FDA Approves Merck’s NOXAFIL® (posaconazole) Delayed-Release Tablets

Release Date: Tuesday, November 26, 2013 9:00 am EST

Terms: Research and Development News Corporate News Latest News

Dateline City: WHITEHOUSE STATION, N.J.

WHITEHOUSE STATION, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved NOXAFIL® (posaconazole) 100 mg delayed-release tablets. NOXAFIL delayed-release tablets are a new formulation with a loading dose of 300 mg (three 100 mg delayed-release tablets) twice daily on the first day, followed by a once-daily maintenance dose of 300 mg (three 100 mg delayed-release tablets) starting on the second day of therapy. Merck also markets NOXAFIL (40 mg/mL) oral suspension, which is dosed three times daily.

NOXAFIL delayed-release tablets and oral suspension are indicated for the prophylaxis of invasive Aspergillus and Candida infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia (low white blood cell counts) from chemotherapy.

NOXAFIL should not be administered to persons allergic to posaconazole, any ingredients of NOXAFIL, or other azole antifungal medicines. The administration of NOXAFIL with sirolimus, pimozide, quinidine, atorvastatin, lovastatin, simvastatin and ergot alkaloids must be avoided. When administered with NOXAFIL, some drugs such as cyclosporine and tacrolimus required dosage adjustments and frequent monitoring of their levels in the blood as serious side effects of the kidney (nephrotoxicity) or brain (leukoencephalopathy) including deaths have been reported in patients with increased cyclosporine or tacrolimus blood levels. NOXAFIL should be administered with caution to patients who may develop an irregular heart rhythm as NOXAFIL has been shown to prolong the QT interval and cases of potentially fatal irregular heart rhythm (torsades de pointes) have been reported in patients taking NOXAFIL. (See Selected Safety Information below.)

“Prophylaxis against invasive Aspergillus and Candida infections plays a key role in the management of severely immunocompromised patients with hematologic malignancies or hematopoietic stem cell transplant recipients who are at high risk for these life-threatening fungal infections,” said Daniel Couriel, M.D., professor of internal medicine and clinical program director, adult blood and marrow transplantation program, University of Michigan Comprehensive Cancer Center. “Posaconazole delayed-release tablets offer physicians a way to help protect these critically ill patients against invasive Aspergillus and Candida infections while they are in the hospital and once they return home.”

FDA approval of NOXAFIL (posaconazole) delayed-release tablets based on a pharmacokinetic study in patients

A non-comparative, multicenter study was performed to evaluate the pharmacokinetic properties, safety and tolerability of NOXAFIL delayed-release tablets in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) who had developed or were anticipated to develop significant neutropenia, and in patients who had undergone HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. In the study, exposures of posaconazole within a pre-specified range were attained. The exposure levels achieved support a 300 mg (three 100 mg delayed-release tablets) once-daily dose of NOXAFIL delayed-release tablets, following a 300 mg (three 100 mg delayed-release tablets) twice-a-day loading dose on the first day of therapy. The most frequently reported adverse reactions (>25%) with NOXAFIL delayed-release tablets were diarrhea, fever and nausea. The type of adverse reactions reported for NOXAFIL delayed-release tablets were generally similar to that reported in trials of NOXAFIL oral suspension. (See Selected Safety Information below.)

The effect of food intake on the oral bioavailability of posaconazole following administration of NOXAFIL delayed-release tablets is not known. However, since the oral bioavailability of posaconazole is significantly increased when NOXAFIL oral suspension is administered with food or a nutritional supplement, or an acidic carbonated beverage (e.g., ginger ale) in patients who cannot eat a full meal, it is also recommended that NOXAFIL delayed-release tablets be taken with food. For patients who cannot eat a full meal, NOXAFIL delayed-release tablets should be used instead of NOXAFIL oral suspension for the prophylaxis indication. NOXAFIL delayed-release tablets provide higher plasma drug exposures than NOXAFIL oral suspension under fasted conditions.

NOXAFIL delayed-release tablets should be swallowed whole, and not be divided, crushed or chewed. Coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections. Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.
Clinical experience with NOXAFIL (posaconazole) oral suspension for antifungal prophylaxis

Two clinical studies of prophylaxis against invasive fungal infections were conducted with NOXAFIL oral suspension. Both studies demonstrated substantially fewer breakthrough infections caused by Aspergillus species in patients receiving posaconazole prophylaxis when compared to patients receiving fluconazole or itraconazole.

In one randomized, open-label study that compared posaconazole oral suspension (200 mg three times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice daily) as prophylaxis against invasive fungal infections in neutropenic patients receiving cytotoxic chemotherapy for AML or MDS (n=602), clinical failure in patients while receiving antifungal prophylaxis and for seven days following the last dose of therapy was lower for posaconazole (27% [82/304]) compared to fluconazole or itraconazole (42% [126/298]), (95% CI for the difference posaconazole-comparator -22.9% to -7.8%). Clinical failure at 100 days post-randomization was 52% (158/304) for posaconazole compared to 64% (191/298) for fluconazole or itraconazole. All-cause mortality was lower at 100 days for patients receiving posaconazole (14% [44/304]) vs. fluconazole or itraconazole (21% [64/298]).

In a randomized, double-blind study that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic HCT recipients with GVHD (n=600), the clinical failure rate on therapy plus 7 days was 17% (50/301) for posaconazole and 18% (55/299) for fluconazole. Clinical failure through 16 weeks post-randomization was similar for posaconazole (33% [99/301]) and fluconazole (37% [110/299]), (95% CI for the difference posaconazole-comparator -11.5% to 3.7%). All-cause mortality was similar at 16 weeks for both treatment arms 19% ([58/301] vs. 20% [59/299]), respectively.

Clinical failure in these studies represented a composite endpoint of breakthrough invasive fungal infections, mortality and use of systemic antifungal therapy.

The most frequently reported adverse reactions (>30%) in these prophylaxis studies with NOXAFIL oral suspension were fever, diarrhea and nausea.

NOXAFIL delayed-release tablets and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation.

Selected Safety Information

NOXAFIL (posaconazole) is contraindicated in persons with known hypersensitivity to posaconazole, any component of NOXAFIL, or other azole antifungal agents.

NOXAFIL is contraindicated with sirolimus. Concomitant administration of NOXAFIL with sirolimus increases the sirolimus blood concentrations by approximately 9-fold and can result in sirolimus toxicity.

NOXAFIL is contraindicated with CYP3A4 substrates that prolong the QT interval. Concomitant administration of NOXAFIL with the CYP3A4 substrates, pimozone and quinidine may result in increased plasma concentrations of these drugs, leading to QT prolongation and cases of torsades de pointes.

NOXAFIL is contraindicated with HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 (e.g., atorvastatin, lovastatin and simvastatin) as increased plasma concentrations of these drugs can lead to rhabdomyolysis.

NOXAFIL is contraindicated with ergot alkaloids. NOXAFIL may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism.

Concomitant administration of NOXAFIL with cyclosporine or tacrolimus increases the whole blood trough concentrations of these calcineurin inhibitors. Nephrotoxicity and leukoencephalopathy (including deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine or tacrolimus concentrations. Frequent monitoring of cyclosporine or tacrolimus whole blood trough concentrations should be performed during and at discontinuation of NOXAFIL treatment and the tacrolimus or cyclosporine dose adjusted accordingly.

Some azoles, including NOXAFIL, have been associated with prolongation of the QT interval on the electrocardiogram. In addition, cases of torsades de pointes have been reported in patients taking NOXAFIL. NOXAFIL should be administered with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs that are known to prolong the QT interval and are metabolized through CYP3A4. Rigorous attempts to correct potassium, magnesium and calcium should be made in these patients before starting NOXAFIL.

Hepatic reactions (e.g., mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin and/or clinical hepatitis) have been reported in clinical trials. The elevations in liver function tests were generally reversible on discontinuation of therapy, and in some instances these tests normalized without drug interruption. Cases of more severe hepatic reactions including cholestasis or hepatic failure including deaths have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with NOXAFIL. Liver function tests should be evaluated at the start of and during the course of therapy. Patients who develop abnormal liver function tests during posaconazole therapy should be monitored for the development of more severe hepatic injury. Consider discontinuation of NOXAFIL (posaconazole) if clinical signs and symptoms consistent with liver disease develop that may be attributable to NOXAFIL.

Concomitant administration of NOXAFIL with midazolam increases the midazolam plasma concentrations by approximately 5-fold which could potentiate and prolong hypnotic and sedative effects. Concomitant use of NOXAFIL and other benzodiazepines metabolized by CYP3A4 (e.g., alprazolam, triazolam) could result in increased plasma concentrations of theses benzodiazepines. Patients must be monitored closely for adverse effects associated with high plasma concentrations of midazolam and other benzodiazepines metabolized by CYP3A4. In addition, benzodiazepine receptor antagonists must be available to reverse these effects.

Posaconazole is primarily metabolized via UDP glucuronidation and is a substrate of p-glycoprotein efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. Coadministration of
drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections. Posaconazole is also a strong inhibitor of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole.

Coadministration of NOXAFIL with rifabutin, phenytoin and efavirenz should be avoided unless the benefit outweighs the risk. Monitoring for toxicity and/or adverse events is recommended when tacrolimus, cyclosporine, benzodiazepines, ritonavir, atazanavir, vinca alkaloids and calcium channel blockers and rifabutin are coadministered with NOXAFIL. Dosage adjustments should also be considered when tacrolimus, cyclosporine, vinca alkaloids, calcium channel blockers and phenytoin are administered with NOXAFIL. Monitor plasma concentrations when coadministering digoxin, phenytoin, tacrolimus and cyclosporine with NOXAFIL. Although no dosage adjustment of glipizide is required, it is recommended to monitor glucose concentrations when coadministering glipizide with NOXAFIL. Monitor for breakthrough fungal infections when coadministering fosamprenavir, rifabutin and phenytoin with NOXAFIL.

Coadministration of NOXAFIL oral suspension with cimetidine (an H2-receptor antagonist) and esomeprazole (a proton pump inhibitor) results in lower posaconazole plasma concentrations and should be avoided unless the benefit outweighs the risk. No clinically relevant effects were observed when posaconazole oral suspension is concomitantly used with antacids and H2-receptor antagonists other than cimetidine.

Coadministration of NOXAFIL oral suspension with metoclopramide decreases posaconazole plasma concentrations; however, loperamide does not affect posaconazole plasma concentrations. Monitor for breakthrough fungal infections when coadministering cimetidine, esomeprazole and metoclopramide with NOXAFIL (posaconazole) oral suspension.

No clinically relevant effects on the pharmacokinetics of posaconazole delayed-release tablets were observed when concomitantly administered with drugs affecting gastric pH (i.e., antacids, H2-receptor antagonists, proton pump inhibitors). Concomitant administration of metoclopramide with posaconazole delayed-release tablets did not affect the pharmacokinetics of posaconazole.

The safety and effectiveness of NOXAFIL in patients below the age of 13 years old have not been established.

Patients weighing greater than 120 kg may have lower posaconazole plasma drug exposures. It is therefore, suggested to closely monitor for breakthrough fungal infections.

About Merck

Today's Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside of the United States and Canada. Through our prescription medicines, vaccines, biologic therapies, and consumer care and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on Twitter, Facebook and YouTube.

Forward-Looking Statement

This news release includes “forward-looking statements” within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; Merck's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Merck patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in Merck's 2012 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).


NOXAFIL® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, N.J., USA.
Ticker Slug:
Ticker: MRK
Exchange: NYSE

Source URL: https://www.mrknewsroom.com/news-release/research-and-development-news/fda-approves-mercks-noxafil-posaconazole-delayed-release-