) 4 weeks after the end of treatment were similar between the treatment arms. Mycologic eradication rates (absence of colony forming units in quantitative culture at the end of therapy, Day 14), as well as mycologic relapse rates (4 weeks after the end of treatment) were also similar between the treatment arms.

Table 3: 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.

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).