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PRESCRIBING ALERT®

Dear Healthcare Professional,

At *MPR* we strive to bring you important drug information in a concise and timely manner. In keeping with this goal, we are pleased to bring you this PRESCRIBING ALERT featuring NOXAFIL® (posaconazole) oral suspension.

Merck, the marketer of NOXAFIL, has paid for these program materials to be developed and provided to you.

NOXAFIL is 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 from chemotherapy.[1]

NOXAFIL is the only antifungal agent indicated for prophylaxis against both *Aspergillus* and *Candida*. National guidelines include NOXAFIL for prophylaxis in the following patient populations: neutropenic patients with acute myelogenous leukemia/myelodysplastic syndrome, allogeneic HSCT patients, and HSCT patients with GVHD.[2-5]

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 simvastatin. Concomitant administration of NOXAFIL with simvastatin increases the simvastatin plasma concentrations by approximately 10-fold. Increased plasma statin concentrations can be associated with rhabdomyolysis.

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

NOXAFIL is contraindicated with the 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.

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.

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.

(Selected Safety Information continued on next page)

Hepatic reactions (eg, 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 (eg, hematologic malignancy) during treatment with NOXAFIL® (posaconazole). 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 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. Consider a dosage adjustment of and monitoring for toxicity and adverse events for tacrolimus, cyclosporine, ritonavir, atazanavir, vinca alkaloids, and calcium channel blockers when co-administered with NOXAFIL. Monitor digoxin plasma concentrations when co-administered with NOXAFIL and monitor for breakthrough fungal infections when NOXAFIL is co-administered with metoclopramide.

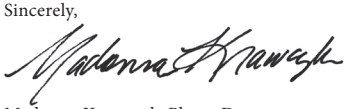
The most common adverse reactions (>30%) in the prophylaxis clinical studies were fever, diarrhea, and nausea.

Before prescribing NOXAFIL (posaconazole), please read the Prescribing Information.

For additional copies of the Prescribing Information, please call 1-800-672-6372, visit noxafil.com, or contact your Merck representative.

More information regarding the use of NOXAFIL is available in the current edition of *MPR*.

Sincerely,



Madonna Krawczyk, PharmD
Director of Clinical Communications
MPR Custom Programs

REFERENCES

1. NOXAFIL [package insert]. Whitehouse Station, NJ: Schering Corporation, a subsidiary of **Merck & Co., Inc.**; 2011. **2.** National Comprehensive Cancer Network. *NCCN Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections*. V.2.2011. http://www.nccn.org. Accessed April 6, 2012. **3.** Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46(3):327-360. **4.** Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(5):503-535. **5.** Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.

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MPR PRESCRIBING ALERT

NOXAFIL®

(posaconazole) Oral Suspension

℞

Indicated for prophylaxis against Aspergillus *and* Candida

Indication: NOXAFIL is a triazole antifungal agent indicated 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 HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy

Dosage and Administration: 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression.

Dosage Forms and Strengths: NOXAFIL Oral Suspension 40 mg per mL.

Contraindications:

- Do not administer to persons with known hypersensitivity to posaconazole, any component of NOXAFIL, or other azole antifungal agents.
- Do not coadminister NOXAFIL with the following drugs; NOXAFIL increases concentrations of:
  - Sirolimus: can result in sirolimus toxicity
  - CYP3A4 substrates (pimozide, quinidine): can result in QTc interval prolongation and rare occurrences of TdP
  - Simvastatin: can result in rhabdomyolysis
  - Ergot alkaloids: can result in ergotism.

Warnings and Precautions:

- Calcineurin Inhibitor Toxicity: NOXAFIL increases concentrations of cyclosporine or tacrolimus; reduce dose of cyclosporine and tacrolimus and monitor concentrations frequently.
- Arrhythmias and QTc Prolongation: NOXAFIL has been shown to prolong the QTc interval and cause rare occurrences of TdP. Administer with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs known to prolong QTc interval and metabolized through CYP3A4. Correct K^+, Mg^{++}, and Ca^{++} before starting NOXAFIL.
- Hepatic toxicity: elevations in LFTs (generally reversible on discontinuation) may occur. Discontinuation should be considered in patients who develop abnormal LFTs or monitor LFTs during treatment.
- Midazolam: NOXAFIL can prolong hypnotic/sedative effects. Monitor patients and benzodiazepine receptor antagonists should be available.

Adverse Reactions: Common treatment-emergent adverse reactions (>30%) in prophylaxis studies are fever, diarrhea and nausea.

Drug Interactions:

- Rifabutin, phenytoin, efavirenz, cimetidine, esomeprazole: avoid co-administration unless benefit outweighs risks.
- Other drugs metabolized by CYP3A4 (tacrolimus, cyclosporine, vinca alkaloids, calcium channel blockers): consider dosage adjustment and monitor for adverse effects and toxicity.
- Digoxin: monitor digoxin plasma concentrations.
- Metoclopramide: monitor for breakthrough fungal infections.

Use in Specific Populations:

- Pregnancy: Based on animal data, may cause fetal harm.
- Nursing Mothers: Discontinue drug or nursing, taking into consideration the importance of drug to the mother.
- Severe renal impairment: Monitor closely for breakthrough fungal infections.

Merck, the marketer of NOXAFIL (posaconazole), has developed these program materials and provided them to you. Before prescribing NOXAFIL, please read the Prescribing Information.

A powerful way to help protect your patients

- NOXAFIL is 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 from chemotherapy[1]
- Prophylaxis against *Aspergillus* and *Candida* plays a role in the management of acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) patients with neutropenia and HSCT patients with GVHD[2-3]

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 simvastatin. Concomitant administration of NOXAFIL with simvastatin increases the simvastatin plasma concentrations by approximately 10-fold. Increased plasma statin concentrations can be associated with rhabdomyolysis.

Before prescribing NOXAFIL, please read the Prescribing Information.

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The only antifungal agent indicated for prophylaxis against both *Aspergillus* and *Candida*

- National guideline recommendations include NOXAFIL® (posaconazole) for prophylaxis against *Aspergillus* and *Candida*[4-7] **(Table 1)**

Table 1

ANTIFUNGAL PROPHYLAXIS RECOMENDATIONS FOR NOXAFIL‡

	AML/MDS (neutropenic)	Allogeneic HSCT	HSCT with GVHD
NCCN Guidelines[4]	**NOXAFIL The only Category 1** recommendation	**NOXAFIL Category 2B** recommendation	**NOXAFIL The only Category 1** recommendation§
IDSA Guidelines for Aspergillosis and Candidiasis[5,6]	**NOXAFIL The only Category A-I** recommendation for *Aspergillus* **NOXAFIL Category A-I** recommendation for *Candida*	**NOXAFIL Category A-I** recommendation for *Candida*	**NOXAFIL The only Category A-I** recommendation for *Aspergillus*
ASBMT Guidelines[7,‖]	Population not addressed	**NOXAFIL Category BI** recommendation	**NOXAFIL Category BI** recommendation

- **In the NCCN Guidelines**, a category 1 rating indicates there is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate. A category 2B rating indicates there is nonuniform consensus based on lower-level evidence, including clinical experience[4]
- **In the IDSA guidelines**, a category A-I rating indicates there is good evidence to support a recommendation for use and evidence from ≥1 properly randomized, controlled trial. A category B-I rating indicates there is moderate evidence to support a recommendation for or against use and evidence from ≥1 properly randomized, controlled trial[5-6]
- **In the ASBMT guidelines**, a category BI rating indicates there is evidence from at least 1 well-executed, randomized, controlled trial and moderate evidence for efficacy—or strong evidence for efficacy, but only limited clinical benefit—supports recommendation for use; should generally be offered[7]

‡For full antifungal guideline recommendations, please consult guideline documents.[4-7]

§Recommended in significant GVHD: Consider antifungal prophylaxis in all patients with GVHD receiving immunosuppressive therapy.

‖ASBMT categorizes allogeneic HSCT patients as standard risk and HSCT patients with GVHD as high risk.

AML = Acute myelogenous leukemia; ASBMT = American Society for Blood and Marrow Transplantation; GVHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplant; IDSA = Infectious Diseases Society of America; MDS = myelodysplastic syndrome; NCCN = National Comprehensive Cancer Network.

Sources: *NCCN Practice Guidelines in Oncology* 2009[4]; Walsh 2008[5]; Pappas 2009[6]; Tomblyn 2009.[7]

The 2010 IDSA Clinical Practice Guidelines for the use of antimicrobial agents in neutropenic patients with cancer state

"Prophylaxis against Candida *infection is recommended in patient groups in whom the risk of invasive candidal infection is substantial, such as HSCT recipients or those undergoing intensive remission-induction or salvage-induction chemotherapy for acute leukemia (A-I)"*[8]

- Posaconazole is an acceptable alternative[8]

"Prophylaxis against invasive Aspergillus *infections with posaconazole should be considered for selected patients ≥13 years of age who are undergoing intensive chemotherapy for AML or MDS in whom the risk of invasive aspergillosis without prophylaxis is substantial (B-I)"*[8]

SELECTED SAFETY INFORMATION (continued)

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

NOXAFIL is contraindicated with the 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.

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.

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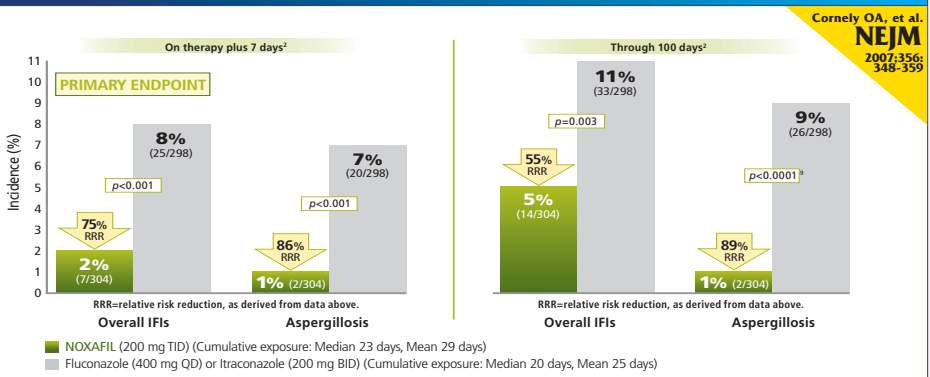
Demonstrated efficacy in a randomized, open-label study (n=602) in AML and MDS patients at high risk of invasive fungal infections (IFI) due to neutropenia[1]

- Clinical failure was significantly lower with NOXAFIL® (posaconazole) (27% [82/304]) vs fluconazole or itraconazole (42% [126/298]) (on therapy plus 7 days; 95% CI [NOXAFIL-comparator group] = -22.9% to -7.8%)[1]
- Composite endpoint was based on breakthrough IFIs, death, and use of systemic antifungal therapies[1]

Significantly fewer IFIs and *Aspergillus* infections vs fluconazole or itraconazole[2] (Figure 1)

Figure 1

NOXAFIL VS FLUCONAZOLE OR ITRACONAZOLE PROPHYLAXIS IN PATIENTS WITH NEUTROPENIA



- A randomized, open-label, evaluator-blinded, active-controlled, multicenter study (n=602) compared NOXAFIL (200 mg 3 times a day) with fluconazole (400 mg daily) or itraconazole (200 mg twice daily)[2]
- Primary endpoint: Incidence of proven or probable IFI during the treatment phase (randomization to 7 days after the last dose of study drug)[2]

IFI = Invasive fungal infections.
Sources: Cornely 2007[2]; Data on file.[9]

SELECTED SAFETY INFORMATION (continued)

Concomitant administration of NOXAFIL (posaconazole) 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.

Hepatic reactions (eg, 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 (eg, 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 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.

Before prescribing NOXAFIL, please read the Prescribing Information.

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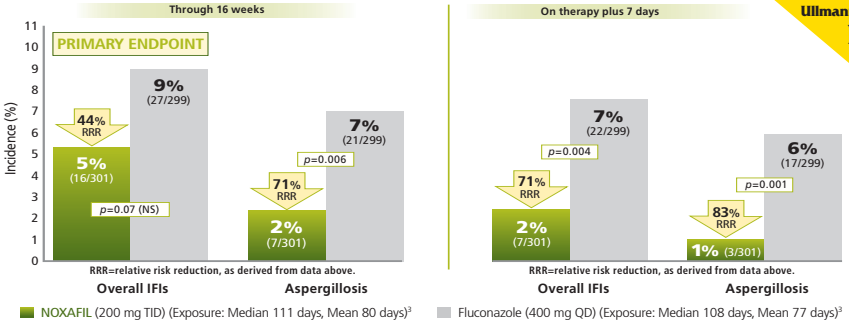
Demonstrated efficacy in a randomized, double-blinded study (n=600) in allogeneic HSCT-GVHD patients[1]

- Clinical failure was similar between NOXAFIL® (posaconazole) (33% [99/301]) and fluconazole (37% [110/299]) (through 16 weeks; 95% CI [NOXAFIL-comparator] = -11.5%, +3.7%)[1]
- Composite endpoint was based on breakthrough IFIs, mortality, and use of systemic antifungal therapies with fluconazole[1]

Similar IFIs and significantly fewer *Aspergillus* infections vs fluconazole in HSCT-GVHD patients[3] (Figure 2)

Figure 2

NOXAFIL VS FLUCONAZOLE PROPHYLAXIS IN PATIENTS WITH SEVERE GRAFT-VERSUS-HOST DISEASE



- A randomized, double-blind, double-dummy, active-control, multicenter study (n=600) compared NOXAFIL (200 mg 3 times a day) vs fluconazole (400 mg daily) as prophylaxis[3]
- Primary endpoint: Incidence of proven or probable IFI during the treatment period (randomization through week 16, regardless of discontinuation of drug)[3]

IFI = Invasive fungal infections.
Source: Ullmann 2007.[3]

Adverse reactions of NOXAFIL were comparable to fluconazole in prophylaxis studies[2,3]

SELECTED SAFETY INFORMATION (continued)

Co-administration of NOXAFIL (posaconazole) with rifabutin, phenytoin, efavirenz, cimetidine and esomeprazole should be avoided unless the benefit outweighs the risk. Consider a dosage adjustment of and monitoring for toxicity and adverse events for tacrolimus, cyclosporine, ritonavir, atazanavir, vinca alkaloids, and calcium channel blockers when co-administered with NOXAFIL. Monitor digoxin plasma concentrations when co-administered with NOXAFIL and monitor for breakthrough fungal infections when NOXAFIL is co-administered with metoclopramide.

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

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

Before prescribing NOXAFIL (posaconazole), please read the Prescribing Information.

For additional copies of the Prescribing Information, please call 1-800-672-6372, visit noxafil.com, or contact your Merck representative.

REFERENCES

1. NOXAFIL [package insert]. Whitehouse Station, NJ: Schering Corporation, a subsidiary of **Merck & Co., Inc.**; 2011. **2.** Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356(4):348-359. **3.** Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007;356:335-347. **4.** National Comprehensive Cancer Network. *NCCN Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections*. V.2.2011. http://www.nccn.org. Accessed April 6, 2012. **5.** Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46(3):327-360. **6.** Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(5):503-535. **7.** Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15(10): 1143-1238. **8.** Freifeld AG, Bow EJ, Sepkowitz KA. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52(4):e56-e93. **9.** Data available on request from Merck & Co., Inc., Professional Services-DAP, WP1-27, PO Box 4, West Point, PA 19486-0004. Please specify information package ANTF-1013725-0000.

 AINF-1018424-0001 05/12