



NEWS RELEASE

## Jan7Merck's New Drug Application for an Investigational Intravenous (IV) Formulation of NOXAFIL® (posaconazole) Receives FDA Priority Review

11/18/2013

Marketing Authorization Application also Filed with the European Medicines Agency

Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that its New Drug Application for an investigational intravenous (IV) solution formulation of the company's antifungal agent, NOXAFIL® (posaconazole), has been accepted for priority review by the U.S. Food and Drug Administration (FDA).

Priority review designation is assigned to applications for drugs that, if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis or prevention of serious conditions.

The company also has filed a marketing authorization application for NOXAFIL IV solution with the European Medicines Agency (EMA) and plans to seek regulatory approval for the IV formulation in other countries around the world.

Merck currently markets NOXAFIL Oral Suspension in the U.S. for 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 patients who have received hematopoietic stem cell transplants and have graft-versus-host disease, or patients with cancers of the blood who are experiencing prolonged low white blood cell counts (neutropenia) as a result of chemotherapy.

In April, Merck announced that it had filed new drug applications for an investigational, tablet formulation of NOXAFIL with both the FDA and EMA. These applications are currently under review.

## Selected safety information about NOXAFIL Oral Suspension

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

NOXAFIL (posaconazole) 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 pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to QTc prolongation and rare occurrences 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 concentration 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 isolated deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine 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, rare cases of torsades de pointes have been reported in patients taking NOXAFIL. NOXAFIL should be administered with caution to patients with potentially proarrhythmic conditions. 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 and rarely

required drug discontinuation. Isolated 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. Discontinuation of NOXAFIL must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to NOXAFIL.

Concomitant administration of NOXAFIL (posaconazole) with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Patients must be monitored closely for adverse effects associated with high plasma concentrations of midazolam and benzodiazepine receptor antagonists must be available to reverse these effects.

NOXAFIL has been shown to interact with several medications, including drugs that suppress the immune system, and these reactions may be serious. NOXAFIL is also a strong inhibitor of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by NOXAFIL. The product label should be consulted when other drugs are prescribed with NOXAFIL.

Co-administration of NOXAFIL with rifabutin, phenytoin, efavirenz, cimetidine and esomeprazole should be avoided unless the benefit outweighs the risk. Monitoring for toxicity and adverse events is recommended when tacrolimus, cyclosporine, ritonavir, atazanavir, vinca alkaloids, and calcium channel blockers and rifabutin are co-administered 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 co-administering digoxin, phenytoin, tacrolimus and cyclosporine with NOXAFIL. Monitor for breakthrough fungal infections when co-administering metoclopramide, fosamprenavir, rifabutin, phenytoin, cimetidine and esomeprazole with NOXAFIL.

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

The most common adverse reactions (>30%) in the prophylaxis clinical studies were fever, diarrhea, and nausea.

## 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](http://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 risks 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](http://www.sec.gov)).

NOXAFIL® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, N.J., USA.

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Please see Prescribing Information for NOXAFIL (posaconazole) at <http://www.spfiles.com/pinoxafil.pdf> and Patient Information for NOXAFIL at <http://www.spfiles.com/ppinoxafil.pdf>.

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