RISK MANAGEMENT PLAN:

EU QPPV FOR THIS RMP

Active substance(s): Posaconazole

Product(s) concerned: Noxafil®

MAH / MAA name: Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

EU Qualified Person for Pharmacovigilance (QPPV) name:	Guy Demol, M.D.

Document ID: 07WV80

File Name: riskmgtsystem-signature

ELECTRONIC SIGNATURES

EU RISK MANAGEMENT PLAN (RMP) FOR Posaconazole

Oral Suspension
Tablet
IV Solution
Gastro-Resistant Powder and Solvent for Oral Suspension

RMP version to be assessed as part of this application:

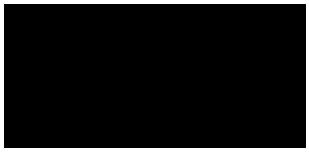
RMP Version number: 18.0

Data lock point for this RMP: 01-Feb-2020

Date of final sign off: 01-NOV-2021

Rationale for submitting an updated RMP:

The RMP was updated primarily due to the submission of the line extension for a new Gastro-Resistant Powder and Solvent for Oral Suspension (PFS) formulation and the proposal to expand the indication for Noxafil to include paediatric patients from 2 to <18 years of age. This version of EU RMP (v18.0) incorporates recommendations provided by the Agency to the MAH in the Assessment Report from both day 120 Request for Supplementary Information and day 180 List of Outstanding Issues (Procedure No. EMEA/H/C/000610/X/0063/G).



Summary of significant changes in this RMP:

RMP Section	Changes
PART I: Product(s) Overview	Updated to include new proposed Gastro-Resistant Powder and Solvent for Oral Suspension (PFS) formulation and proposal to expand the indication for Noxafil (IV, Tablet, and PFS formulations) to include paediatric patients from 2 to <18 years of age.
PART II: MODULE SIII – Clinical trial exposure	Updated overall exposure and demographic information.
PART II: MODULE SV - Post-Authorization Experience	Updated patient exposure data.
PART II: MODULE SVII.2 - New Safety Concerns and Reclassification with a Submission of an Updated RMP	Added the important potential risk of Medication error related to substitution between different formulations (oral suspension and PFS). Updated Missing information from experience in children to Safety in children below 2 years of age.
PART II: MODULE SVII.3.2 Presentation of the Missing Information	Updated Table SVII.3.2.1 Summary of Missing Information –from experience in children to Safety in children below 2 years of age.
PART V: MODULE V.1 Routine Risk Minimization Measures	Added label language about the PFS formulation.
PART V: MODULE V.2 Additional Risk Minimization Measures	Add a one-time DHPC regarding the potential risk of Medication error related to substitution between different formulations (oral suspension and PFS).
PART VI: Summary of the Risk Management Plan by Product	Updated to include product information on PFS formulation, including labelling and indication Added potential risk of Medication error related to substitution between different formulations (oral suspension and PFS). Added one-time dissemination of DHPC related to medication error.

Other RMP versions under evaluation:

There are no previously submitted versions of this RMP that are still under evaluation by the Agency.

Details of the currently approved RMP:

Version number: 16.2

Approved with procedure: EMEA/H/C/000610/ II/0062

Date of approval (opinion date): 16-Sep-2021

QPPV name*:* Guy Demol, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

[redacted]

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LIST OF TABLES

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Experience
ATC	Anatomical Therapeutic Chemical classification system
AmB	Lipid Amphotericin B
ATMP	Advanced Therapy Medicinal Product
BID	Twice A Day
BSI	Bloodstream Infection
BNZ	Benznidazole
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
DHPC	Dear Healthcare Provider Communication
DUS	Drug Utilization Study
ECG / EKG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPITT	European Pharmacovigilance Issues Tracking Tool
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EU	European Union
GVHD	Graft versus-host disease
HAART	Highly Active Antiretroviral Therapy
HLGT	High Level Group Term
HLT	High Level Term
HSCT	Hematopoietic Stem Cell Transplantation
IA	Invasive aspergillosis
ICH	International Council for Harmonization
IDSA	Infectious Diseases Society of America
IFI	Invasive fungal infection
IM	Intramuscular(ly)
INN	International Nonproprietary Name
IV	Intravenous(ly)

MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
NTD	Neglected Tropical Disease
OPC	Oropharyngeal Candidiasis
PAES	Post-authorization Efficacy Study
PASS	Post-authorization Safety Study
PFS	Gastro-Resistant Powder and Solvent for Oral Suspension
PO	Oral(ly)
POS	Posaconazole
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QD	Once Daily
QOD	Every Other Day
QPPV	Qualified Person for Pharmacovigilance
QWK	Once Weekly
RMP	Risk Management Plan
SC	Subcutaneous
SOC	System Organ Class
SOT	Solid Organ Transplant
SmPC	Summary of Product Characteristics
TDM	Therapeutic drug monitoring
TIW	Three Times Per Week
VOR	Voriconazole
WBC	White Blood Cell Count

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) **(INN or common name)**	Posaconazole
Pharmacotherapeutic group(s) (ATC Code)	Antimycotics for systemic use-triazole derivatives ATC code: J02A C04
Marketing Authorisation Holder	Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem The Netherlands
Number of medicinal products to which this RMP refers	One (1)
Invented name(s) in the European Economic Area (EEA)	Noxafil®
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Posaconazole is a broad-spectrum triazole antifungal compound.
	Summary of mode of action: Posaconazole inhibits the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.
	Important information about its composition: *Oral Suspension* The other ingredients include polysorbate 80, simeticone, sodium benzoate, sodium citrate, citric acid monohydrate, glycerol, xanthan gum, liquid glucose, titanium dioxide, artificial cherry flavour and purified water. *Posaconazole Gastro-resistant Tablet (herein referred to as "Posaconazole Tablet")* The other ingredients include hypromellose acetate succinate, microcrystalline cellulose, hydroxypropylcellulose, silicon dioxide, sodium croscarmellose, magnesium stearate, and a yellow coloured coating material. *Posaconazole concentrate for solution for infusion (herein referred to as "POS IV solution")* The other ingredients include Betadex Sulfobutyl Ether Sodium (SBECD), Edetate Disodium, Hydrochloric acid, Sodium Hydroxide, Water for Injection. *Posaconazole Gastro-resistant Powder and Solvent for Oral Suspension* The other ingredients include hypromellose acetate succinate and suspending vehicle (purified water, glycerol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium dihydrogen phosphate monohydrate, citric acid anhydrous, xanthan gum, sodium citrate, saccharin sodium, microcrystalline cellulose and carmellose sodium, carrageenan calcium sulfate trisodium phosphate, sorbitol solution, potassium sorbate, flavour berry citrus sweet PF - containing propylene glycol , water, natural and artificial flavour -and antifoam Af emulsion - containing polyethylene glycol, octamethyl cyclotetrasiloxane, decamethylcyclopentasiloxane and poly(oxy-1,2-ethanediyl), .alpha.-(1-oxooctadecyl)-.omega.-hydroxy).

Table I.1: Product Overview

Hyperlink to the Prescribing Information	See latest approved Prescribing information in Module 1.3 from submission sequence 0130.
Indication(s) in the EEA	**Current:** Noxafil (IV and tablet) is indicated for use in the treatment of invasive aspergillosis in adults. Noxafil (IV, tablet, oral suspension) is indicated for use in the treatment of the following fungal infections in adults: • Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products; • Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B; • Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole; • Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products; Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy. In addition, Noxafil oral suspension is also indicated in adults for the treatment of oropharyngeal candidiasis as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor. Noxafil (IV, tablet, oral suspension) is also indicated for prophylaxis of invasive fungal infections in the following patients: • Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections; • Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

Table I.1: Product Overview

	Proposed:
	In addition to the approved indications,
	Noxafil (Tablet, IV, and PFS) is proposed for use in paediatric patients from 2 to <18 years of age for:
	• Treatment of the following fungal infections:
	  • Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
	  • Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
	  • Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
	  • Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products;
	Refractory disease is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.
	• Prophylaxis of invasive fungal infections in the following patients:
	• Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
	• Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections

Dosage in the EEA	**Current:** *Oral Suspension* Refractory Invasive Fungal Infections (IFI)/Patients with IFI intolerant to 1st line therapy: 200 mg (5 mL) four times a day, or 400 mg (10 mL) twice a day during or immediately following a meal or nutritional supplement. Oropharyngeal candidiasis: Loading dose of 200 mg (5 mL) once a day on the first day, then 100 mg (2.5 mL) once a day for 13 days. Prophylaxis of Invasive Fungal Infections: 200 mg (5 mL) three times a day. Each dose of Noxafil should be administered during or immediately after a meal, or a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption and to ensure adequate exposure. *Tablet* For all indications: Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. *IV Solution* For all indications: Loading dose of 300 mg Noxafil infusion twice a day on the first day, then 300 mg once a day thereafter.

Table I.1: Product Overview

<table>
<tr><td></td><td>Proposed:
<u>Gastro-Resistant Powder and Solvent for Oral Suspension</u>
For all approved paediatric indications
Recommended dose in paediatric patients (2 years to less than 18 years of age) and weighing 10 to 40 kg
<table><tr><th>Weight (kg)</th><th>Dose (volume)</th></tr><tr><td>10-<12 kg</td><td>90 mg (3 mL)</td></tr><tr><td>12-<17 kg</td><td>120 mg (4 mL)</td></tr><tr><td>17-<21 kg</td><td>150 mg (5 mL)</td></tr><tr><td>21-<26 kg</td><td>180 mg (6 mL)</td></tr><tr><td>26-<36 kg</td><td>210 mg (7 mL)</td></tr><tr><td>36-40 kg</td><td>240 mg (8 mL)</td></tr></table>On Day 1, the recommended dose is administered twice. After Day 1, the recommended dose is administered once daily.
<u>IV Solution</u>
For all approved paediatric indications
Loading dose of 6 mg/kg (to a maximum of 300 mg) twice a day on the first day, then 6 mg/kg (to a maximum of 300 mg) once a day thereafter.</td></tr>
<tr><td rowspan="2">Pharmaceutical form(s) and strengths</td><td>Current:
Oral suspension 40 mg/mL is a white, cherry-flavoured immediate release suspension containing 40 milligrams (mg) of posaconazole per milliliter (mL).
Gastro-resistant tablet 100 mg is a yellow-coated capsule-shaped tablet containing 100 mg of posaconazole.
IV solution (concentrate for solution for infusion), 18 mg/mL, clear colourless to yellow liquid.</td></tr>
<tr><td>Proposed: Gastro-resistant powder and solvent for oral suspension 300 mg is a white to off-white powder.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication: Invasive *Aspergillosis*

Invasive aspergillosis (IA), an invasive fungal infection (IFI), is a rapidly progressive often fatal pulmonary infection that may disseminate to the brain, skin, and bone. This infection occurs almost exclusively in patients who are severely immunosuppressed.

Incidence:

The incidence of IA is rare and occurs in immunocompromised patients or patients undergoing treatments that result in prolonged neutropenia and immunosuppression. As more people are surviving with treatment related or chronic conditions that cause immune suppression, it is generally understood that the population at risk for IA has increased. Yet, with the availability of newer therapies that can combat IA, the associated mortality has decreased. Obtaining precise estimates of the global incidence of IA can be challenging because there is no obligatory reporting of fungal infections, no regular national surveillance systems for IFI, poor clinical suspicion of fungal infections and often poor diagnostic tests.

The global estimate, based on a thorough review of literature at the country level, is 300,000+ cases of invasive aspergillosis per year [Ref. 5.4: 0555LN]. Among 40 countries, the reported incidence of IFI ranged from 0.1 per 100,000 in Tanzania to 16.0 per 100,000 in Vietnam. In Europe, the incidence of IFI ranged from 1.8 per 100,000 in France to 10.4 per 100,000 in Greece. Incidence of IFI is often reported by subgroups at greatest risk for IFI. Aspergillus infections have been reported in 2 to 26% of HSCT recipients and in 1 to 15% of organ transplant recipients [Ref. 5.4: 00W8W0]. The burden of invasive aspergillosis in patients with hematologic malignancy and HSCT has declined as antifungal prophylaxis is being used more widely in high-risk patients. For instance, a recent literature review and meta-analysis reported the crude incidence was 6.3% (1,056 IA cases/16,815 patients); the incidence ranged from 4% in patients during remission-induction who received antifungal prophylaxis to 11% in patients during remission-induction who did not receive antifungal prophylaxis [Ref. 5.4: 055P6W]. Among solid organ transplant (SOT) recipients, IA is more common in lung and heart transplants compared to other organ types [Ref. 5.4: 00W8H4, 00W8W0]. In a recent Swiss cohort study among 2,868 solid organ transplant patients, the overall incidence of IA was 2.4%, with organ-specific IA incidence 8.3%, 7.1%, 2.6%, 1.3%, and 1.2% in lung, heart, combined, kidney, and liver transplant recipients, respectively [Ref. 5.4: 055KY4].

Prevalence:

Since this is a disease that is typically shorter in duration and does not develop into a chronic condition, incidence is reported and not prevalence.

Demographics of the population in the Invasive Aspergillosis indication and risk factors for the disease:

Demographics of the target population:

The demographics of individuals with aspergillosis infection are consistent with the demographics of individuals with immunocompromised conditions with which this infection is associated. Though it is rare in children, they are also at risk for IA.

Risk factors for the disease:

Well-established risk factors for invasive aspergillosis include underlying lung disease, prolonged neutropenia, primary immunodeficiency disorders (including chronic granulomatous disease), immunosuppressive therapy, corticosteroid therapy, allogenic hematopoietic stem cell transplantation (HSCT), heart, lung and pancreas organ transplants and graft versus-host disease (GVHD) and its treatment. HSCT recipients more frequently develop disseminated disease, while persons with hematologic malignancies more commonly develop diffuse invasive pulmonary disease, as do persons with AIDS [Ref. 5.4: 00W895]. Patients with chronic obstructive pulmonary disease (COPD) are considered low risk for IFI, however because there are many patients with COPD, they constitute a substantial number of patients with IFI [Ref. 5.4: 0555LN].

The main existing treatment options:

Current Infectious Diseases Society of America (IDSA, 2016) guidelines recommend voriconazole (VOR) and/or isavuconazole for the primary treatment of IA, with liposomal amphotericin B being the first alternative [Ref. 5.4: 04K7W2]. POS, as well as echinocandins, are mainly recommended for salvage treatment, triazoles, including posaconazole, are the preferred therapies for treatment and prevention of IA in most patients. For patients who receive a prolonged course of azole therapy or who may also receive concomitant therapies susceptible to a drug-drug interaction, therapeutic drug monitoring (TDM) is recommended. Lipid amphotericin B (AmB) is appropriate as initial or salvage therapy. However, it should be reserved for resource-limited settings or settings in which recommended azoles are contraindicated or not recommended. Aerosolized AmB may be appropriate as prophylaxis in patients with prolonged neutropenia or in lung transplant patients [Ref. 5.4: 04K7W2].

Natural history of Invasive Aspergillosis, including mortality and morbidity:

Invasive aspergillosis is a rapidly progressive, often fatal pulmonary infection that may disseminate to the brain, skin, and bone. The outcome of invasive aspergillosis remains poor. Invasive aspergillosis is associated with significant mortality. Depending on underlying disease and length of follow-up, mortality ranges from 15-85% [Ref. 5.4: 055P6W, 055KY4, 0555LN]. Among SOT recipients, case-fatality was highest among liver transplant recipients (6/7, 85.7% compared to others (10/63, 15.9%) [Ref. 5.4: 055KY4]. In the cohort study of IA in patients with hematological malignancy, the pooled case fatality rate within 100 days was 29% (95% CI: 20-38%) [Ref. 5.4: 055P6W].

Indication: Fusariosis

Fusarium species are found in the soil and can cause a range of infections in humans, from superficial or locally invasive skin infections to disseminated infections involving the bloodstream, sinuses, and lower respiratory tract. Immunocompetent and immunocompromised persons are vulnerable to fusarial infections, although more severe disseminated infections usually only occur in the immunocompromised. The most frequent species causing infections in humans include members of the *Fusarium solani* complex, *Fusarium oxysporum, Fusarium verticillioidis* and *Fusarium moniliforme* [Ref. 5.4: 055SQF].

Incidence:

While fusarial infection in immunocompromised individuals can be very serious, it is rare. The incidence of fusarial infection among HSCT recipients is typically not higher than 2% [Ref. 5.4: 055SQF, 00W893, 00W8HP, 00W8H3]. Furthermore, among HSCT recipients, the incidence is highest in allogeneic mismatched HSCT recipients (20 per 1000), then matched allogeneic HSCT recipients (2.28 to 5.0 per 1000) and lowest in autologous HSCT recipients (1.4 to 2.0 per 1000) [Ref. 5.4: 00W8HP].

Prevalence:

Since this is a disease that is typically shorter in duration and does not develop into a chronic condition, incidence is reported and not prevalence.

Demographics of the population in the Fusariosis indication and risk factors for the disease:

Demographics of the target population:

The demographics of individuals with severe, disseminated fusarial infection are consistent with the demographic profile of individuals with immunocompromised conditions with which this infection is associated.

Risk factors for the disease:

Risk factors for disseminated fusariosis include severe immunosuppression (neutropenia, lymphopenia, GVHD, corticosteroids), colonization, tissue damage, and receipt of graft from an HLA-mismatched or unrelated donor. *Fusarium* has recently emerged as the second most common pathogenic mold (after *Aspergillus*) in high-risk patients with hematological cancer and in recipients of solid organ and allogenic bone marrow or stem cell transplants [Ref. 5.4: 00W897]. In the latter patient population, the distribution of fusariosis is considered to be trimodal, with the first peak in the early post-transplant period (during neutropenia). The second peak occurs approximately 70 days after transplant among patients experiencing acute GVHD and receiving corticosteroids. The third peak occurs more than a year after transplant among patients experiencing chronic GVHD and receiving immunosuppressive therapies [Ref. 5.4: 055SQF, 00W8HP]. Though rare, fusarial infections also impact SOT recipients [Ref. 5.4: 055KYS, 055KXL].

[redacted]

Main treatment options:

Treatment options include amphotericin B lipid formulations or voriconazole. Posaconazole is used when treatments with other antifungal therapy cannot be tolerated or have failed. Surgical options should also be considered.

Natural history of Fusariosis, including mortality and morbidity:

Fusarial infections can range from superficial or locally invasive skin infections to disseminated infections involving the bloodstream, sinuses, and lower respiratory tract. Mortality from fusarial infections in immunocompromised patients ranges from 50% to 80% [Ref. 5.4: 00W897].

Indication: Chromoblastomycosis

Chromoblastomycosis is a chronic granulomatous infection of the skin and subcutaneous tissues due to a group of dematiaceous fungi including *Fonsecaea pedrosoi*, *Cladophialophora carrionii*, *Phialophora verrucosa*, *Fonsecaea compacta* and *Rhinocladiella aquaspersa.* This infection occurs in tropical and subtropical regions and results from traumatic implantation of material contaminated by the fungus. It has been reported mainly from Madagascar, Africa, North, Central and South America, Australia, Caribbean Islands, India, Japan, and in Europe as an imported infection [Ref. 5.4: 00W9W8]. This disease was recently considered a neglected tropical disease (NTD) by the WHO [Ref. 5.4: 0555LN].

Incidence:

The incidence and prevalence are difficult to determine due to the fact that there is no tracking of this disease. While the disease is considered endemic in certain areas, the global burden has been reported as uncommon [Ref. 5.4: 0555LN]. Cases are most often reported from Latin America, the Caribbean, Africa and Asia [Ref. 5.4: 055SQG].

Prevalence:

Since this is a disease that is typically shorter in duration and does not develop into a chronic condition, incidence is reported and not prevalence.

Demographics of the population in the Chromoblastomycosis indication and risk factors for the disease:

Demographics of the target population:

Chromoblastomycosis occurs in adult males of 30–50 years of age in rural areas and is rare in children. Male predominance most likely associated with farming/agricultural work. However, it has also been suggested that there may be hormonal protection against infection for women [Ref. 5.4: 055SQF].

Risk factors for the disease:

Risk factors for this infection include being male, and farming/agricultural work in subtropical or tropical regions.

Main treatment options:

To remove lesions, therapeutic options include, surgical removal, applied heat therapy, cryosurgery, laser therapy and photodynamic therapy. These procedures are often done in combination antifungal drug therapy. Treatment options also include triazoles. In a review article, Queiroz-Telles et al report "Posaconazole is the best potential option for treatment of all clinical presentations of chromoblastomycosis, including severe or refractory clinical forms." For refractory cases, posaconazole may be used in combination with oral flucytosine [5-FC]) [Ref. 5.4: 055SQG].

Natural history of Chromoblastomycosis, including mortality and morbidity:

Morbidity is directly related to severity of the disease. The infection may initially be asymptomatic. Infection may progress to involve the whole limb resulting in serious complications: ulceration, lymphedema, and secondary infections. Mortality due to chromoblastomycosis infection is rare.

Indication: Mycetoma

Mycetoma is a chronic, granulomatous disease of the skin and subcutaneous tissue, which sometimes involves muscle, bones, and neighboring organs. Mycetomas are caused by fungus or actinomycetes. Deep-seated infection caused by these fungi is often referred to as phaeohyphomycosis. Mycetoma infections most often start in the foot after a trauma and can spread to the muscle and bone [Ref. 5.4: 055KYY]. The most common fungal cause is *Madurella mycetomatis* worldwide and *Pseudallescheria boydii* in the United States. Other responsible organisms include *Madurella grisea, Leptosphaeria senagalensis,* and *Scedosporium apiospermu.* Mycetoma is rare in the US, occurring occasionally in the South. Mycetoma is endemic around the Tropic of Cancer, in tropical, subtropical, and temperate regions. Mexico, Venezuela, Sudan, India, Pakistan, Senegal, and Somalia have the highest reports of this disease worldwide [Ref. 5.4: 00W8HQ].

Incidence:

The incidence and prevalence of Mycetoma is not well understood because there is no formal reporting and tracking of this disease. It has been estimated that the global burden of this disease is approximately 9,000 cases [Ref. 5.4: 055KYY]. This disease is now considered a neglected tropical disease (NTD) [Ref. 5.4: 055KYY, 0555LN].

Prevalence*:*

Since this is a disease that is typically shorter in duration and does not develop into a chronic condition, incidence is reported and not prevalence.

Demographics of the population in the Mycetoma indication and risk factors for the disease:

Demographics of the target population:

Mycetoma occurs more frequently in males, ages 11-40 years, in subtropical and tropical regions [Ref. 5.4: 055KYY].

Risk factors for the disease:

Males working outdoors in subtropical and tropical regions are at high risk of infection.

Main treatment options:

Treatment includes surgery or antifungals, including triazoles voriconazole, posaconazole and itraconazole. Posaconazole is also useful as salvage therapy after the failure of other antifungals [Ref. 5.4: 055KXB].

Natural history of Mycetoma, including mortality and morbidity:

Mycetoma is a chronic, granulomatous disease of the skin and subcutaneous tissue, which sometimes involves muscle, bones, and neighboring organs. Complications include secondary bacterial infections. Mycetoma is rarely fatal.

Indication: Coccidioidomycosis

Coccidioidomycosis is a fungal disease of the western hemisphere caused by *Coccidioides immitis* and *Coccidioides posadasii*, dimorphic fungi that grow as mold in the soil. Endemic areas include the southwestern US, parts of Mexico and South America.

Incidence:

The estimated number of infections in the US is approximately 150,000 per year [Ref. 5.4: 00W8H2]. In Arizona, a highly endemic area, the incidence increased from 43 cases per 100,000 people in 2001 to 63 per 100,000 in 2004 [Ref. 5.4: 00W8GZ]. The incidence further increased in 2009 and 2011 to 154 per 100,000 and 248 per 100,000, respectively [Ref. 5.4: 055KVG, 055KX3]. In 2009, there was a change by a large commercial laboratory in which a practice was changed to conform with that used by other laboratories to report positive enzyme immunoassay (EIA) results as coccidioidomycosis cases without confirmation by immunodiffusion. Furthermore, the performance of EIA may vary across different patient groups. As a result, the increased incidence of coccidioidomycosis may be attributed, in part, to newer diagnostic procedures resulting in a high false-positive rate [Ref. 5.4: 055KVG].

The risk of coccidioidomycosis among solid-organ transplant recipients living in endemic areas was 4%-9% with the majority of infections occurring 1 year after transplantation. Before the introduction of highly active antiretroviral therapy (HAART), coccidioidomycosis was a major opportunistic infection in endemic areas among individuals infected with HIV-1. The incidence of clinically apparent coccidioidal infection has since decreased [Ref. 5.4: 00W8H2].

Prevalence*:*

Since this is a disease that is typically shorter in duration and does not develop into a chronic condition, incidence is reported and not prevalence.

Demographics of the population in the Coccidioidomycosis indication and risk factors for the disease:

Demographics of the target population:

All age and race groups can be infected. The risk of dissemination or progressive pulmonary disease depends on underlying immune condition. Coccidioidomycosis is more common in men than in women.

Risk factors for the disease:

Coccidioidomycosis is typically transmitted by inhalation of airborne spores in endemic areas or on contaminated material from the endemic areas. Individuals with a compromised immune system are at increased risk of infection. Additional risk factors include: Filipino or African ethnicity, HIV/AIDS, exposure to immunosuppressive therapies such as prednisone, TNF-α inhibitors, chemotherapy, therapies such as tacrolimus for organ transplantation, diabetes mellitus, and pregnancy [Ref. 5.4: 055KVG].

Main treatment options:

Treatment options include amphotericin B, fluconazole, or itraconazole. Posaconazole is used when treatments with other antifungal therapy (amphotericin B, itraconazole or fluconazole) cannot be tolerated or have failed.

Natural history of Coccidioidomycosis, including mortality and morbidity:

Many who are exposed to *Coccidioides* do not develop infection; after inhaling *Coccidioides* spores, 60% of infected persons remain asymptomatic and 40% develop mild-to-severe symptomatic pulmonary infections including cough, headache, fever and rash. The minority, about 1% develop disseminated disease, which can involve the skin, joints, bones, central nervous system, or other organs. Those who are immunocompromised are most likely to develop severe, disseminated disease. Though rare, fatalities are associated with coccidioidomycosis. Despite increasing incidence of coccidioidomycosis, there is no corresponding increase in mortality [Ref. 5.4: 055KVG].

Indication: Cryptococcosis

Cryptococcus neoformans, yeast most commonly found in the soil, can cause cryptococcosis in immunocompromised patients such as those who have AIDS; those who have hematologic malignancies; those who have undergone solid organ transplantation; and those undergoing systemic corticosteroid therapy or other immunosuppressive treatments. The infection can spread to the lungs and to the brain causing cryptococcal meningitis.

Incidence:

An active surveillance study showed that the incidence of cryptococcosis in patients who did not have AIDS was approximately 0.2 to 0.8 per 100,000, depending on the geographic areas [Ref. 5.4: 00W894]. The incidence in 2000 was 7 per 1,000 and 2 per 1,000 in Atlanta, Georgia and Houston, Texas, respectively[Ref. 5.4: 00W8HK]. The incidence is higher in those with HIV. However, after HAART became widely available in the US and other developed countries, the incidence of cryptococcosis decreased significantly. Globally, the annual incidence of cryptococcosis (cryptococcal meningitis) among the HIV-infected population is estimated to be 223,000; when accounting for and including those without HIV, the estimate increases by 10% [Ref. 5.4: 0555LN, 055SQH]. Nearly three quarters of cases of cryptococcal meningitis among those infected with HIV are estimated to occur in Sub-Saharan Africa where there is a large population with HIV and limited access to HAART [Ref. 5.4: 055SQH].

Prevalence*:*

Since this is a disease that is typically shorter in duration and does not develop into a chronic condition, incidence is reported and not prevalence.

Demographics of the population in the Cryptococcosis indication and risk factors for the disease:

Demographics of the target population:

The demographics of cryptococcal infection are consistent with the immunocompromised conditions with which this infection is associated, especially HIV.

Risk factors for the disease:

Risk factors for Cryptococcal infection is immunocompromised status. The majority of infections are in patients with HIV.

Main treatment options:

Amphotericin B is used to treat severe cryptococcal infections, including those with central nervous system involvement. Flucytosine may be added to amphotericin in the treatment of cryptococcal meningitis and serious cryptococcal infection [Ref. 5.4: 055P3C]. Fluconazole, itraconazole or posaconazole are used to treat asymptomatic or mild- to-moderate cryptococcosis. Posaconazole has been used as second line therapy (salvage therapy) in cases of cryptococcal meningitis or systemic cryptococcal infection.

Natural history of Cryptococcosis, including mortality and morbidity:

The most common manifestation of cryptococcal infection is meningitis. In immunocompromised individuals, disseminated disease is also common.

However, the incidence and mortality of cryptococcosis are still extremely high in countries with uncontrolled HIV epidemics and limited access to HAART or health care, such as certain areas within Africa and Asia [Ref. 5.4: 055SQH]. Globally, cryptococcal meningitis results in 15% of AIDS-related mortality (95% CI 10–19%) with the majority of fatalities occurring in Sub-Saharan Africa[Ref. 5.4: 055SQH].

Indication: Oropharyngeal Candidiasis

Oropharyngeal candidiasis (OPC) is an opportunistic fungal infection that affects the oral cavity, almost always caused by *Candida albicans.* There are four types of OPC: 1) pseudomembranous (thrush), 2) erythematous, 3) hyperplastic and 4) denture-induced stomatitis [Ref. 5.4: 043375]. Although OPC is defined as superficial candidiasis with shallow levels of tissue invasion, the infection can progress to systemic candidiasis in immunocompromised patients.

Incidence:

Candida species are common and often do not affect people. Oropharyngeal candidiasis affects 15%-60% of people with hematological or oncological malignancies during periods of immunosuppression. Oropharyngeal candidiasis occurs in 7%-48% of people with HIV infection and in over 90% of those with advanced disease [Ref. 5.4: 00W8J6]. Oropharyngeal candidiasis is among the most common opportunistic infections in HIV-infected patients and increases in frequency and intensity as the patient's CD4 cell count decreases. Oropharyngeal candidiasis is often one of the first clinical signs of underlying HIV infection and will occur in 50% to 95% of all HIV-infected persons at some point during their progression to acquired immunodeficiency syndrome (AIDS) [Ref. 5.4: 00W898]. Oropharyngeal candidiasis is also a common manifestation of chronic mucocutaneous candidiasis, and also occurs in patients with lymphoma, those undergoing steroid therapy, and in transplant recipients.

Precise and generalizable incidence rates of oropharyngeal candidiasis are unavailable. Globally, there are an estimated 2 million cases or oral candidiasis among HIV patients per year and an estimated 1.3 million cases of oesophageal candidiasis per year [Ref. 5.4: 0555LN].

Prevalence*:*

Since this is a disease that is typically shorter in duration and does not develop into a chronic condition, incidence is reported and not prevalence.

Demographics of the population in the Oropharyngeal Candidiasis indication and risk factors for the disease:

Demographics of the target population:

OPC can occur in normal newborns. However, OPC occurs more frequently and with greater severity in individuals with a compromised immune system, especially in individuals with HIV infection/AIDS.

Risk factors for the disease:

OPC is an opportunistic infection with risk factors including conditions associated with a weakened or compromised immune system such as solid organ or stem cell transplants and HIV-infection/AIDS. Risk factors for OPC also include being less than 1 month old, wearing dentures, diabetes, cancer, smoking, use of antibiotics, corticosteroids or medications that cause dry mouth. Other risk factors include hematologic disorders, broad-spectrum antibiotic use, inhaled or systemic corticosteroids, xerostomia, diabetes, wearing dentures, obturators or other orthodontic appliances and smoking [Ref. 5.4: 043375].

Main treatment options:

Clotrimazole troches and nystatin suspension usually provide effective treatment. If infections do not respond to these treatments, systemic antifungals may be necessary. The options for systemic antifungals include: fluconazole, miconazole, itraconazole, and posaconazole. In infants and children, nystatin is less effective than the azoles [Ref. 5.4: 043375].

Natural history of Oropharyngeal Candidiasis, including mortality and morbidity:

Individuals with OPC infection usually have painless, white patches in the mouth. OPC infections spreading to the esophagus (referred to as esophageal candidiasis) may be associated with pain and difficulty swallowing. OPC has a low attributable mortality. However, OPC infection can, but rarely, progress to invasive candidiasis.

Indication: Invasive Candidiasis

Invasive candidiasis occurs when Candida enters the bloodstream by direct penetration from epithelial tissues causing bacteremia and then spreads throughout the body. There are two forms of invasive candidiasis, candidemia and disseminated candidiasis. Candidemia is the isolation of Candida species in a blood culture [Ref. 5.4: 04S9XW]. Disseminated candidiasis is associated with multiple deep organ infections and can be difficult to diagnose. [Ref. 5.4: 04S9XW]

Incidence:

Candida species are the most common cause of IFIs in hospitalized patients and the fourth most common cause of nosocomial bloodstream infection (BSI) in the US, at least in ICUs [Ref. 5.4: 03RLM6]. Candida blood infections have steadily increased since the 1980s and account for 8-15% of all blood infections [Ref. 5.4: 00W8J9]. However, some evidence suggests that the incidence of invasive *Candida* infections peaked in the early 1990s and have started to fall thereafter, probably due to improvements in hygiene and disease management [Ref. 5.4: 04S9XW]. The global disease burden of invasive *Candida* infections is difficult to quantify because of wide geographic variation. Conservatively, there are 250,000 people with invasive candidiasis annually. A recent report estimates the global annual incidence of invasive candidiasis to be approximately 720,000 cases per year [Ref. 5.4: 0555LN]. The incidence of candidemia in population-based studies ranges from 2-14 cases per 100,000 persons with the Centers for Disease Control and Prevention reporting the invasive candidiasis incidence rate as 8-10 per 100,000 persons per year [Ref. 5.4: 03RLM8, 04T70M, 00W895, 04S9XW]. The US rates have been higher in infants (75 per 100,000) and the elderly (45 per 100,000) [Ref. 5.4: 00W8H5].

Candidemia is the fourth most common catheter-related BSI in Europe. The incidence of candidemia in Europe, based upon a few small studies, ranges from 1.4 cases per 100,000 to 4.9 cases per 100,000 population [Ref. 5.4: 00W890, 00W8J8, 00W88Z].

Previously, *C. albicans* was the most common pathogen [Ref. 5.4: 00W8J9]. In more recent studies, *C. albicans* accounts for only half of the isolates. In northern Europe, the US and Canada, *C. glabrata* has become a leading pathogen and in Southern Europe, Asia and South America, *C. parapsilosis* has become the more prominent pathogen [Ref. 5.4: 04T70M], 00W8W3, 00W892]. The shift in pathogenic Candida species may be due to the increased use of azole prophylaxis, although this remains unclear.

Prevalence*:*

Since this is a disease that is typically shorter in duration and does not develop into a chronic condition, incidence is reported and not prevalence.

Demographics of the population in the Invasive Candidiasis indication and risk factors for the disease:

Demographics of the target population:

The highest rates in the population under surveillance occurred in infants (75 per 100,000) and the elderly (45 per 100,000) [Ref. 5.4: 00W8H5].

Risk factors for the disease:

The two most common factors that predispose to invasive *Candida* infections are immunosuppression, usually as a result of chemotherapy for hematological malignancy or solid tumors, and treatment in an ICU. Critical illness with particular risk among patients with long-term ICU stay, abdominal surgery, especially among patients who have

anastomotic leakage or have had repeat laparotomies, acute necrotizing pancreatitis, recent antibiotic use, prematurity or low birthweight, total parenteral nutrition, and importantly central venous catheterization are other risk factors. [Ref. 5.4: 04S9XW]

Main treatment options:

Per recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, echinocandins (caspofungin, anidulafungin, micafungin) are the first-line treatment for candidiasis. Additionally, Infectious Diseases Society of America (IDSA) guidelines note that echinocandins are the preferred treatment for unstable patients, patients receiving prior azole prophylaxis, and patients with documented *C. glabrata* or *C. krusei* infections. Azoles (fluconazole, voriconazole and posaconazole) are also used to treat candidiasis infection. Finally, Amphotericin B is another treatment option, and has been used for decades to treat candidiasis infection but is associated with significant nephrotoxicity. At this time, antifungal prophylaxis should be limited to patients with gastrointestinal anastomotic leakage, patients undergoing transplantation of the pancreas or the small bowel, selected patients undergoing liver transplantation at high risk for candidiasis and extremely low-birthweight neonates in settings with high incidence of neonatal candidiasis [Ref. 5.4: 04T70M].

Natural history of Invasive Candidiasis, including mortality and morbidity:

Candida infections have been associated with significant mortality, especially among critically ill patients. The crude mortality rate of these infections is high (40-75%), and the attributable mortality of candidemia has been estimated at 25%-38% [Ref. 5.4: 00W9WX]. Even with antifungal therapy, the mortality is as high as 40% [Ref. 5.4: 04S9XW].

Indication: Mucormycosis (previously called zygomycosis)

Mucormycosis (also known as zygomycosis) is the infection caused by fungi belonging to the class Zygomycetes, order Mucorales and Entomophthorales. The Mucorales order contains 2 families—Mucoraceae and Cunninghamellaceae. The majority of human infections are caused by Mucorales fungi, and the term Mucormycosis is now used to designate this infection instead of Zygomycosis. Overall, molds of the class Zygomycetes are a less frequent cause of infection than are *Aspergillus* species. Unlike other filamentous fungi that are largely opportunistic in patients with cancer, transplant recipients, and patients with inherited immunodeficiencies, mucormycosis also can be a frequently lethal infection in hosts with greater immunocompetency, such as those with diabetes mellitus, those with iron overload, injection drug users, and those with no apparent immune impairment. In a recent review of 929 reported cases, persons with no underlying condition and patients with diabetes represented >50% of all infected patients [Ref. 5.4: 00W8W8].

Incidence:

The true incidence of invasive mucormycosis is not known, although a population-based survey in the United States estimated an incidence of 1.7 cases per 1 million people per year, that is, approximately 500 cases per year [Ref. 5.4: 04F3R0]. The incidence can be

considerably higher in institutions that have larger populations of immunocompromised patients. In a multi-year, multi-center study of stem cell transplant patients, 6% (N-983) developed an IFI. Of the IFI, 8% (N=77 cases) were mucormycosis infections; thus, the incidence was 0.46% [Ref. 5.4: 04F7JH]. Among solid organ transplant patients, 2% of IFI were due to mucormycosis [Ref. 5.4: 00QXK8].

Prevalence*:*

Since this is a disease that is typically shorter in duration and does not develop into a chronic condition, incidence is reported and not prevalence.

Demographics of the population in the Mucormycosis indication and risk factors for the disease:

Demographics of the target population:

The demographics of individuals with mucormycosis infection are consistent with the demographic profile of the conditions with which this infection is associated.

Risk factors for the disease:

Risk factors for mucormycosis include individuals with severe neutropenia, recipients of corticosteroids or other immunosuppressive medications, poorly controlled diabetes mellitus, and those with iron overloaded states.

Main treatment options:

Mucormycosis is treated with antifungals including amphotericin B, posaconazole and isavuconazole. Surgical intervention is often needed to remove infected tissue.

Natural history of Mucormycosis, including mortality and morbidity:

Zygomycetes infection is rapidly progressive and often fatal [Ref. 5.4: 00WBCV]. The most common sites of infection include the sinuses, lung, and skin. Disseminated infection is also common. The patient's underlying health conditions influence both the clinical presentation and mortality rates.

Important co-morbidities for invasive fungal infections (IFIs):

Risk for IFIs is greatest for patients who are immunocompromised, such as HIV/AIDS patients, transplant recipients, cancer patients, and other individuals receiving immunosuppressive treatment. See SI.1 for further information on the occurrence of IFIs in specific at-risk populations.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Nonclinical toxicology studies conducted with posaconazole consist of studies by oral and IV routes.

In support of oral administration:

- Single dose oral studies in dogs and monkeys
- Oral toxicology studies up to three months' duration in mice, up to six months' duration in rats and up to 12 months' duration in dogs and monkeys
- Genetic toxicology studies (bacterial mutagenicity; chromosomal aberration, Chinese hamster ovary (CHO) cells studies, mouse micronucleus)
- Carcinogenicity studies in rats and mice
- Fertility and embryo-fetal development studies in rats and rabbits and a peri-postnatal study in rats

In support of IV administration:

- One-month monkey study (IV solution)
- Three-month studies in monkeys and rats (IV suspension) and dogs (IV solution)
- Local irritation studies in rabbits (IV Solution and IV suspension)

In support of pediatric administration:

- Oral studies in juvenile rats and juvenile dogs
- IV studies in juvenile dogs.

Because there is a potential for cardiovascular effects with azoles, cardiovascular safety pharmacology studies in rats and monkeys were also performed.

Posaconazole causes several toxicological effects that occur with other antifungal substances in the azole class, i.e., hyperplasia of the adrenal glands (mice, rats and dogs), phospholipidosis of lung and lymphoid tissues (all species), disseminated intravascular coagulation (DIC; dogs only), bone thinning/fractures (rats only), hepatocellular adenomas (mice only), and findings secondary to the interruption of steroidogenesis and fetal toxicity (rats and rabbits). Posaconazole findings not reported with other marketed antifungal agents are neuronal phospholipidosis in dogs, increased urinary calcium excretion in dogs and rats, histiocytic

hyperplasia in lymph nodes in mice, and adrenal gland cortical cell tumors in rats. Posaconazole was not mutagenic or clastogenic.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Repeated dose toxicity studies	
Hyperplasia of the adrenal glands (mice, rats and dogs), phospholipidosis of lung and lymphoid tissues (all species), disseminated intravascular coagulation (dogs only), bone thinning/fractures (rats only), hepatocellular adenomas (mice only), findings secondary to the interruption of steroidogenesis and fetal toxicity (rats and rabbits).	Non-clinical effects observed with other antifungal substances in the azole class. 'Occurrence of any neoplasm/malignancy' was previously classified as an important potential risk in EU RMP. However, accumulating clinical study and post marketing pharmacovigilance do not support the initial supposition based on findings from the animal study.
Posaconazole findings not reported with other marketed antifungal agents are neuronal phospholipidosis in dogs, increased urinary calcium excretion in dogs and rats, histiocytic hyperplasia in lymph nodes in mice and adrenal gland and cortical cell tumors in rats.	The relevance of neuronal phospholipidosis and increased urinary calcium excretion (dog and rat) are unknown. Hyperplasia/tumor is no longer considered of significant implication as discussed above. Based on a favorable risk benefit profile, which includes extensive clinical experience, these findings are acceptable for the proposed indication.
Reproductive / developmental toxicity	
Embryo resorptions, post-implantation losses, delayed parturition and dystocia are consistent with decreased estrogen and/or progesterone levels (not measured) caused by posaconazole-induced inhibition of P450 enzymes involved in the steroid synthetic pathways in females (not tested). These effects, as well as fetal skeletal malformations and variations, occur with several azole antifungal drugs.	Non-clinical effects observed with other antifungal substances in the azole class. The relevance to human use is unknown.
Safety Pharmacology	
Increased heart weights and increases in arterial blood pressure in rats at 90 mg/kg and arterial blood pressure increases in monkeys at 40 mg/kg.	The relevance of these findings to human use is supported by clinical studies. Based on a favorable risk benefit profile, these findings are acceptable for the proposed indication.
A measured concentration of 770 ng/mL (1.1 uM) posaconazole decreased hERG current by 7% relative to vehicle control. In Purkinje fibers isolated from dog heart, exposure to posaconazole at measured concentrations of 25ng/mL (36nM), 69 ng/mL (98 nM) and 365 ng/mL (521 nM) induced a small (<10%) but statistically significant increase in action potential duration at 60% (APD60) and/or 90% (APD90) repolarization.	These findings may have relevance to the rare occurrence of Torsade de Pointes/QTc prolongation in human. The benefits of the product outweighed the potential risks.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Juvenile toxicity	
Enlarged ventricles in the brains of juvenile dogs, with no neurological or behavioural or developmental abnormalities were observed with POS IV solution administration from post-natal days 14-56 (human equivalent age <2 years). This finding was shown to be reversible after treatment cessation and was not observed with oral administration in juvenile rats or dogs or when POS IV was administered to juvenile dogs aged 70-154 days of age.	Uncertain relation to administration in children aged 3 months-2 years. No human relevance for adult indications and for clinical development in paediatrics of ≥ 2 years of age. Human relevance unknown for paediatrics < 2 years of age.
Non-clinical In vitro OATP Studies	
OATP-Mediated Uptake of Posaconazole	
The potential for posaconazole to be a substrate of human hepatic uptake transporters was studied in recombinant cells lines and in human hepatocytes. The uptake of posaconazole (0.1 and 1 µM) into HEK293 cells transiently expressing OATP1B1 and OATP1B3 was limited, with a maximal 1.4-fold increase in OATP1B1 cell uptake, and 1.5-fold increase in OATP1B3 cell uptake, compared to the parental HEK293 cells. In parallel experiments, uptake of the positive control substrates $E_2$17βG and CCK-8 were 69- to 105-fold and 247- to 432-fold greater in OATP1B1 and OATP1B3 expressing cells, respectively, as compared to parental HEK293 cells.	Based on the minimal uptake in OATP1B1 and OATP1B3 cell lines compared to the positive controls, as well as its relatively high bioavailability and permeability, posaconazole is not expected to have pharmacokinetic drug interactions with OATP inhibitors.
In human hepatocytes, uptake of posaconazole was found to be variable. The maximal uptake of posaconazole was 1.7-fold in the absence of a transporter inhibitor cocktail as compared to that in the presence of inhibitors; however, this uptake could not be reproduced in the same lot of hepatocytes or in an alternative lot.	Based on the low and variable uptake in human hepatocytes, as well as its relatively high bioavailability and high permeability, transporter-mediated uptake is unlikely to contribute significantly to the disposition of posaconazole.
Inhibition of OATP by Posaconazole	
The potential for posaconazole to inhibit the human hepatic uptake transporters OATP1B1 and OATP1B3 was studied in recombinant cells lines. At 1 µM, the highest concentration tested due to the maximum solubility of posaconazole, posaconazole inhibited OATP1B1-mediated pitavastatin (PTV) and OATP1B3-mediated CCK-8 uptake by 16% and 24%, respectively. Inhibition at 0.1 and 0.3 µM was 0-10%.	In-vitro data reveals non-clinically meaningful interaction. Based on these data and those described by Vaidyanathan et al., 2016 [Ref. 5.4: 04GST9], posaconazole would not be expected to cause clinically significant pharmacokinetic interactions with OAT1B1 and OATP1B3 substrates. The highest concentration tested, 1 µM, is still approximately 19-fold higher than the unbound plasma Cmax after IV administration and approximately 4-fold higher than the estimated hepatic inlet maximal concentration.

Conclusions on Non-clinical Data

Non-clinical toxicology and safety pharmacology studies indicate that posaconazole has a safety profile similar to other antifungal substances in the azole class. Any findings not reported for other azoles pose a low human safety risk and are acceptable for the intended indication.

Overall, the risk associated with the nonclinical findings of potential human relevance is appropriately managed by routine pharmacovigilance and/or current product labeling.

[redacted]

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

In summary, POS has been evaluated in more than 60 completed clinical studies, from Phase 1 through Phase 3. Overall, 6,789 subjects have been randomized and treated in the posaconazole clinical program, of which approximately 6,378 subjects have received posaconazole monotherapy and 28 received posaconazole in combination with benznidazole. Estimates of overall cumulative subject exposure are provided in Table SIII.1, based upon actual exposure data from completed studies and estimates of exposure data using the randomization schemes from ongoing studies.

Table SIII.1: Cumulative Estimated Subject Exposure in Clinical Trials

Treatment	Number of subjects[2]
Posaconazole (POS)[1, 2]	**6378**
Placebo	**30**
Posaconazole (POS) + Benznidazole (BNZ)	**28**
Benznidazole (BNZ)	**30**
Voriconazole (VOR)	**323**

[1] Includes patients and healthy volunteers in both ongoing and completed studies, as of 25-Oct-2019.

[2] Includes studies C96-104, C96-120, C96-173, C96-201, C97-444, I95-098, I95-099, I96-089, I96-099, I96-172, I96-207, I97-016, P02418, P02810, P02811, P02812, P02489, P02862, P03409, P04482, P04490, P04547, P04802, P04931, P05011, P05014, P05179, P05359, P05270, P05533, P05560, C96-190, C96-247, I97-195, P01940, C/I96-421, P03742, P05115, C/I96-209, C/I97-331, C/I97-330, P00298, C/I97-280, P04558, P00041, P01893, P02095, P05113, C/I98-316, P01899, P05082, P02749, P02874, P04985, P03536, P04975, P05637, P03579/PN032, P05090, P05267/PN055, P05520, P05615, P06356, P07764, P05387, P05551, P07691, P07783, P08547/PN091, P06200/PN069, P05684/PN067, PN 097, PN101, PN105, PN106, PN111, PN112,PN117 and PN120.

Table SIII.2: Cumulative Subject Exposure to Posaconazole from Completed Clinical Trials by Age and Sex

Age Range (year)	Number of Subjects[1]		
	Male	Female	Total
<18	**154**	**114**	**268**
18 to 65	**3840**	**1832**	**5672**
66 to 75	**137**	**86**	**223**
Total	**4197**	**2038**	**6235**

[1] Data from completed trials as of 25-Oct-2019 (excludes P08547/PN091)

Table SIII.3: Cumulative Subject Exposure to Posaconazole from Completed Clinical Trials by Racial/Ethnic Group

Racial Group	Number of subjects[1]
Asian	**746**
Black	**678**
Caucasian	**4049**
Other	**761**
Unknown	**1**
Total	**6235**

[1] Data from completed trials as of 25-Oct-2019 (excludes P08547/PN091)

Approximately 3,767 subjects received posaconazole (POS) oral suspension formulation in Phase 1, 2, 3, and 4 clinical studies.

POS tablet has been evaluated in 9 completed clinical studies including 230 patient subjects and 122 healthy volunteer subjects. Of the patient subjects, a total of 210 subjects were treated with POS tablet at the proposed labeled dose of 300 mg BID on Day 1 followed by 300 mg QD.

A total of 455 subjects have received POS IV solution in completed clinical trials including 268 patient subjects and 72 healthy volunteer subjects. An additional 115 subjects were treated in the pediatric study with varying weight-based doses of 3.5, 4.5 and 6 mg/kg. (Protocol No. MK-5592-097, Section SIV.3 Pediatric population).

In the same Phase 1 paediatric study (P097), a total of 63 paediatric subjects have received posaconazole PFS, the newly developed age-appropriate paediatric formulation.

In addition to the studies for prophylaxis of IFI, POS tablet and IV were also evaluated in a Phase 3 randomized, double-blind study of posaconazole versus voriconazole in subjects with invasive aspergillosis as defined by modified EORTC/MSG consensus criteria (PN069). Subjects with features consistent with proven, probable, or possible invasive aspergillosis were enrolled in the study. Overall 575 subjects were treated in the trial, of whom 288 subjects received one or more doses of POS 300 mg QD (BID on Day 1) and 287 subjects received one or more doses of VOR. The median duration of the treatment was 67 days for POS and 64 days for VOR, with 55% to 60% of subjects starting treatment with the IV formulation of either drug. The median duration of the first instance of IV treatment (before switching to oral treatment or discontinuing or completing study treatment) was 9 days for both groups. POS was well tolerated in patients with IA, and the overall AE profile was reflective of a critically ill study population (with underlying conditions such as hematological malignancies, neutropenia post-chemotherapy, HSCT with GVHD) and consistent with that established in previous POS studies.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

The main exclusion criteria in the clinical trial development programme applicable to oral and IV POS formulations are summarized in Table SIV.1.1. Additional exclusion criteria applicable to POS IV formulation only are summarized in Table SIV.1.2.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
A subject must not have a history of Type I hypersensitivity or idiosyncratic reactions to azole agents.	Avoid life-threatening anaphylactic reactions	No	Managed via product label (SmPC 4.3 Contraindication, 4.4 Special warnings & precautions (section 4.3 and 4.4 of SmPC)
Prohibited medications prior to and during study treatment: • Ergot alkaloids • HMG-CoA reductase inhibitors metabolized via CYP3A4 • Medications known to interact with azoles astemizole, cisapride, ebastine, halofantrine, pimozide, quinidine, and terfenadine.	Known CYP3A4 substrates, co-administration with POS may significantly increase the drug levels and lead to life-threatening side effects.	No	Managed via product label (SmPC 4.3 Contraindication)
A subject must not have moderate or severe liver dysfunction at baseline	Liver toxicity of azole class agents and the possibility that posaconazole plasma levels may be higher in these patients.	No	Managed via product label (SmPC 4.2 Posology and method of administration, 4.4 Special warnings & precautions for use, 5.2 pharmacokinetic properties)
A subject must not have an ECG with prolonged QTc interval or clinically significant abnormalities	Preclinical findings and clinical reports of cardiac arrhythmia and heart failure with itraconazole.	No	Managed via product label (SmPC 4.4 Special warnings and precautions for use)
Medications known to lower the serum concentration/efficacy of azole antifungals: barbiturates, carbamazepine, cimetidine, isoniazid, phenytoin, rifabutin, rifampin, and St. John's Wort (hypericum perforatum).	Increased risk of breakthrough fungal infection or deterioration of existing IFI.	No	Managed via product label (SmPC 4.4 Special warnings & precautions for use; 4.5 Interactions with other medicine products)

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
No central line available for infusion	POS IV solution was not tolerated in Phase-1 trials with healthy subjects and can cause several infusion site reactions	No	Managed via product label (SmPC 4.2 Posology and Method of Administration)
Children <13 years of age. (except for PN032 and PN097)	A separate clinical program in pediatric subjects is underway.	Yes	
A female subject must not be pregnant, must not intend to become pregnant during the study, and must not be nursing.	POS has been shown to cause skeletal malformations in rats at exposures lower than those obtained at therapeutic doses in humans. In rabbits, POS was embryotoxic at exposures greater than those obtained at therapeutic doses. POS is excreted in milk of lactating rats. The excretion of POS in human breast milk has not been investigated.	No	Managed via product label (SmPC 5.4 Pregnancy and Lactation; 7.1 Preclinical safety data)

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure

Common adverse reactions (incidence >1 per 100) are well characterized, as detailed in the current Summary of Product Characteristics. The sample size of the clinical development program also allowed detection of uncommon reactions (>1 per 1000). Events that may be missed include rare events (<1 per 1000), those uncommon events for which the background incidence is similar to (at least half) that of the reaction, uncommon events occurring after long-term use (>6 months), and events associated with specific concomitant diseases and/or therapy for which the clinical trials were not designed or powered to detect differences compared to controls.

The number of exposed subjects is large enough to observe possible latency (e.g., occurring more frequently over time or with delayed onset) for drug reactions of reasonable frequency (e.g., in the range of 0.5%-5%).

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Pediatric population:

Overall, the number of pediatric subjects exposed to any formulations of POS is limited, and the safety profile of POS in the pediatric population has not been fully established. Up to 25-Oct-2019, a total of 401 subjects below 18 years of age have exposed to POS. A total of 284 pediatric subjects received at least one dose of the Oral Suspension formulation, including 4 in the pivotal trials for prophylaxis (C/I98-316, P01899), 16 in salvage treatment trial (P00041), 136 in a Phase 1B study of the safety, tolerance, and pharmacokinetics of oral posaconazole in immunocompromised children with neutropenia (PN032/P03579) and 128 in a compassionate-use program (P02095). In the pediatric trial P097, 115 pediatric patients received IV/PFS. Additionally, 2 adolescents were treated with POS and 3 were treated with VOR in PN069 investigating POS IV and Tablet in invasive aspergillosis.

There were 142 pediatric subjects (ranging in age from 11 months to 17 years) enrolled in Study PN032/P03579 of which 136 were treated with POS oral suspension.

The Company, in alignment with plans endorsed by the Paediatric Committee (PDCO) in PIP modification procedure EMEA- 000468-PIP02-M01, terminated development of the oral suspension in the pediatric population on the grounds that the established PK exposure target cannot be met with this formulation based on the results from the multiple dose groups evaluated in PN032/P03579. Because of this, a study to assess the pharmacokinetics, safety and tolerability of POS IV and POS PFS (a formulation based on POS tablet), Protocol 097 was conducted.

PN097, a study to evaluate the PK, safety and tolerability of POS IV and POS Powder for Oral Suspension (PFS; a formulation based on the POS tablet) in immunocompromised children and adolescents (2 to 17 years) with neutropenia or expected neutropenia, has completed. PN097 was a multicenter, nonrandomized, open-label, pharmacokinetic and safety study in 3 ascending dose-cohorts in 2 pediatric age groups. Overall, 115 subjects were enrolled in the trial. The pharmacokinetics following IV and oral PFS administration of POS at doses of 3.5, 4.5 or 6 mg/kg/day were well characterized in pediatric subjects aged 2 to 17 years.

POS was also generally well tolerated in pediatric subjects aged 2 to 17 years at all administered doses as both an IV solution and PFS formulation; and there was no apparent pattern to suggest a dose-related, exposure-related, or age-related difference in the safety profile of POS with the PFS and IV formulations in this pediatric population.

As expected in this critically ill patient population, the incidence of AEs was high (98.3%) and SAEs were reported for 27% of subjects. Rates of AEs across all AE categories, including drug-related AEs and SAEs, were generally comparable between age groups and dose cohorts. Increasing study treatment dosage was not associated with higher AE rates or drug-related AE rates. Overall AE rates, including rates of drug-related AEs and discontinuation of study treatment due to AEs, were lower during treatment with the PFS

formulation than during treatment with the IV formulation. AEs were distributed across a variety of SOCs for both the POS IV and POS PFS cohorts.

The most common AEs in the study population (occurring in >20% of subjects) included pyrexia, mucosal inflammation, vomiting, diarrhea, and febrile neutropenia. There was no apparent pattern to AEs that would indicate a clear difference between the age groups or dose cohorts. Observed AEs were generally consistent with those expected in a pediatric oncology population undergoing treatment for malignancy or with the known safety profile of POS.

Drug-related AEs were reported in 17 (14.8%) subjects overall. There were no drug-related AEs that were reported in >5% of subjects overall. The most frequent drug related AEs (occurring in >2% of subjects overall) were Gastrointestinal disorders, AST increased and rash (Table SIV.3.1). Overall, 4 (3.5%) subjects discontinued study treatment due to drug-related AEs. The incidence of drug-related AEs by dose was 11.4%, 25.8%, and 10.2% for the 3.5, 4.5, and 6 mg/kg cohorts, respectively. There was no apparent pattern to drug-related AEs that would indicate a clear difference among the dose groups.

An analysis of drug-related AEs by steady-state Cavg concentrations for the POS IV and POS PFS formulations was conducted. No correlation between drug-related AEs and POS exposures was observed for either the POS IV or POS PFS formulations.

Although there appears to be a similarity in the proportion of subjects reporting clinically significant adverse events between pediatric subjects in PN097 and adult participants in the development programs, the overall clinical safety profile in the pediatric population remains to be fully established. ‘Safety in children below 2 years of age’ is considered as a missing information for posaconazole.

PN069, a double-blind study to evaluate safety and efficacy of posaconazole (POS) versus voriconazole (VOR) in subjects ≥13 years of age with proven, probable, or possible invasive aspergillosis (IA) enrolled 5 pediatric participants; 2 were treated with POS. The safety of posaconazole in children will be further characterized in clinical trials including PN104 (Phase 3 Open-Label, Non-comparative, Estimation Study to Evaluate the Efficacy and Safety of Posaconazole for the Treatment of Invasive Aspergillosis in Pediatric Patients 2 to 18 Years of Age) and PN127 (Phase 1B,Open Label, Uncontrolled Study of PK, Safety, Tolerability & Efficacy of Noxafil IV & PFS formulations in prophylaxis of IFI & Treatment of IA in patients < 2 years of age).

Table SIV.3.1: Subjects with Drug-Related Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) By Dose Cohort, All Subjects as Treated

	Treatment 3.5 mg/kg		Treatment 4.5 mg/kg		Treatment 6 mg/kg		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
Subjects in population	35		31		49		115	
with one or more drug-related adverse events	4	(11.4)	8	(25.8)	5	(10.2)	17	(14.8)
with no drug-related adverse events	31	(88.6)	23	(74.2)	44	(89.8)	98	(85.2)
Gastrointestinal disorders	0	(0.0)	2	(6.5)	0	(0.0)	2	(1.7)
Hepatobiliary disorders	0	(0.0)	2	(6.5)	0	(0.0)	2	(1.7)
Hyperbilirubinaemia	0	(0.0)	2	(6.5)	0	(0.0)	2	(1.7)
Investigations	3	(8.6)	3	(9.7)	2	(4.1)	8	(7.0)
Aspartate aminotransferase increased	1	(2.9)	2	(6.5)	1	(2.0)	4	(3.5)
Drug level increased	2	(5.7)	0	(0.0)	0	(0.0)	2	(1.7)
Skin and subcutaneous tissue disorders	0	(0.0)	2	(6.5)	2	(4.1)	4	(3.5)
Rash	0	(0.0)	2	(6.5)	1	(2.0)	3	(2.6)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Geriatric population:

A total of 600 subjects ≥65 years of age were treated with POS (oral suspension, tablet and IV formulations) in clinical trials as of 25-Oct-2019. Of these, 557 (93%) reported any TEAE. There were SAE reports for 328 (55%) subjects, and 46 (8%) subjects had SAEs that were considered at least possibly related to POS by the investigator. There were 8 (2%) deaths that resulted from SAEs that were considered at least possibly related to POS.

In POS oral suspension studies, an increase in observed maximum plasma concentration (Cmax; 26%) and area under the concentration-time curve (AUC; 29%) was observed in elderly subjects (24 subjects >65 years of age) relative to younger subjects (24 subjects 18-45 years of age). However, in a population PK analysis (POS oral suspension Study P01899), age did not influence the pharmacokinetics of posaconazole.

Further, in clinical efficacy trials, the safety profile of posaconazole between the young and elderly patients was similar. Therefore, no dosage adjustment is necessary for age [Ref. 5.4: 00W3NV]. There was no upper age limit in any studies.

Pregnancy and Nursing Mothers:

There is insufficient information on the use of POS in pregnant women. Studies in animals have shown reproductive toxicity. POS has been shown to cause skeletal malformations in rats at exposures lower than those obtained at therapeutic doses in humans. In rabbits, POS was embryotoxic at exposures greater than those obtained at therapeutic doses. The potential risk for the foetus and neonate is unknown.

Women of childbearing potential must use effective contraception during treatment. POS should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

A total of 6 pregnancies were reported in 5 subjects enrolled in the POS oral suspension Phase 2/3 program. Two pregnancies occurred in the same female subject, one resulted in an elective abortion and the other resulted in the delivery of a healthy male infant at full- term gestation. Pregnancies of two other female subjects resulted in the delivery of a healthy male infant at full-term gestation and an ectopic pregnancy. Two pregnancies were reported in female partners of two male subjects treated with POS, one resulted in the delivery of a healthy infant with a report of congenital ventriculoseptal defect that did not require surgery, and the other resulted in a spontaneous abortion at approximately 5 weeks of gestation.

In a subsequent Phase 1 PK study, another pregnancy occurred in a subject who received two doses of POS three weeks apart. The pregnancy was documented during follow-up. The subject underwent an elective abortion.

There were no pregnancies reported in the POS tablet or IV formulation studies (Studies P05615 and P05520, respectively).

POS is excreted in milk of lactating rats. The excretion of POS in human breast milk has not been investigated. POS should not be used by nursing mothers unless the benefit to the mother clearly outweighs the potential risk to the infant. Breast-feeding must be stopped on initiation of treatment with POS.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

A summary of the worldwide distribution of posaconazole (all formulations: oral suspension, tablets and solution for infusion) cumulatively (i.e. from market introduction) to 25-Oct-2019 is presented in Table SV.1.2.1.

Patient exposure estimates for posaconazole were calculated from information provided by IMS Health, from our Company's internal distribution data from the Worldwide Financial Reporting System (WFRS), and the Financial Sharing Area database(s), as specified in the table below. This data provides a more complete and consistent methodology for the estimate of patient exposure worldwide for current Company products. Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide.

The estimated patient exposure was based upon the following assumptions for each formulation.

The SmPC and CCDS recommend posaconazole oral suspension be administered with food or nutritional supplement at a dose of 400 mg (i.e. 10 mL) BID for treatment of refractory IFIs and 200 mg (i.e. 5 mL) TID for prophylaxis of IFIs. The recommended dosage for the treatment of oropharyngeal candidiasis is 200 mg (i.e. 5 mL) QD on the first day and then 100 mg (i.e. 2.5 mL) QD for 13 days. For the purpose of patient exposure estimation, the average daily dose is assumed to be 800 mg (i.e. 20 mL).

The recommended dosage of posaconazole tablet and posaconazole solution for infusion is 300 mg BID on the first day, then 300 mg QD thereafter for treatment of refractory IFIs as well as for prophylaxis of IFIs. For the purposes of patient exposure estimation, the average daily dose is assumed to be 300 mg.

SV.1.2 Exposure

Table SV.1.2.1: Post-authorization (non-study) Exposure: Units Distributed and Patient-Days of Treatment and Patient-Years of Treatment for Posaconazole Cumulative (25-Oct-2005 (IBD) through 25-Oct-2019)

Formulation	Units Distributed	Patient-Days of Treatment*	Patient-Years of Treatment**
Oral Suspension (40mg/ml, 105 ml bottles	3,268,960 bottles [13,729,632,000 total mg]	17,162,040	46,987
Tablet (100mg/tablet)	65,295,645 tablets	21,765,215	59,590
IV solution (300mg/unit)	363,305 units	363,305	995

*Patient-Days of treatment: For oral suspension 13,729,632,000 ÷ 800 = 17,162,040. For tablets = 65,295,645 ÷ 3 =21,765,215. For IV solution 363,305 ÷ 1 = 363,305.

**Patient-Years of Treatment = Patient-Days of Treatment ÷ 365.25.

Patient exposure for oral suspension from 25-Oct-2005 to 25-Oct-2013 was estimated from unit sales data provided by IMS Health MIDAS market research database. Patient exposure from November 2013 is based on the availability of monthly drug distribution figures; hence, this estimate has been calculated for the cumulative period ending 30-Sep-2019, rather than 25-Oct-2019.

Total worldwide patient exposure for posaconazole oral formulations was estimated to be 38,927,255 patient-days of treatment days or 106,577 patient-years of treatment. Assuming average daily treatment duration of 90 days, the number of patients exposed to oral formulations of posaconazole is estimated to be 432,525 cumulatively through 30-Sep-2019.

Total worldwide patient exposure for posaconazole solution for infusion was estimated to be 363,305 patient-days of treatment or 995 patient-years of treatment. Assuming average daily treatment duration of 14 days (period of time when patients require IV therapy because they are unable to take oral therapy), the number of patients exposed to posaconazole IV is estimated to be 25,950 cumulatively through 30-Sep-2019.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

This topic is not relevant for posaconazole oral suspension, tablet or IV solution. As an antifungal agent, posaconazole would not likely be used for illegal purposes. The product is available by medical prescription only.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

As a result of the introduction of Noxafil (posaconazole) gastro-resistant powder and solvent for oral suspension (PFS), medication errors related to substitution between different formulations (oral suspension [OS] and PFS) has been added as a new important potential risk.

The new posaconazole gastro-resistant powder and solvent for oral suspension (PFS) formulation offers the benefits of Noxafil tablet formulation including improved absorption and exposure characteristics as compared to the OS formulation. Importantly, the PFS formulation has different bioavailability and PK properties from OS formulation and, as a paediatric formulation, will use weight-based dosing. Therefore, Noxafil PFS will be prescribed at a different dose than the OS and is not to be used interchangeably with Noxafil OS. Incorrect dosing as a result of unintended substitution between Noxafil PFS and Noxafil OS could occur in clinical practice and possibly lead to loss of efficacy due to underdosing or adverse reactions due to overdosing in paediatric patients.

During the assessment of the recent paediatric submission, Procedure No. EMEA/H/C/000610/X/0063/G, the Company was requested to add medication error to the RMP as an important potential risk.

To mitigate this risk, the proposed labeling (package leaflet and outer carton) will have a clear and prominent statement regarding the non-interchangeability between the OS formulation and PFS. Additionally, the Company was requested to disseminate a one-time DHPC letter to inform healthcare professionals about this new PFS formulation and the potential risk of medication error.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Potential Risks

Table SVII.3.1.1: Details of Important Potential Risk: Injury, Poisoning, and Procedural Complications - Medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension)

Frequency	Not applicable as no clinical trial utilized the oral suspension (OS) and PFS together and the PFS formulation is not yet marketed.
Seriousness / Outcomes	Not applicable as there were no reports prior to product launch.
Severity and Nature of the Risk	With the co-existence of Noxafil oral suspension and Noxafil gastro-resistant powder and solvent for oral suspension on the market, there is a risk of confusion between these formulations leading to potential dosing error. Substitution of one oral suspension formulation for the other could result in potential overdosing or underdosing of the medication. The PFS formulation has different bioavailability and PK properties from the OS formulation, and as a paediatric formulation, Noxafil PFS will use weight-based dosing. Prescribers are advised to follow specific dosage recommendations for each formulation. While the maximum threshold for posaconazole has not been established, overdosing in paediatric patients could lead to adverse reactions. Underdosing of posaconazole could result in lack of efficacy.
Background Incidence / Prevalence	Medication errors, the most common type of medical errors, are associated with an increased risk of morbidity and mortality [Ref. 5.4: 00WBCX]. These errors can occur at any point of the medication use process: prescription, transcription, documentation, preparation, dispensation and administration. Errors are categorized as errors of omission (i.e., failure to perform appropriate action such as failed to administer drug) or commission (i.e., perform an inappropriate action such as administered wrong drug or dose). The reported incidence of medication errors varies greatly between clinical settings and patient populations (hospitalized ICU versus non-ICU patients, outpatients in ambulatory care). In addition, variability is introduced between studies due to significant methodologic differences (e.g. definition of medication errors, including numerator or denominator in rate calculations, method of reporting errors (e.g. chart review, spontaneous reports, direct patient monitoring or observation). One study in a US hospital found that there can be errors and, in some cases, subsequent adverse events, related to medications that are available in multiple or special dose formulations [Ref. 5.4: 00WBCT]. For example, the “failure to specify unique dosage form with significant pharmacodynamic differences” accounted for 0.7% and 5.8% of all errors and serious adverse events related to special dose formulations, respectively.

Table SVII.3.1.1: Details of Important Potential Risk: Injury, Poisoning, and Procedural Complications - Medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension)

Risk Groups or Risk Factors	Risk factors associated with medication errors include: [Ref. 5.4: 00WBCX] • Patient factors: severity of illness, extreme of ages, prolonged hospitalization, sedation. • Medication factors: type of medications, number of medications, number of interventions. • Hospital factors: ICU environment, emergency admissions, multiple caregivers.
Potential Mechanisms	Not applicable
Preventability	Mitigation measures to support differentiation of formulations and prevention of medication errors related to the substitution of OS and PFS were considered in the dosage form design, product labeling, and commercial image. Dosage Form Design: • Posaconazole oral suspension 40 mg/mL, is a white opaque, immediate release, oral suspension formulation packaged in amber glass bottles with child-resistant caps. Each oral suspension package contains a package leaflet that provides information to the provider and consumer on the appropriate use of the medication. A plastic, dosing spoon is provided with each bottle, calibrated for measuring 2.5 mL and 5.0 mL doses. Use of the spoon will minimize the potential for medication errors as the dosages are clearly marked on the spoon and one spoon is provided with each bottle. • Noxafil 300 mg gastro-resistant powder and solvent for oral suspension is supplied as a pack containing: Package 1: The kit contains 8 child resistant single use sachets (PET/aluminium/LLDPE), two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, one 473 mL solvent bottle (HDPE) with polypropylene (PP) closure with a foil induction seal liner, and one bottle adapter for the solvent bottle. Package 2: A box of six 3 mL (green) and six 10 mL (blue) notched tip syringes. Each single-use sachet contains 300 mg of posaconazole which is suspended in 9 mL of solvent to obtain 10 mL total of suspension with a final concentration of approximately 30 mg per mL. Product Labeling: • To prevent potential medication errors, the non-interchangeability statement is updated to include the PFS. The following statement is included in the summary of product characteristics: "Non-Interchangeability between Noxafil gastro-resistant powder and solvent for oral suspension and Noxafil oral suspension Noxafil gastro-resistant powder and solvent for oral suspension is indicated for paediatric population (<18 years old) only. Another formulation (Noxafil oral suspension) is available for adult patients ≥18 years old. [redacted]

Table SVII.3.1.1: Details of Important Potential Risk: Injury, Poisoning, and Procedural Complications - Medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension)

	The gastro resistant powder and solvent for oral suspension is not to be used interchangeably with oral suspension due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations. Treatment should be initiated by a physician experienced in the management of fungal infections or in the supportive care in the high risk patients for which posaconazole is indicated as prophylaxis." • To prevent potential medication errors the following statement is included in the package leaflet information for the user: "Do not switch between taking Noxafil gastro-resistant powder and solvent for oral suspension and Noxafil oral suspension." Outer Carton: • To prevent potential medication errors the following statement is included on the outer carton: "Noxafil gastro-resistant powder and solvent for oral suspension is NOT interchangeable with Noxafil oral suspension." Additional Risk Minimization Measure: A one-time DHPC is to be issued at launch of the new PFS formulation in EEA countries that market both the OS and PFS to inform healthcare professionals about the new PFS formulation and the potential risk of medication errors as a result of prescriber confusion between the formulations.
Impact on the Individual Patient	Not Applicable/Unknown
Potential Public Health Impact of Safety Concern	Minimal
Evidence Source	Not applicable
MedDRA Terms	Not applicable

SVII.3.2 Presentation of the Missing Information

Table SVII.3.2.1: Summary of Missing Information - Safety in Children Below 2 Years of Age

Missing Information	Safety in children below 2 years of age
Evidence sources	The safety profile in pediatric patients aged 2-17 years appears similar to the safety profile observed in adults [ref to SIV.3]. A recently completed pediatric study (PN097) has shown that nausea, vomiting, pruritus, and elevated liver enzymes experienced by patients between the ages of 2-17 years who received posaconazole to prevent invasive fungal infections are not different from the adverse events seen in adults who received posaconazole to prevent invasive fungal infections. However, the overall experience of posaconazole use in pediatric population is limited. The safety of posaconazole in patients below the age of 2 years has not been established. Invasive fungal infections are common in premature infants and may cause infections in the blood, urine, or brain. Children under the age of 18 years often experience the same fungal infections that adults experience. There have been numerous reports of off-label use of posaconazole in children under 2 years of age in the literature [Ref. 5.4: 05CKSP], [Ref. 5.4: 053NJQ].
Risk anticipated in Children	The clinical safety and efficacy profile of POS in pediatric subjects under 2 years of age has not been fully established with controlled clinical trials. However, off-label use of POS in real-world clinical practice is expected. The risks associated with the use of posaconazole in adults may occur in pediatric patients. In addition, the PK profile of posaconazole in children may differ from that in adults, which in theory may alter the tolerability, efficacy, and drug interactions of posaconazole.
Ongoing characterization	There are no additional pharmacovigilance activities for this safety concern. However, the safety of posaconazole in children will be further characterized in two paediatric studies under the Paediatric Investigation Plan (PN104 and PN127), one of which (P127) will enroll infants under 2 years of age.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• None*
Important potential risks	• Injury, Poisoning, and Procedural Complications - Medication error related to substitution between different formulations (oral suspension and PFS)*
Missing information	• Safety in children below 2 years of age

* The important identified or potential risks included in prior versions of the RMP have been removed based the review of accumulating clinical data and the guidance in GVP module 5 (Rev 2), as per routine updates of the RMP during the life cycle of the product.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific Adverse Reaction Follow-Up Questionnaires for Safety Concerns:

As part of the routine pharmacovigilance activities, the Company uses event-specific questionnaires to obtain structured information about the following events: hepatic disease, cardiac arrhythmia, QT prolongation, adrenal insufficiency, seizure/convulsion, venous thromboembolism, myocardial infarction, neutropenia/agranulocytosis, cerebrovascular accident, and drug adverse experience.

These adverse event-specific questionnaires are provided in Annex 4.

Other Forms of Routine Pharmacovigilance Activities for Safety Concerns:

Not applicable

III.2 Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities for posaconazole.

The safety of posaconazole in children will be further characterized in two additional clinical studies in pediatric patients under the Pediatric Investigation Plan (PN104 and PN127), one of which (PN127) will enroll infants under the age of 2 years.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for posaconazole.

The MAH completed MK-5592-069, a Phase 3 study of the efficacy and safety of posaconazole versus voriconazole for the treatment of invasive aspergillosis (PN069) to fulfill the post approval follow-up measures (FUM 003 and 004) issued by the CHMP in July 2005 in the scope of the initial MAA and re-stated in February and July 2014, in the scope of procedures EMEA/H/C/000610/X/0028 and EMEA/H/C/000610/X/0033 respectively.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimization Measures

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Important Potential Risks	
Injury, Poisoning, and Procedural Complications - Medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension)	Communication via healthcare provider and patient product information Listed under SmPC Sections 4.2 (Posology and method of administration) Package leaflet - Section 3, How to take Noxafil Outer carton Design of product and packaging
Missing Information	
Safety in children below 2 years of age	Communication via healthcare professional and patient product information Listed under SmPC Section 4.2 (Posology and method of administration) and 5.2 (Pharmacodynamic properties) Package leaflet -Section 2, What you need to know before you use Noxafil

V.2 Additional Risk Minimization Measures

A one-time DHPC regarding the potential risk of Medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension) will be disseminated to the EEA countries that market both the oral suspension and PFS at the time of launch of the new PFS formulation. The DHPC informs healthcare professionals about the new PFS formulation and the potential risk of medication errors as a result of prescriber confusion between the formulations.

V.3 Summary of Risk Minimization Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Routine Risk Minimisation Activities	Pharmacovigilance Activities
Important Identified Risks		
None	N/A	N/A
Important Potential Risks		
Injury, Poisoning, and Procedural Complications: Medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension)	Communication via healthcare provider and patient product information Listed under SmPC Sections 4.2 (Posology and method of administration) Package leaflet - Section 3, How to take Noxafil Design of product and packaging Outer carton Additional Risk Minimisation measure: Dissemination of a one-time DHPC	Routine pharmacovigilance activities
Missing Information		
Safety in children below 2 years of age	Communication via healthcare professional and patient product information Listed under SmPC Section 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetic properties) Package leaflet -Section 2, What you need to know before you use Noxafil	Routine pharmacovigilance activities

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for Noxafil (posaconazole)

This is a summary of the risk management plan (RMP) for Noxafil. The RMP details important risks of Noxafil, how these risks can be minimised, and how more information will be obtained about Noxafil's risks and uncertainties (missing information).

Noxafil's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Noxafil should be used. Along with the introduction of the Noxafil gastro-resistant powder and solvent for oral suspension (PFS), the product labeling and package carton will clearly state that Noxafil oral suspension (OS) and Noxafil PFS are not to be used interchangeably. Unlike Noxafil OS, which is a ready-to-use suspension, Noxafil PFS is provided as a powder that must be mixed with the suspending vehicle (also provided in the same product kit) before use. Notch-tip oral dosing syringes, a bottle of suspending vehicle, bottle adapter, mixing cups and a step-by-step Instruction for Use (IFU) are provided to guide the preparation and administration of weight-based dosing of the PFS. Additional syringes will be supplied with Noxafil PFS.

This summary of the RMP for Noxafil should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Noxafil's RMP.

I. The Medicine and What It Is Used For

Noxafil (IV and tablet) is indicated for use in the treatment of invasive aspergillosis in adults.

Noxafil is authorised for treatment of the following fungal infections in adults (tablet, IV and oral suspension formulations) and in paediatric patients aged 2 years and above (tablet for patients who weigh greater than 40 kg, IV and PFS formulations):

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products;

- Oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor. (approved only in adults for Oral Suspension formulation)

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Noxafil is also indicated for prophylaxis of invasive fungal infections in adults (tablet, IV and oral suspension formulations) and paediatric patients aged 2 years and above (tablet for patients who weigh greater than 40 kg, IV and PFS formulations):

- Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;

- Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

See the SmPC for the full indication.

Noxafil contains posaconazole as the active substance and it is given orally or by intravenous injection.

Further information about the evaluation of Noxafil's benefits can be found in Noxafil's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/noxafil

II. Risks Associated With the Medicine and Activities To Minimise or Further Characterise the Risks

Important risks of Noxafil, together with measures to minimise such risks and the proposed studies for learning more about Noxafil's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Noxafil, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Noxafil is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Noxafil are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Noxafil. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None*
Important potential risks	Injury, Poisoning, and Procedural Complications - Medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension)*
Missing information	Safety in children below 2 years of age*

* The important identified or potential risks included in prior versions of the RMP have been removed based on the review of accumulating clinical data and the guidance in GVP module 5 (Rev 2), as per routine updates of the RMP during the life cycle of the product.

II.B Summary of Important Risks

Table II.B.1: Important Potential Risk: Injury, Poisoning, and Procedural Complications - Medication error – related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension)

Evidence for linking the risk to the medicine	There is a risk for medication errors since the 2 oral suspension formulations have different dosage recommendations.
Risk factors and risk groups	None identified
Risk minimisation measures	Communication via healthcare provider and patient product information Listed under SmPC Sections 4.2 (Posology and method of administration) Package leaflet- Section 3 (How to take Noxafil) Outer carton A one-time Direct Healthcare Professional Communication will be distributed to healthcare providers to alert them of the new formulation and that the formulations are not interchangeable. Design of product and packaging

Table II.B.2: Missing Information: Safety in children below 2 years of age

Risk minimisation measures	Communication via healthcare professional and patient product information Listed under SmPC Section 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetic properties) Package leaflet –Section 2, What you need to know before you use Noxafil
Additional pharmacovigilance	There are no additional pharmacovigilance activities for this safety concern. The safety of posaconazole in children will be further characterized in an ongoing clinical trial.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Noxafil.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Noxafil.

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ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

MSD

HEPATIC DISEASE

MARRS#: [INSERT MARRS NUMBER]

The name of entity "Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. "or "Merck" is only used in the U.S. and may need to be replaced throughout this document depending on your location. Please use the correct entity name for the country/region in which the letter is being sent.

[LETTER DATE]

[Correspondence Contact Name]
[Institution]
[Address]
[City], [STATE], [Zip Code]

Dear [Correspondence Contact Name],

We have been notified of a report concerning an event of interest following exposure to an MSD product.

Patient Name	[Patient Name]
Patient Initials	[PATIENT INITIALS]
Age	[Patient Age]
Gender	[Patient Gender]
Product (All Merck suspect products)	[INSERT, ALL, PRODUCTS, SEPARATED, BY, COMMA, AND, SPACE, LIKE, THIS,]
Event(s) – All events	[INSERT, ALL, EVENT PREFERRED TERMS, SEPARATED, BY, COMMA, AND, SPACE, LIKE, THIS,]

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, MSD subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that MSD respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated. For instructions on how to return this form, please contact your local MSD representative or office.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about our company's privacy commitment at www.merck.com/privacy/

Sincerely,

Global Pharmacovigilance

MERCK

HEPATIC DISEASE

MARRS#: [INSERT MARRS NUMBER]

[LETTER DATE]

[Correspondence Contact Name]
[Institution]
[Address]
[City], [STATE], [Zip Code]

Dear [Correspondence Contact Name],

We have been notified of a report concerning an event of interest following exposure to an Merck product.

Patient Name	[Patient Name]
Patient Initials	[PATIENT INITIALS]
Age	[Patient Age]
Gender	[Patient Gender]
Product (All Merck suspect products)	[INSERT, ALL, PRODUCTS, SEPARATED, BY, COMMA, AND, SPACE, LIKE, THIS,]
Event(s) – All events	[INSERT, ALL, EVENT PREFERRED TERMS, SEPARATED, BY, COMMA, AND, SPACE, LIKE, THIS,]

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that Merck respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated. You may provide this information by calling us at 800-705-1885, Monday-Friday 8AM to 5PM ET, or you can return the completed form via fax at 215-661-6229.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about Merck's privacy commitment at www.merck.com/privacy/

Sincerely,

Global Pharmacovigilance
Phone: 1-800-705-1885
Fax: 215-661-6229

HEPATIC DISEASE

MARRS#: [INSERT MARRS NUMBER]

DRUG ADVERSE EXPERIENCE REPORT

Program ID Number:

Today's date:

Please use this format throughout form → DD/MM/YY

1. Reporter Information		**2. Patient Information**			
Name:		Name or initials:			Date of birth:
Title:		Zip code:	Age:		☐ Male ☐ Female
Institution:		Occupation:	Height: ☐LB ☐KG		Weight: ☐IN ☐CM
Address:		Is the patient pregnant? ☐ No ☐ Yes	Weeks gestation: Date of LMP:		Gravida: Para:
Telephone #:	Fax #:	Race/ethnicity: ☐Caucasian ☐Black ☐Asian ☐Hispanic ☐Native American ☐Multiracial ☐Other:			

3. Merck Product Information

Merck Product Name	Suspect Therapy	Dose/ Route	Frequency	Indication	Start Date	Stop Date	LOT Number/ Expiration Date	Was product interrupted or discontinued?	Re-start date if applicable
	☐No ☐ Yes							☐ Interrupted ☐ Discontinued	
	☐ No ☐ Yes							☐ Interrupted ☐ Discontinued	
	☐ No ☐ Yes							☐ Interrupted ☐ Discontinued	

4. Patient's experience(s) (list most significant first)	Onset date/ Duration	Did experience abate after stopping drug?	Did experience reappear after reintroduction?	Event Criteria	Outcome
		☐ No ☐ Yes ☐ N/A	☐ No ☐ Yes ☐ N/A	☐Hospitalization/Prolonged hospitalization ☐Permanent or significant disability/incapacity ☐Congenital Anomaly ☐Life-threatening ☐**Important Medical Event (*IME*)	☐Unknown ☐Worsening ☐Fatal ☐Not recovered/Not resolved ☐Recovered/Resolved ☐Resolved/Recovered with sequelae ☐Recovering/resolving
		☐ No ☐ Yes ☐ N/A	☐ No ☐ Yes ☐ N/A	☐Hospitalization/Prolonged hospitalization ☐Permanent or significant disability/incapacity ☐Congenital Anomaly ☐Life-threatening ☐**Important Medical Event (*IME*)	☐Unknown ☐Worsening ☐Fatal ☐Not recovered/Not resolved ☐Recovered/Resolved ☐Resolved/Recovered with sequelae ☐Recovering/resolving
		☐ No ☐ Yes ☐ N/A	☐ No ☐ Yes ☐ N/A	☐Hospitalization/Prolonged hospitalization ☐Permanent or significant disability/incapacity ☐Congenital Anomaly ☐Life-threatening ☐**Important Medical Event (*IME*)	☐Unknown ☐Worsening ☐Fatal ☐Not recovered/Not resolved ☐Recovered/Resolved ☐Resolved/Recovered with sequelae ☐Recovering/resolving

**** Important Medical Event (IME): Required Medical/Surgical intervention to prevent one of the event criteria listed.**

5. Only complete this section if there was a medication error. (Medication error: an unintended failure in the drug treatment process that led to, or had the potential to lead to an adverse event):

Indicate at which point in the process the medication error occurred:
☐Prescribing ☐Storage in clinical Practice ☐Dispensing ☐Preparation for Administration ☐Administration
Please describe the error, any contributing factors that led to the error, and any corrective actions taken (if applicable) in the fields and narrative description.

6. Did the patient die?	**7. Was autopsy performed?**	**8. Was prescription drug treatment for the experience required?**
☐No ☐Yes List date and cause of death in narrative section.	☐No ☐Yes If available, please provide copy of death certificate and/or autopsy results.	☐No ☐Yes List in narrative section, with start and stop date (or ongoing).

HEPATIC DISEASE

MARRS#: [INSERT MARRS NUMBER]

9. Please list all concomitant medications:							
Product Name	Suspect Therapy	Route	Dose	Total Daily Dosage	Start Date	Stop Date	Indication
	☐No ☐Yes						
	☐No ☐Yes						
	☐No ☐Yes						
	☐No ☐Yes						

10. Concurrent Conditions: (Medical conditions that developed prior to the initiation of drug therapy and were unresolved at the time of the first adverse event)	11. Past Medical History: (Events preceding the occurrence of the adverse event – list any pertinent information, including past drug reaction or allergies, start and stop dates)

12. Provide a Narrative Description of the events including labs/diagnostic tests to support AE information or attach results:

(Please attach additional pages as necessary)

****Required Medical/Surgical intervention to prevent one of the event criteria listed? ☐No ☐Yes**
(if yes, please be sure to include above in EVENT CRITERIA as IME) Notes:

HEPATIC DISEASE

MARRS#: [INSERT MARRS NUMBER]

- **If necessary, please use the Additional Information page to provide additional details for the applicable section.**
- **Please provide the total # of pages (including Additional Information pages and Attachments for supportive documentation.**

Total # of pages of Additional Information pages and Attachments for supportive documentation: _____

A. Patient Medical History:			
1.	Any known history of liver and/or biliary abnormalities?	☐ Yes ☐ No	If yes, specify abnormality(ies) and date(s) of diagnosis:
2.	Any known history of heart failure and/or hypotension?	☐ Yes ☐ No	If yes, specify and date(s) of diagnosis:
3.	Any known underlying viral hepatitis?	☐ Yes ☐ No	If yes, specify type/genotype and date(s) of diagnosis:
4.	Any known underlying autoimmune, alcoholic hepatitis, or nonalcoholic steatohepatitis (NASH)?	☐ Yes ☐ No	If yes, specify:
5.	Any known alcohol use?	☐ Yes ☐ No	If yes, specify:
6.	Any known recreational drug use?	☐ Yes ☐ No	If yes, specify:
7.	Any known acetaminophen (paracetamol) use?	☐ Yes ☐ No	If yes, specify:
8.	Any known exposure to hazardous environmental /occupational chemical agents?	☐ Yes ☐ No	If yes, specify:
9.	Any known current or recent viral infection, (i.e., Epstein-Barr virus, herpes simplex virus, cytomegalovirus, varicella, toxoplasmosis, parvovirus)?	☐ Yes ☐ No	If yes, specify:
10.	Any known history of genetic diseases that could affect the liver?	☐ Yes ☐ No	If yes, specify:
11.	Were there other known concomitant medications, including non-prescription drugs, herbal and dietary supplements, used?	☐ Yes ☐ No	If yes, specify including doses used:

HEPATIC DISEASE

MARRS#: [INSERT MARRS NUMBER]

B. Event Details:			
1.	Any known clinical evidence of liver failure, altered mental status, coagulopathy/ bleeding, jaundice or anemia?	☐ Yes ☐ No	If yes, specify:
2.	Any known signs/symptoms related to liver disorder, such as liver enlargement, fatigue, malaise, anorexia, pruritus, abdominal pain, fever, or eosinophilia?	☐ Yes ☐ No	If yes, specify:
3.	Treatment of event:	☐ Yes ☐ No ☐ Unknown	If yes, provide details:
4.	After the event, was the patient given the suspect product again?	☐ Yes ☐ No	If yes, provide details of re-exposure and outcome:

C. Lab/Diagnostic Data: Please provide baseline, highest, last on suspect product and newest values. In lieu of completing this section, please provide supportive documentation (e.g., laboratory test results, liver imaging studies, liver biopsy results, etc.)**, if available.**

	TEST(S)	DATE(S)	RESULTS
1.	AST, ALT, bilirubin (total, direct and indirect), gamma- GT, LDH, and alkaline phosphatase values		
2.	Albumin level		
3.	PT/PTT/INR		
4.	Ammonia level		
5.	Results of liver imaging (ultrasound, CT, MRI, X-ray, etc.)		
6.	Liver biopsy results, if performed		
7.	Hepatitis and any other serology test results (ANA, antimitochondrial antibody, anti-DNA, etc.)		
8.	Alpha-fetoprotein		

HEPATIC DISEASE

MARRS#: [INSERT MARRS NUMBER]

D. Enclosed Documentation: List documents attached and include MARRS Case ID #.	
☐ Lab test results	Specify:
☐ Liver imaging studies	Specify:
☐ Liver biopsy results	Specify:
☐ Other:	Specify:

In US PLEASE RETURN VIA FAX TO: 215-661-6229

In other countries, contact your local MSD representative or office

[Letter Date]

Name
Address
Address2
City, State, Zip Code

MARRS #:

Dear ,

We have been notified of a report concerning an experience following exposure to a Merck product.

Patient Name / Initial	
Age	
Gender	
Product (All Merck suspect products)	
Event(s) – All events	

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

We would like to inform you that your inquiry is being documented with the aim to process it appropriately. Any personal data provided by you will be used to keep track of the inquiry with you and treated by Merck with full respect of your privacy. Please read more about Merck's privacy commitment at www.merck.com/privacy/

Enclosed is a form for you to complete and return to us at your earliest convenience. Your assistance in this matter is greatly appreciated.

Sincerely,

Global Safety

MERCK

NEUTROPENIA/AGRANULOCYTOSIS

MARRS #:_____ Product: _____

This form is being sent to you, as a health care provider for a patient, who has been reported to our company as having sustained a decrease in neutrophil count in association with one of our medicinal products. The purpose of this questionnaire is to collect additional information on the reported event(s).

Please **COMPLETE ALL PAGES** of this questionnaire.

REPORTER INFORMATION:

Name and title: _____

Affiliation: _____

Address: _____

_____

Daytime Telephone Number: _____ Signature and date: _____

Patient Name / Initial	

Medical History			
1.	Age: [age] or DOB: [dob]_____(DD/MMM/YYYY)	Gender: [sex]	Nationality / Race: [ethnicity]
3.	Does the patient have a medical history of: (mm/dd/yyyy)		Date of diagnosis
	- neutropenia or agranulocytosis?	Yes / No	_____
	- other blood disorders?	Yes / No	_____
	- vitamin deficiencies (e.g. Vit. B12, folate)	Yes / No	_____
	- malignancies?	Yes / No	_____
	- recent bacterial /viral/fungal infections? (e.g. EBV, hepatitis, HIV, typhoid, tuberculosis)	Yes / No	_____
	- immunosuppression?	Yes / No	_____
	- autoimmune disease?	Yes / No	_____
	- hypersplenism?	Yes / No	_____
	- chronic liver disease?	Yes / No	_____
	- chronic renal disease?	Yes / No	_____
	- recent exposure to toxic chemicals or radiation?	Yes / No	_____
	If any of the above is answered "Yes", please provide diagnosis and relevant details:		

4.	Please provide any other relevant medical history in the table below:		
	Diagnosis/Condition	Date of diagnosis	Description

MERCK

NEUTROPENIA/AGRANULOCYTOSIS

MARRS #:_____ Product: _____

Medical History			

5.	Does the patient have a family history of disorders as mentioned in items 3 and 4 above? Yes / No / Unknown If yes, please specify:

Please provide start and stop dates of all concurrent and discontinued medications within 2 months of event onset, including prescription and OTC drugs, herbals, nutritional supplements and vaccinations:

6. Drug name	Dose regimen	Start date (mm/dd/yyyy)	Stop date (mm/dd/yyyy)

Event Details	
1.	Please provide start date of therapy with suspect drug or provide duration of treatment prior to event onset. Start date of suspect drug (mm/dd/yyyy): Duration of treatment:
2.	Was the suspect drug discontinued or interrupted? Yes / No If yes, please indicate the date of interruption or discontinuation:
3.	Were there any clinical signs and symptoms associated with the reported event(s), such as fever or oral infections? Yes / No If yes, please specify:
4.	Was there any medical intervention for the reported event(s)? Yes / No If yes, please provide details and outcome:
5.	What was the final outcome of the reported event(s)? Ongoing / Recovered If recovered, please provide date of recovery:
6.	Was rechallenge with the suspect drug performed? Yes / No If yes, please provide results:
7.	Please provide your assessment of the causal relationship between the reported event(s) and the suspect drug:

MERCK

NEUTROPENIA/AGRANULOCYTOSIS

MARRS #:_____ Product: _____

Event Details	
8.	Are there in your opinion any confounding factors or alternative explanations for the reported event(s), such as concomitant disease or medication?Yes / No If yes, please provide details:
9.	Please provide any additional information considered relevant to the reported event(s):
10.	Were white blood cell counts and/or neutrophil counts completed prior to introduction of suspect drug? Yes / No If yes, please provide results and dates in the table below.

Please provide relevant hematological laboratory test results in the table below, including values prior to drug (if available), lowest value, last value on drug and newest values

or

provide copies of relevant laboratory results

TEST(S)	NORMAL RANGE and UNITS	DATE: RESULT	DATE: RESULT	DATE: RESULT	DATE: RESULT	DATE: RESULT
Neutrophil count						
White blood cell count						
Thrombocyte count						
Erythrocyte count						
Hemoglobin						
Were there any other relevant laboratory abnormalities?		**Yes / No**	**If yes, please specify:**			

PLEASE RETURN VIA FAX TO:

Brazil 55 11 5181 0773 ext. 7998
Spain 34 91 571 6466
Germany 49 89 4561 1352
France 01 80 46 46 47
Canada 800-369-3090
All other including United States 215 993 1220

MERCK

CARDIAC ARRHYTHMIA

MARRS#:_____

The name of entity " Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. " or "Merck" is only used in the U.S. and may need to be replaced throughout this document depending on your location. Please use the correct entity name for the country/region in which the letter is being sent.

[Letter Date]

Name
Address
Address2
City, State, Zip Code

MARRS #

Dear ,

We have been notified of a report concerning an event of interest following exposure to a Merck product.

Patient Name / Initial	
Age	
Gender	
Product (All Merck suspect products)	
Event(s) – All events	

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that Merck respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about Merck's privacy commitment at www.merck.com/privacy/

Sincerely,

Merck Global Safety

MERCK

CARDIAC ARRHYTHMIA

Proprietary

MARRS#:_____

REPORTER INFORMATION:

Date:_____

Name, title Institution:	
Address:	
Telephone Number: Fax Number:	Program Identification Number:

PATIENT INFORMATION:

Patient name or initials:		Date of Birth:____/____/____	Age:	❑Male ❑Female	
Patient Zip code:	Occupation:	Weight: ❑LB ❑KG	Height: ❑IN ❑CM	Is patient pregnant? ❑ No ❑ Yes If pregnant, weeks gestation_____ Date of LMP:_____	Gravida: Para:
Race/ethnicity:	❑ Caucasian ❑ Black ❑ Asian ❑ Hispanic ❑ Native American ❑ Multiracial ❑Other: _____				

MERCK PRODUCT INFORMATION:

MERCK PRODUCT NAME	DOSE/ ROUTE	FREQUENCY	INDICATION FOR USE	START DATE	STOP DATE	LOT NO. AND EXPIRATION DATE	WAS PRODUCT INTERRUPTED OR DISCONTINUED?	RE-START DATE IF APPLICABLE
				/ /	/ /	/ /	☐ Interrupted ☐ Discontinued	/ /
				/ /	/ /	/ /	☐ Interrupted ☐ Discontinued	/ /
				/ /	/ /	/ /	☐ Interrupted ☐ Discontinued	/ /

ADVERSE EXPERIENCE INFORMATION:

List of patient's experience(s) List most significant first	Date of onset	Duration	Did experience abate after stopping drug? (circle one)	Did experience reappear after reintroduction? (circle one)	Serious Criteria: 1-Hospitalized/Proloned Hospitalization; 2-Disability; 3-Important Medical Event (IME)*; 4-Congenital Anomoly; 5- Cancer; 6- Overdose	Outcome: 1-Fatal; 2- Not recovered/Not resolved; 3-Recovered/Resolved; 4-Resolved/Recovered with sequelae; 5-Recovering/resolving; 6- Unknown

			NO YES N/A	NO YES N/A		Date: / /
			NO YES N/A	NO YES N/A		Date: / /
			NO YES N/A	NO YES N/A		Date: / /
			NO YES N/A	NO YES N/A		Date: / /

Your Answers to the following questions are vital:

1. Was prescription drug treatment for the experience required? ❑ No ❑ Yes List in narrative section

2. If the event result in DEATH list Date & Cause of Death: Was autopsy performed? ❑ No ❑ Yes
(If available, please provide copy of death certificate and/or autopsy results):

3. Required medical/surgical intervention to prevent one of the outcomes listed?* ❑ No ❑Yes

4. Is the experience still being treated? ❑ No ❑ Yes

Please provide a narrative description of the events including Labs/Diagnostic Tests to support AE information or attach results:

MEDICAL HISTORY: list any pertinent medical history, including past drug reaction or allergies:

CONCOMITANT THERAPIES (do not list drugs used to treat adverse experiences):

PRODUCT	ROUTE	DOSE	TOTAL DAILY DOSAGE	START DATE	STOP DATE	INDICATION

MERCK

CARDIAC ARRHYTHMIA

MARRS#:_____

HISTORY:

Does the patient have a history of cardiac arrhythmias? *If yes, specify onset, type of event and outcome.*	☐ Yes, specify: ☐ No ☐ Unknown
Are there any family members with cardiac arrhythmias/cardiac disease? *If yes, specify relation to patient, type of event and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have a known underlying cardiac condition? For example: • Congenital heart abnormality • Coronary artery disease • Cardiomyopathy • Narrowed heart arteries • Abnormal valves • Conduction disorder • Prior heart surgery • Prior Myocardial Infarction • Prior Cardiac Arrest *If yes, specify disorder and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have (a history of) other relevant medical conditions? For example: • Thyroid disorder • Artherosclerosis • Hypertension • Diabetes • Obstructive sleep apnea *If yes, specify condition and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown

RISK FACTORS:

Does the patient smoke or have a smoking history? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Is the patient exposed to second-hand smoke? *If yes, specify age, duration and extent of exposure*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient consume or is there a history of alcohol consumption? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient consume or is there a history of caffeine consumption? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Is there (a history of) drug/substance abuse? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown

MERCK

CARDIAC ARRHYTHMIA

MARRS#:_____

Does the patient have electrolyte imbalances? *If yes, specify. In addition, if available, provide lab data.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have high cholesterol? *If yes, specify. In addition, if available, provide lab data.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have artherosclerosis? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have a high fat intake?	☐ Yes ☐ No ☐ Unknown
Please provide patient BMI, height, and weight:	BMI: Height: Weight:
Is the patient exposed to stress on a regular basis or has the patient been exposed to stress recently? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown
Did the patient use any concomitant medication (including dietary supplements and/or herbal remedies) with a known cardiac risk? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown
Is there any other relevant information concerning the reported arrhythmia? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown

RELEVANT TESTS:

What was (were) the method(s) of diagnosis?	
Have any of the following tests been performed? *If yes, specify the dates and the results.*	**Results**
ECG ☐ Yes ☐ No ☐ Unknown	
Holter Monitor ☐ Yes ☐ No ☐ Unknown	
Echocardiogram ☐ Yes ☐ No ☐ Unknown	
Electrophysiology study ☐ Yes ☐ No ☐ Unknown	
Coronary angiography/ cardiac catheterization ☐ Yes ☐ No ☐ Unknown	

PLEASE RETURN VIA FAX TO:

Brazil 55 11 5181 0993
Spain 34 91 571 6466
Germany 49 89 4561 1352
France 01 80 46 46 47
Canada 514 426 84 78
All other including United States 215 993 1220

The name of entity " Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. " or "Merck" is only used in the U.S. and may need to be replaced throughout this document depending on your location. Please use the correct entity name for the country/region in which the letter is being sent.

[Letter Date]

Name
Address
Address2
City, State, Zip Code

Dear ,

We have been notified of a report concerning an experience following exposure to a Merck product.

Patient Name / Initial	
Age	
Gender	
Product (All Merck suspect products)	
Event(s) – All events	

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

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Sincerely,

Merck Global Safety

MERCK

QT PROLONGATION

Proprietary

MARRS #: [case_num]

REPORTER INFORMATION: Date:_____

Name, title Institution:	
Address:	
Telephone Number: Fax Number:	Program Identification Number:

PATIENT INFORMATION:

Patient name or initials:			Date of Birth:_____/_____/____	Age:	❑Male ❑Female
Patient Zip code:	Occupation:	Weight: ❑LB ❑KG	Height: ❑IN ❑CM	Is patient pregnant? ❑ No ❑ Yes If pregnant, weeks gestation_____ Date of LMP:_____	Gravida: Para:
Race/ethnicity:	❑ Caucasian ❑ Black ❑ Asian ❑ Hispanic ❑ Native American ❑ Multiracial ❑Other: _____				

MERCK PRODUCT INFORMATION:

MERCK PRODUCT NAME	SUSPECT THERAPY	DOSE/ ROUTE	FREQUENCY	INDICATION FOR USE	START DATE	STOP DATE	LOT NO. AND EXPIRATION DATE	WAS PRODUCT INTERRUPTED OR DISCONTINUED?	RE-START DATE IF APPLICABLE
	❑ No ❑Yes				//	//	//	Interrupted Discontinued	//
	❑ No ❑Yes				//	//	//	Interrupted Discontinued	//
	❑ No ❑Yes				//	//	//	Interrupted Discontinued	//

ADVERSE EXPERIENCE INFORMATION:

List of patient's experience(s) List most significant first	Date of onset	Duration	Did experience abate after stopping drug? (circle one)	Did experience reappear after reintroduction? (circle one)	Event Criteria: Hospitalized/Prolonged Hospitalization; Permanent or significant disability/incapacity; **Important Medical Event (IME); Congenital Anomaly; Life-threatening	Outcome: Fatal; Not recovered/Not resolved; Recovered/Resolved; Resolved/Recovered with sequelae; Recovering/resolving; Worsening; Unknown
			NO YES N/A	NO YES N/A		Date: //
			NO YES N/A	NO YES N/A		Date: //
			NO YES N/A	NO YES N/A		Date: //

Your Answers to the following questions are vital: **1** Was prescription drug treatment for the experience required? ☒ No ☒ Yes List in narrative section, with start and stop date (or ongoing)	**2.** Did the patient DIE? ❑ No ❑ Yes List Date & Cause of Death: Was autopsy performed? ❑ No ❑ Yes (If available, please provide copy of death certificate and/or autopsy results):

3. Please only complete this question if there was a medication error. (Medication error: an unintended failure in the drug treatment process that led to, or had the potential to lead to an adverse event): Please indicate at which point in the process the medication error occurred: Prescribing | Storage in clinical Practice | Dispensing | Preparation for Administration | Administration
Please provide a **Narrative Description** of the events including Labs/Diagnostic Tests to support AE information or attach results:

**Required Medical/Surgical intervention to prevent one of the event criteria listed? ❑ No ❑Yes (if Yes, please be sure to include above in EVENT CRITERIA as IME)

CONCURRENT CONDITIONS: (Medical conditions that developed prior to the initiation of drug therapy and were unresolved at the time of the first adverse event)	**PAST MEDICAL HISTORY:** (Events preceding the occurrence of the adverse event-list any pertinent information, including past drug reaction or allergies, start and stop dates)

CONCOMITANT/ OTHER THERAPIES (do not list drugs used to treat adverse experiences):

PRODUCT	SUSPECT THERAPY	ROUTE	DOSE	TOTAL DAILY DOSAGE	START DATE	STOP DATE	INDICATION
	❑ No ❑Yes						
	❑ No ❑Yes						
	❑ No ❑Yes						

MARRS #:_____

Please **COMPLETE ALL PAGES** of this questionnaire.

Patient Initial	

Event		
1.	What was the length of the QT prolongation? What was the baseline of the QT interval prior to prolongation?	
2.	In what setting was the QT prolongation observed (routine ECG monitoring, because of symptoms, etc)?	
3.	How many times has the QT prolongation been observed?	
4.	Results of ECG monitoring:	
5.	Was the QT prolongation associated with ventricular arrhythmia, Torsades de Pointe, or any other arrhythmia? If yes, please provide details.	
6.	Did the patient experience any symptoms (dizziness, palpitations, sweating, fainting, etc.)? If yes, please describe.	
7.	Please provide the patient's blood pressure, pulse, and oxygenation status recordings at the time of the event, if available.	
8.	Provide treatment of the event, including action taken regarding the administered S-P sponsored drug and outcome.	
9.	After the event, was the patient given the suspect drug again? If yes, provide outcome.	

Risk Factors		
1.	Does the patient have known baseline QT prolongation?	
2.	Does the patient have a family history of congenital Long QT syndrome or sudden death? Has the patient had genetic testing for Romano-Ward syndrome or Lange-Nielsen syndrome performed? If yes, please provide details.	

MARRS #:_____

Risk Factors		
3.	Does the patient have angina, coronary artery disease, heart failure or recent cardiac ischemia?	
4.	Does the patient have a history of ventricular tachycardia, frequent premature ventricular contractions, or bradycardia?	
5.	Does the patient have renal or hepatic insufficiency? If yes, please provide dates and details.	
6.	Does the patient drink grapefruit juice on a regular basis, or have any dietary factors, or social history that could contribute to the QT prolongation?	
7.	Please list all medications taken by the patient, including any over the counter products; provide details of start date, indications for use, and recent dosage changes. In particular, was there any recent/current use of the following: a. Antiarrhythmic drugs, especially class 1A and III b. Diuretics c. Laxatives d. Quinolone antibiotics, erythromycin or other macrolide antibiotics e. Antipsychotic drugs, especially phenothiazines, atypical antipsychotics and droperidol f. Tricyclic antidepressants g. Antihistamines h. Dolasetron	

Product	Start Date	Indication(s) for Use	Recent Dosage Changes	Misc.

8.	Other Risk Factors:	

MARRS #:_____

INVESTIGATIONS: *Please provide results of the following investigations if performed (baseline and surrounding the event).*		
TEST(S)	**DATE(S)**	**RESULTS**
Electrocardiograms, before the event		
Serum electrolytes, especially potassium, magnesium, and calcium		
Cardiac enzymes		
LFTs		
BUN/Cr		
Echocardiogram		
Exercise stress test		
Cardiac catheterization		
Electrophysiologic studies		
Holter monitor		

NOTE: Please provide 12-lead ECGs.

PLEASE RETURN VIA FAX TO:
United States 215 993 12

MARRS #:_____

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[Letter Date]

Name
Address
Address2
City, State, Zip Code

MARRS #

Dear ,

We have been notified of a report concerning an event of interest following exposure to a Merck product.

Patient Name / Initial	
Age	
Gender	
Product (All Merck suspect products)	
Event(s) – All events	

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

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Sincerely,

Merck Global Safety

MERCK

ADRENAL INSUFFICIENCY

Pr Proprietary

MARRS #:_____

REPORTER INFORMATION:

Date:_____

Name, title Institution:	
Address:	
Telephone Number: Fax Number:	Program Identification Number:

PATIENT INFORMATION:

Patient name or initials:		Date of Birth:____/____/____		Age:	❑Male ❑Female
Patient Zip code:	Occupation:	Weight: ❑LB ❑KG	Height: ❑IN ❑CM	Is patient pregnant? ❑ No ❑ Yes If pregnant, weeks gestation_____ Date of LMP:_____	Gravida: Para:
Race/ethnicity:	❑ Caucasian ❑ Black ❑ Asian ❑ Hispanic ❑ Native American ❑ Multiracial ❑Other: _____				

MERCK PRODUCT INFORMATION:

MERCK PRODUCT NAME	DOSE/ ROUTE	FREQUENCY	INDICATION FOR USE	START DATE	STOP DATE	LOT NO. AND EXPIRATION DATE	WAS PRODUCT INTERRUPTED OR DISCONTINUED?	RE-START DATE IF APPLICABLE
				/ /	/ /	/ /	☐ Interrupted ☐ Discontinued	/ /
				/ /	/ /	/ /	☐ Interrupted ☐ Discontinued	/ /
				/ /	/ /	/ /	☐ Interrupted ☐ Discontinued	/ /

ADVERSE EXPERIENCE INFORMATION:

List of patient's experience(s) List most significant first	Date of onset	Duration	Did experience abate after stopping drug? (circle one)	Did experience reappear after reintroduction? (circle one)	Serious Criteria: 1-Hospitalized/Proloned Hospitalization; 2-Disability; 3-Important Medical Event (IME)*: 4-Congenital Anomoly; 5- Cancer; 6- Overdose	Outcome: 1-Fatal; 2- Not recovered/Not resolved; 3-Recovered/Resolved; 4-

						Resolved/Recovered with sequelae; 5-Recovering/resolving; 6- Unknown
			NO YES N/A	NO YES N/A		Date: / /
			NO YES N/A	NO YES N/A		Date: / /
			NO YES N/A	NO YES N/A		Date: / /
			NO YES N/A	NO YES N/A		Date: / /

Your Answers to the following questions are vital:

1. Was prescription drug treatment for the experience required? ❑ No ❑ Yes List in narrative section

2. If the event result in DEATH list Date & Cause of Death: Was autopsy performed? ❑ No ❑ Yes
(If available, please provide copy of death certificate and/or autopsy results):

3. Required medical/surgical intervention to prevent one of the outcomes listed?* ❑ No ❑Yes

4. Is the experience still being treated? ❑ No ❑ Yes

Please provide a narrative description of the events including Labs/Diagnostic Tests to support AE information or attach results:

MEDICAL HISTORY: list any pertinent medical history, including past drug reaction or allergies:

CONCOMITANT THERAPIES (do not list drugs used to treat adverse experiences):

PRODUCT	ROUTE	DOSE	TOTAL DAILY DOSAGE	START DATE	STOP DATE	INDICATION

ADRENAL INSUFFICIENCY

MARRS #:_____

	Medical History	Additional Information/Explanation
1.	Define relationship of suspect drug to event by duration of product use prior to event onset and abatement/rechallenge.	
2.	Any history of adrenal or pituitary abnormality? If so, indicate date of diagnosis: _____	☐ Adrenal tumor _____ ☐ Adrenal failure_____ ☐ Pituitary pathology _____ ☐ Other _____
3.	Any concomitant medications such as steroids, aminoglutethimide, ketoconazole, metyrapone or mitotane? ☐ Yes ☐ No	
4.	Any problem associated glucose level abnormalities? ☐ Yes ☐ No	☐ Diabetes type I _____ ☐ Diabetes type II _____
5.	History of weight or growth disorder since childhood. Indicated any significant problems since birth?	☐ If None
6.	Other metabolic/endocrine/neoplastic conditions? ☐ Yes ☐ No	☐ Thyroid insufficiency _____ ☐ Lymphoma _____
7.	History of tuberculosis? ☐ Yes ☐ No	
8.	Family history of endocrine problems? ☐ Yes ☐ No	

	Event Details:	
1.	Any current clinical events associated with adrenal failure:	☐ Abdominal pain ☐ Weight loss ☐ Fatigue ☐ Weight gain ☐ Fever ☐ Weakness ☐ Vomiting ☐ Depression ☐ Hypertension ☐ Hypoglycemia ☐ Orthostatic changes ☐ Hyperglycemia ☐ Other _____
2.	Treatment: Indicate treatment for any current events (include medications, therapy and clinical course).	

ADRENAL INSUFFICIENCY

MARRS #:_____

Lab/Diagnostic Data: Please provide baseline, highest, last on drug and newest values.		
TEST($)	**DATE($)**	**RESULTS**
Electrolytes: ☐ Yes ☐ No		
ACTH stimulation test results: ☐ Yes ☐ No		
Results of CT scan of Abdomen/Skull: ☐ Yes ☐ No		
Tuberculosis testing? ☐ Yes ☐ No		Type ☐ Tine _____ ☐ Mantoux PPD _____ ☐ Chest X-Ray _____

PLEASE RETURN VIA FAX TO:

Brazil 55 11 5181 0993
Spain 34 91 571 6466
Germany 49 89 4561 1352
France 01 80 46 46 47
Canada 514 426 84 78
All other including United States 215 993 1220

MERCK

SEIZURE CONVULSION

[Letter Date]

Name
Address
Address2
City, State, Zip Code

MARRS #:

Dear ,

We have been notified of a report concerning an experience following exposure to a Merck product.

Patient Name / Initial	
Age	
Gender	
Product (All Merck suspect products)	
Event(s) – All events	

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that Merck respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated. You may provide this information by calling us at 800-705-1885, Monday-Friday 8AM to 5PM ET, or you can return the completed form via fax at 215-661-6229.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about Merck's privacy commitment at www.merck.com/privacy/

Sincerely,

Global Pharmacovigilance
Phone: 1-800-705-1885
Fax: 215-661-6229

MERCK

SEIZURE CONVULSION

MARRS #:_____

REPORTER INFORMATION:

Name and title: _____

Affiliation: _____

Address: _____

_____

Daytime Telephone Number: _____ Signature and date: _____

PATIENT INFORMATION:

Patient Name / Initials		
Age:	DOB: (DD/MMM/YYYY)	Gender:

A. ANTECEDENTS OF SEIZURES / CONVULSIONS / EPILEPSY	
1. Does the patient have a history of seizures, convulsions or epilepsy?	☐ Yes, specify date of diagnosis: ____/____/____(DD/MMM/YYYY) ☐ No, if No, proceed to Section B.
2. When did the patient experience his/her first seizure / convulsion?	Date: ____/____/____(DD/MMM/YYYY)
3. How often do the seizures occur?	(Number) _____seizures / convulsions every _____ (specify period of time i.e. day, week, month, etc.)
4. What was the date of the last seizure / convulsion before this event?	Date: ____/____/____ (DD/MMM/YYYY)
5. If patient is on antiepileptic medication, have blood levels of antiepileptic(s) been monitored recently?	☐ No ☐ Not Applicable ☐ Yes, please provide the date of the last test before the event: ____/____/____ (DD/MMM/YYYY) Please specify the result(s):

Antiepileptic Medication	Results: Under Therapeutic Level	Within Therapeutic Level	Over Therapeutic Level
A.	☐	☐	☐
B.	☐	☐	☐
C.	☐	☐	☐

B. INFORMATION IMMEDIATELY PREVIOUS TO THE EVENT (SEIZURE / CONVULSION) ONSET

1. Did your patient use any concomitant medication(s), over the counter (OTC), herbal or nutritional products within one month prior to the event? ☐ No ☐ Yes, please specify dose regimen, start and stop dates:

A.	dose	start date: ____/____/____	stop date: ____/____/____
B.	dose	start date: ____/____/____	stop date: ____/____/____
C.	dose	start date: ____/____/____	stop date: ____/____/____

If the patient uses more than 3 concomitant medications please attach another page.

MERCK

SEIZURE CONVULSION

MARRS #:_____

B. INFORMATION IMMEDIATELY PREVIOUS TO THE EVENT (SEIZURE / CONVULSION) ONSET	
2. Did the patient recently change dose of any concomitant medication?	Specify name: Specify date of change dose: ____/____/____
3. Did the patient have any of the following risk factors for triggering seizures? A. Recent alcohol intake? ☐ No ☐ Yes, specify quantity: B. Sleep deprivation? ☐ No ☐ Yes, specify: C. Exposure to flashes of light (stroboscope or television or video games) or strident sounds? ☐ No ☐ Yes, specify: D. Recent intake of large amounts of coffee? ☐ No ☐ Yes, specify quantity: E. Recent intake of energy boosting supplements? ☐ No ☐ Yes, specify product and quantity: F. Other risk factors? ☐ No ☐ Yes, specify:	
4. What activity(ies) was the patient engaged in at the time of event onset?	

C. DIAGNOSTIC AND CLASSIFICATION OF THE SEIZURE/CONVULSION	
1. Please describe all signs and symptoms of the event as detailed as possible. *(e.g. consciousness, movements/muscles involved, aura)*	☐ Described by the patient ☐ Described by a witness
2. Please specify the date and duration of the event (in minutes).	Date of the event: ____/____/____ (DD/MMM/YYYY) Duration of the event: _____minutes
3. Please specify the duration of treatment with the drug at event onset.	Specify the period of time (in hours, days, months, etc):
4. Classify the seizure using the 1981 Classification for Seizures of the International League Against Epilepsy (ILAE). **Note**: Please choose only one option	☐ A. Partial Seizures, please specify below: ☐ Simple Partial Seizures (consciousness not impaired) ☐ Complex Partial Seizures (consciousness impaired) or ☐ Partial Seizure Evolving to Secondarily Generalized Seizures (simple or complex partial seizures secondarily generalized)

C. DIAGNOSTIC AND CLASSIFICATION OF THE SEIZURE/CONVULSION	
from A, B, or C or check here if you are unfamiliar with this classification: ☐	☐ B. Generalized Seizures, please specify below: ☐ Absence Seizures (typical or atypical) ☐ Myoclonic Seizures ☐ Clonic Seizures ☐ Tonic Seizures ☐ Tonic-clonic Seizures ☐ Atonic Seizures
	☐ C. Unclassified Seizures *Includes all seizures that cannot be classified because of inadequate or incomplete data.*

5. Does the patient have a history of any of the following?	
A. Brain tumor	☐ No ☐ Yes, please specify :
B. Stroke	☐ No ☐ Yes, please specify :
C. Alzheimer disease	☐ No ☐ Yes, please specify :
D. Abuse of alcohol or illicit drugs	☐ No ☐ Yes, please specify :
E. Head trauma or injury	☐ No ☐ Yes, please specify :
F. CNS Infections	☐ No ☐ Yes, please specify :
G. Diabetes / hyperglycemia / hypoglycemia	☐ No ☐ Yes, please specify :
H. Electrolyte imbalance	☐ No ☐ Yes, please specify :
I. Other	☐ No ☐ Yes, please specify :

D. LAB/DIAGNOSTIC DATA: Provide details on any tests performed prior to the event, right after and/or at time of recovery.

TEST($)	DATE($)	RESULTS
Electrocardiogram (ECG)	___/___/___	
Relevant biochemistry tests (e.g. glucose, electrolytes (Na, K, Ca, Cl), creatinine)	___/___/___	
Others: (e.g. EEG, CT-scan, MRI, Lumbar puncture for cerebrospinal fluid (CSF))	___/___/___	
	___/___/___	
	___/___/___	

MERCK

SEIZURE CONVULSION

MARRS #:_____

PROVIDE ADDITIONAL DETAILS:

PLEASE RETURN VIA FAX TO:

Brazil 55 11 5181 0773 ext. 7998
Spain 34 91 571 6466
Germany 49 89 4561 1352
France 01 80 46 46 47
Canada 800 369 3090
All other including United States 215 661 6229

MERCK

CEREBROVASCULAR ACCIDENT

MARRS #:_____

The name of entity "Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. " or "Merck" is only used in the U.S. and may need to be replaced throughout this document depending on your location. Please use the correct entity name for the country/region in which the letter is being sent.

[Letter Date]

Name
Address
Address2
City, State, Zip Code

MARRS #

Dear ,

We have been notified of a report concerning an event of interest following exposure to a Merck product.

Patient Name / Initial	
Age	
Gender	
Product (All Merck suspect products)	
Event(s) – All events	

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that Merck respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about Merck's privacy commitment at www.merck.com/privacy/

Sincerely,

Merck Global Safety

MERCK

CEREBROVASCULAR ACCIDENT

MARRS #:_____

REPORTER INFORMATION:

Date:_____

Name, title Institution:	
Address:	
Telephone Number: Fax Number:	Program Identification Number:

PATIENT INFORMATION:

Patient name or initials:		Date of Birth:____/____/____		Age:	❑Male ❑Female
Patient Zip code:	Occupation:	Weight: ❑LB ❑KG	Height: ❑IN ❑CM	Is patient pregnant? ❑ No ❑ Yes If pregnant, weeks gestation_____ Date of LMP:_____	Gravida: Para:
Race/ethnicity:	❑ Caucasian ❑ Black ❑ Asian ❑ Hispanic ❑ Native American ❑ Multiracial ❑Other:_____				

MERCK PRODUCT INFORMATION:

MERCK PRODUCT NAME	DOSE/ ROUTE	FREQUENCY	INDICATION FOR USE	START DATE	STOP DATE	LOT NO. AND EXPIRATION DATE	WAS PRODUCT INTERRUPTED OR DISCONTINUED?	RE-START DATE IF APPLICABLE
				/ /	/ /	/ /	☐ Interrupted ☐ Discontinued	/ /
				/ /	/ /	/ /	☐ Interrupted ☐ Discontinued	/ /
				/ /	/ /	/ /	☐ Interrupted ☐ Discontinued	/ /

ADVERSE EXPERIENCE INFORMATION:

List of patient's experience(s) List most significant first	Date of onset	Duration	Did experience abate after stopping drug? (circle one)	Did experience reappear after reintroduction? (circle one)	Serious Criteria: 1-Hospitalized/Proloned Hospitalization; 2-Disability; 3-Important Medical Event (IME)*; 4-Congenital Anomoly; 5- Cancer; 6- Overdose	Outcome: 1-Fatal; 2- Not recovered/Not resolved; 3-Recovered/Resolved; 4-Resolved/Recovered with sequelae; 5-Recovering/resolving; 6- Unknown
			NO YES N/A	NO YES N/A		Date: / /

			NO YES N/A	NO YES N/A		Date: / /
			NO YES N/A	NO YES N/A		Date: / /
			NO YES N/A	NO YES N/A		Date: / /

Your Answers to the following questions are vital:

1. Was prescription drug treatment for the experience required? ❑ No ❑ Yes List in narrative section

2. If the event result in DEATH list Date & Cause of Death: Was autopsy performed? ❑ No ❑ Yes
(If available, please provide copy of death certificate and/or autopsy results):

3. Required medical/surgical intervention to prevent one of the outcomes listed?* ❑ No ❑Yes

4. Is the experience still being treated? ❑ No ❑ Yes

Please provide a narrative description of the events including Labs/Diagnostic Tests to support AE information or attach results:

MEDICAL HISTORY: list any pertinent medical history, including past drug reaction or allergies:

CONCOMITANT THERAPIES (do not list drugs used to treat adverse experiences):

PRODUCT	ROUTE	DOSE	TOTAL DAILY DOSAGE	START DATE	STOP DATE	INDICATION

MERCK

CEREBROVASCULAR ACCIDENT

MARRS #:_____

UNDERLYING ETIOLOGY;

Did the patient have a Cerebrovascular Accident (CVA) and/or Transient Ischemic Attack (TIA)?	☐ CVA ☐ TIA ☐ Unknown
Is the CVA ischemic or hemorrhagic?	☐ Ischemic ☐ Hemorrhagic ☐ Unknown
What is the underlying etiology of the CVA?	☐ Athero-thromboembolism (specify artery if known):
	☐ Emboli from heart (specify): ☐ Originating from heart valves (specify): ☐ Mural thrombus (specify):
	☐ Intracranial hemorrhage (specify):
	☐ Vasculitis (specify):
	☐ Hypercoagulable state (specify):
	☐ Other (specify):
	☐ Unknown

HISTORY / PATIENT CHARACTERISTICS:

Does the patient have a history of CVA or TIAs (other than the event reported)? *If yes, specify date of onset, type of event, duration and outcome.*	☐ Yes, specify: ☐ No ☐ Unknown
Are there any family members with a history of CVA or TIAs? *If yes, specify relation to patient, type of event and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient smoke or have a smoking history? *If yes, specify (include duration and extent).* *If ex-smoker indicate how long since cessation*	☐ Yes, specify: ☐ No ☐ Unknown
Is the patient a passive smoker (exposed to second-hand smoke)? *If yes, specify age, duration and extent of exposure.*	☐ Yes, specify: ☐ No ☐ Unknown
Is there (a history of) excessive alcohol consumption? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Is there (a history of) drug/substance abuse? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Has the patient taken any hormonal treatment in the past? *If yes, specify product, dose and duration of exposure (start and stop dates, last date taken prior to event).*	☐ Yes, specify: ☐ No ☐ Unknown

RISK FACTORS:

Presence/ absence of (risk factors for) atherosclerosis	
Does the patient have hypertension? *If yes, specify age at onset, type of hypertension, most recent blood pressure readings prior to the event, medications.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have dyslipidemia? *If yes, specify age at onset, most recent cholesterol and lipid levels prior to the event or outcome of other investigations, medications.*	☐ Yes, specify: ☐ No ☐ Unknown

Does the patient have diabetes? *If yes, specify age at onset, type of diabetes and level of diabetic control, most recent HbA1C prior to the event, medications.*	☐ Yes, specify: ☐ No ☐ Unknown
Have symptoms of atherosclerosis been detected before?	☐ Yes, specify: ☐ Angina ☐ Claudication ☐ Other ☐ No ☐ Unknown
Have signs of atherosclerosis been detected before? *If yes, specify by which investigation and provide results.*	☐ Yes (specify below) ☐ No ☐ Unknown ☐ Arteriography ☐ US ☐ CT ☐ MRI ☐ Percutaneous Coronary Intervention (PCI) ☐ Other (specify): Results:
Does the patient smoke or have a smoking history? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Is the patient exposed to second-hand smoke? *If yes, specify age, duration and extent of exposure.*	☐ Yes, specify: ☐ No ☐ Unknown
Has the patient taken any hormonal treatment in the past? *If yes, specify product, dose and duration of exposure.*	☐ Yes, specify: ☐ No ☐ Unknown

Presence or absence of cardiac diseases

Does the patient have any past or present cardiovascular diseases? (E.g. Atrial fibrillation, Other arrhythmias, Myocardial infarction, Valvular diseases, Infective endocarditis, cerebrovascular disease, peripheral arterial disease, carotid stenosis, carotid endarterectomy/stenting)? *If yes, specify which cardiac disease, give date of onset and other relevant details.*	☐ Yes, specify: ☐ No ☐ Unknown

Presence or absence of any (risk factors for) other possible causes of CVA

Does the patient have any hematological abnormalities? *If yes, specify which abnormality.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have any head injury or trauma? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have increased homocysteine levels? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have migraine? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown

Does the patient have any inflammatory diseases, e.g. vasculitis, arteritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis? *If yes, specify disease and date of onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient consume or is there a history of alcohol consumption? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Is there (a history of) drug/substance abuse? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown

RELEVANT DIAGNOSTIC TESTS:

What was the method of diagnosis of the CVA?	
Have the following tests been performed? *If yes, specify the dates and the results of the tests, in particular in relation to valvular diseases, arrhythmias and ischemic heart disease.*	**Results**
MRI ☐ Yes ☐ No ☐ Unknown	
ECG ☐ Yes ☐ No ☐ Unknown	
CT-scan ☐ Yes ☐ No ☐ Unknown	
Ultrasound ☐ Yes *(specify type below)* ☐ No ☐ Unknown Type:	
Echocardiography ☐ Yes ☐ No ☐ Unknown	
PET ☐ Yes ☐ No ☐ Unknown	
EEG ☐ Yes ☐ No ☐ Unknown	
Stress Test ☐ Yes ☐ No ☐ Unknown	
Have the following tests been performed? *If yes, specify the dates and the results of the tests...*	**Values (Units)**
PT/APTT ☐ Yes ☐ No ☐ Unknown	
AT III level/activity ☐ Yes ☐ No ☐ Unknown	
Protein S level/activity ☐ Yes ☐ No ☐ Unknown	
Protein C level/activity ☐ Yes ☐ No ☐ Unknown	
Factor VII ☐ Yes ☐ No ☐ Unknown	
Factor VIII ☐ Yes ☐ No ☐ Unknown	
Prothrombin mutation G20210 ☐Yes ☐ No ☐ Unknown	
Platelet Count ☐ Yes ☐ No ☐ Unknown	

MERCK

CEREBROVASCULAR ACCIDENT

MARRS #:_____

APC resistance (factor V Leiden) ☐Yes ☐ No ☐ Unknown	☐ Homozygous ☐ Heterozygous ☐ Unknown whether it is homozygous - or heterozygous
Antiphospholipid antibodies (SLE/lupus) ☐ Yes ☐ No ☐ Unknown	
Homocysteine blood levels ☐ Yes ☐ No ☐ Unknown	

PLEASE RETURN VIA FAX TO:

Brazil 55 11 5181 0993
Spain 34 91 571 6466
Germany 49 89 4561 1352
France 01 80 46 46 47
Canada 514 426 84 78
All other including United States 215 993 1220

[Letter Date]

Name
Address
Address2
City, State, Zip Code

MARRS #:

Dear ,

We have been notified of a report concerning an experience following exposure to a Merck product.

Patient Name / Initial	
Age	
Gender	
Product (All Merck suspect products)	
Event(s) – All events	

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

We would like to inform you that your inquiry is being documented with the aim to process it appropriately. Any personal data provided by you will be used to keep track of the inquiry with you and treated by Merck with full respect of your privacy. Please read more about Merck's privacy commitment at www.merck.com/privacy/

Enclosed is a form for you to complete and return to us at your earliest convenience. Your assistance in this matter is greatly appreciated.

Sincerely,

Global Safety

MERCK

VENOUS THROMBOEMBOLIC-VTE

MARRS #: _____

REPORTER INFORMATION:

Name and title: _____

Affiliation: _____

Address: _____

_____

Daytime Telephone Number: _____ Signature and date: _____

PATIENT INFORMATION:

Patient Name / Initials		
Age:	DOB:	Gender:

UNDERLYING ETIOLOGY:	
Type of venous thromboembolism (VTE)?	☐ Deep vein thrombosis (DVT) ☐ Pulmonary embolism (PE) ☐ Other: specify:
What is the underlying etiology of the VTE?	☐ hypercoagulable state (specify): ☐ Other (specify): ☐ Unknown:

HISTORY	
Does the patient have a history of VTE other than the event reported)? *If yes, specify onset, type of event and outcome.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have a history of any of the following procedures? *If yes, specify date of procedure, indication for the procedure and outcome?*	☐ Doppler Ultrasound ☐ Inferior vena cava filter insertion
Are there any family members with VTE? *If yes, specify relation to patient, type of event and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have a known clotting or fibrinolytic system disorder? *If yes, specify type of disorder and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have (a history of) other relevant medical conditions (e.g. Sickle cell anemia, myeloproliferative disease (hyperviscosity), nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, cancer)? *If yes, specify condition and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown

MARRS #: _____

Has the patient taken any hormonal contraceptives/estrogen therapy in the past? *If yes, specify which contraceptive/treatment, dose and duration of exposure (start and stop dates, last date taken prior to the event).*	☐ Yes, specify: ☐ No ☐ Unknown
Were there (earlier) pregnancy(s)? *Provide number and indicate if "0". Do not leave these fields blank.*	Gravida (No. of pregnancies): Para (Number of deliveries): Elective Abortions: Spontaneous Abortions:

RISK FACTORS:	
Does the patient smoke or have a smoking history? *If yes, specify age, duration and extent of smoking* *If ex-smoker indicate how long since cessation*	☐ Yes, specify: ☐ No ☐ Unknown
Is the patient a passive smoker (exposed to second-hand smoke)? *If yes, specify age, duration and extent of exposure*	☐ Yes, specify: ☐ No ☐ Unknown
Is there (a history of) excessive alcohol consumption? *If yes, specify (include duration and extent).*	☐ Yes, specify: ☐ No ☐ Unknown
Is the patient obese?	☐ Yes, specify: ☐ No ☐ Unknown
Did the patient have a history of trauma? *If Yes, specify dates and nature and anatomical location of trauma.*	☐ Yes, specify: ☐ No ☐ Unknown
Has the patient undergone surgery recently (in the past 3 months)? *If yes, specify dates and type of surgery.*	☐ Yes, specify: ☐ No ☐ Unknown
Has the patient had a history of an indwelling venous catheter? *If yes, specify dates and reason for catheter.*	☐ Yes, specify: ☐ No ☐Unknown
Has the patient been immobilized recently? *If yes, specify dates, duration and degree of immobilization.*	☐ Yes, specify: ☐ No ☐ Unknown
Has the patient recently taken a long journey by air/car/bus/train? *If yes, specify dates, nature and duration of travel.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have varicose veins? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown

MARRS #: _____

RISK FACTORS:	
Has the patient had recent intravenous injections/infusions? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown
Has the patient been diagnosed with cancer? *If yes, specify type, dates of diagnosis, treatment and outcome.*	☐ Yes, specify: ☐ No ☐ Unknown
Is there any other relevant information about the patient? *If yes, specify.*	☐ Yes, specify: ☐ No ☐ Unknown

RELEVANT DIAGNOSTIC TESTS	
What was the method of diagnosis of the VTE?	
Have the following tests been performed? If yes, specify the dates and results	**Results**
Ultrasound (i.e. Doppler, Duplex) ☐ Yes (specify type below) ☐ No ☐ Unknown Type:	
Venography (i.e. Contrast venography , MRI venography, Computed axial tomography venography) ☐ Yes (specify type below) ☐ No ☐ Unknown Type:	
Computed tomographic pulmonary angiography (CTPA) ☐ Yes ☐ No ☐ Unknown	
Ventilation-perfusion scan ☐ Yes ☐ No ☐ Unknown	
Pulmonary angiography ☐ Yes ☐ No ☐ Unknown	
CT scan ☐ Yes ☐ No ☐ Unknown	
MRI scan ☐ Yes ☐ No ☐ Unknown	
Have the following parameters been determined? *If yes, specify and provide values.*	**Values**
PT/APTT ☐ Yes ☐ No ☐ Unknown	
AT III level/activity ☐ Yes ☐ No ☐ Unknown	
Protein S level/activity ☐ Yes ☐ No ☐ Unknown	
Protein C level/activity ☐ Yes ☐ No ☐ Unknown	

MERCK

VENOUS THROMBOEMBOLIC-VTE

MARRS #: _____

RELEVANT DIAGNOSTIC TESTS	
Factor VII ☐ Yes ☐ No ☐ Unknown	
Factor VIII ☐ Yes ☐ No ☐ Unknown	
Factor XI ☐ Yes ☐ No ☐ Unknown	
Prothrombin mutation G20210 ☐ Yes ☐ No ☐ Unknown	
APC resistance (factor V Leiden) ☐ Yes ☐ No ☐ Unknown	☐ Homozygous ☐ Heterozygous ☐ Unknown whether it is homozygous - or heterozygous
Antiphospholipid antibodies (SLE/lupus) ☐ Yes ☐ No ☐ Unknown	
D-dimer ☐ Yes ☐ No ☐ Unknown	☐ Normal ☐ Increased ☐ Decreased
Homocysteine blood levels ☐ Yes ☐ No ☐ Unknown	
Other (specify)	
PROVIDE ADDITIONAL DETAILS/OUTCOME OF EVENT(s):	

PLEASE RETURN VIA FAX TO:
Brazil 55 11 5181 0773 ext. 7998
Spain 34 91 571 6466
Germany 49 89 4561 1352
France 01 80 46 46 47
Canada 800 369 3090
All other including United States 215 993 1220

MSD

DRUG ADVERSE EXPERIENCE

MARRS#: [INSERT MARRS NUMBER]

The name of entity "Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. "or "Merck" is only used in the U.S. and may need to be replaced throughout this document depending on your location. Please use the correct entity name for the country/region in which the letter is being sent.

[LETTER DATE]

[Correspondence Contact Name]
[Institution]
[Address]
[City], [STATE], [Zip Code]

Dear [Correspondence Contact Name],

We have been notified of a report concerning an event of interest following exposure to an MSD product.

Patient Name	[Patient Name]
Patient Initials	[PATIENT INTITIALS]
Age	[Patient Age]
Gender	[Patient Gender]
Product (All Merck suspect products)	[INSERT, ALL, PRODUCTS, SEPERATED, BY, COMMA, AND, SPACE, LIKE, THIS,]
Event(s) – All events	[INSERT, ALL, EVENT PREFERRED TERMS, SEPERATED, BY, COMMA, AND, SPACE, LIKE, THIS,]

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, MSD subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that MSD respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated. For instructions on how to return this form, please contact your local MSD representative or office.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about our company's privacy commitment at www.merck.com/privacy/

Sincerely,

Global Pharmacovigilance

MERCK

DRUG ADVERSE EXPERIENCE

MARRS#: [INSERT MARRS NUMBER]

[LETTER DATE]

[Correspondence Contact Name]
[Institution]
[Address]
[City], [STATE], [Zip Code]

Dear [Correspondence Contact Name],

We have been notified of a report concerning an event of interest following exposure to an Merck product.

Patient Name	[Patient Name]
Patient Initials	[PATIENT INTITIALS]
Age	[Patient Age]
Gender	[Patient Gender]
Product (All Merck suspect products)	[INSERT, ALL, PRODUCTS, SEPERATED, BY, COMMA, AND, SPACE, LIKE, THIS,]
Event(s) – All events	[INSERT, ALL, EVENT PREFERRED TERMS, SEPERATED, BY, COMMA, AND, SPACE, LIKE, THIS,]

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that Merck respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated. You may provide this information by calling us at 800-705-1885, Monday-Friday 8AM to 5PM ET, or you can return the completed form via fax at 215-661-6229.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about Merck's privacy commitment at www.merck.com/privacy/

Sincerely,

Global Pharmacovigilance
Phone: 1-800-705-1885
Fax: 215-661-6229

DRUG ADVERSE EXPERIENCE

MARRS#: [INSERT MARRS NUMBER]

DRUG ADVERSE EXPERIENCE REPORT	Program ID Number: Today's date: Please use this format throughout form → DD/MM/YY

1. Reporter Information		**2. Patient Information**		
Name:		Name or intitials:		Date of birth:
Title:		Zip code:	Age:	☐ Male ☐ Female
Institution:		Occupation:	Height: ☐IN ☐CM	Weight: ☐LB ☐KG
Address:		Is the patient pregnant? ☐ No ☐Yes	Weeks gestation: Date of LMP:	Gravida: Para:
Telephone #:	Fax #:	Race/ethnicity: ☐Caucasian ☐Black ☐Asian ☐Hispanic ☐Native American ☐Multiracial ☐Other:		

3. Merck Product Information

Merck Product Name	Suspect Therapy	Dose/ Route	Frequency	Indication	Start Date	Stop Date	LOT Number/ Expiration Date	Was product interrupted or discontinued?	Re-start date if applicable
	☐No ☐ Yes							☐ Interrupted ☐ Discontinued	
	☐ No ☐ Yes							☐ Interrupted ☐ Discontinued	
	☐ No ☐ Yes							☐ Interrupted ☐ Discontinued	

4. Patient's experience(s) (list most significant first)	Onset date/ Duration	Did experience abate after stopping drug?	Did experience reappear after reintroduction?	Event Criteria	Outcome
		☐ No ☐ Yes ☐ N/A	☐ No ☐ Yes ☐ N/A	☐Hospitalization/Prolonged hospitalization ☐Permanent or significant disability/incapacity ☐Congenital Anomaly ☐Life-threatening ☐**Important Medical Event (*IME*)	☐Unknown ☐Worsening ☐Fatal ☐Not recovered/Not resolved ☐Recovered/Resolved ☐Resolved/Recovered with sequelae ☐Recovering/resolving
		☐ No ☐ Yes ☐ N/A	☐ No ☐ Yes ☐ N/A	☐Hospitalization/Prolonged hospitalization ☐Permanent or significant disability/incapacity ☐Congenital Anomaly ☐Life-threatening ☐**Important Medical Event (*IME*)	☐Unknown ☐Worsening ☐Fatal ☐Not recovered/Not resolved ☐Recovered/Resolved ☐Resolved/Recovered with sequelae ☐Recovering/resolving
		☐ No ☐ Yes ☐ N/A	☐ No ☐ Yes ☐ N/A	☐Hospitalization/Prolonged hospitalization ☐Permanent or significant disability/incapacity ☐Congenital Anomaly ☐Life-threatening ☐**Important Medical Event (*IME*)	☐Unknown ☐Worsening ☐Fatal ☐Not recovered/Not resolved ☐Recovered/Resolved ☐Resolved/Recovered with sequelae ☐Recovering/resolving

**** Important Medical Event (IME): Required Medical/Surgical intervention to prevent one of the event criteria listed.**

5. Only complete this section if there was a medication error. (Medication error: an unintended failure in the drug treatment process that led to, or had the potential to lead to an adverse event):

Indicate at which point in the process the medication error occurred:
☐Prescribing ☐Storage in clinical Practice ☐Dispensing ☐Preparation for Administration ☐Administration
Please describe the error, any contributing factors that led to the error, and any corrective actions taken (if applicable) in the fields and narrative description.

6. Did the patient die?	**7. Was autopsy performed?**	**8. Was prescription drug treatment for the experience required?**
☐No ☐Yes List date and cause of death in narrative section.	☐No ☐Yes If available, please provide copy of death certificate and/or autopsy results.	☐No ☐Yes List in narrative section, with start and stop date (or ongoing).

DRUG ADVERSE EXPERIENCE

MARRS#: [INSERT MARRS NUMBER]

9. Please list all concomitant medications:							
Product Name	Suspect Therapy	Route	Dose	Total Daily Dosage	Start Date	Stop Date	Indication
	☐No ☐Yes						
	☐No ☐Yes						
	☐No ☐Yes						
	☐No ☐Yes						

10. Concurrent Conditions: (Medical conditions that developed prior to the initiation of drug therapy and were unresolved at the time of the first adverse event)	11. Past Medical History: (Events preceding the occurrence of the adverse event – list any pertinent information, including past drug reaction or allergies, start and stop dates)

12. Provide a Narrative Description of the events including labs/diagnostic tests to support AE information or attach results:

(Please attach additional pages as necessary)

****Required Medical/Surgical intervention to prevent one of the event criteria listed? ☐No ☐Yes**
(if yes, please be sure to include above in EVENT CRITERIA as IME)

MERCK

MYOCARDIAL INFARCTION

[Letter Date]

Name
Address
Address2
City, State, Zip Code

MARRS #:

Dear ,

We have been notified of a report concerning an experience following exposure to a Merck product.

Patient Name / Initial	
Age	
Gender	
Product (All Merck suspect products)	
Event(s) – All events	

The information will be provided to regulatory authorities such as the Food and Drug Administration, other regulatory agencies, Merck subsidiaries worldwide, and business partners with whom we have certain contractual agreements. Any information that identifies the patient directly, such as the patient's name and address, will be handled confidentially.

Enclosed is a form that Merck respectfully suggests you complete and return to us at your earliest convenience. The objective is to obtain additional information to better understand the experience you reported which may improve patient safety. Your assistance in this matter is greatly appreciated. You may provide this information by calling us at 800-705-1885, Monday-Friday 8AM to 5PM ET, or you can return the completed form via fax at 215-661-6229.

The information provided concerning the reported event will be handled according to current worldwide regulatory requirements. Please read more about Merck's privacy commitment at www.merck.com/privacy/

Sincerely,

Global Pharmacovigilance
Phone: 1-800-705-1885
Fax: 215-661-6229

MERCK

MYOCARDIAL INFARCTION

MARRS #:_____ Product: _____

Please **COMPLETE ALL PAGES** of this questionnaire.

REPORTER INFORMATION:

Name and title: _____

Affiliation: _____

Address: _____

_____

Daytime Telephone Number: _____ Signature and date: _____

PATIENT INFORMATION:

Patient Name / Initial		
Age:	DOB:	Gender:

MEDICAL HISTORY:	
Does the patient have a history of myocardial infarction or coronary artery disease (e.g. angina pectoris)? *If yes, specify onset, type of event and outcome.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have a history of any arterial thromboembolic events, including strokes? *If yes, specify onset, type of event and outcome.*	☐ Yes, specify:
Are there any family members with myocardial infarction or coronary heart disease? *If yes, specify relation to patient, type of event and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have a known clotting or fibrinolytic system disorder? *If yes, specify type of disorder and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Does the patient have (a history of) other relevant medical conditions (e.g. chronic kidney disease, sleep apnea, chronic stress levels, hypothyroidism)? *If yes, specify which condition and age at onset.*	☐ Yes, specify: ☐ No ☐ Unknown
Has the patient taken any hormonal contraceptives/treatment in the past? *If yes, specify which contraceptive/treatment, dose and duration of exposure.*	☐ Yes, specify: ☐ No ☐ Unknown
Has the patient taken other medication? *If yes, specify which medication, dose and duration of exposure.*	☐ Yes, specify: ☐ No ☐ Unknown

MYOCARDIAL INFARCTION

MARRS #:_____ Product: _____

RISK FACTORS:	
Atherosclerosis	
Does the patient have (a history of) artherosclerosis? *If yes, specify onset, type of event and outcome.*	☐ Yes. Specify:
Does the patient have (a history of) hypertension? *If yes, specify onset, nature/severity of event and outcome.*	☐ Yes. Specify: ☐ No ☐ Unknown
Does the patient have (a history of) diabetes? *If yes, specify onset, nature/severity of event and outcome.*	☐ Yes. Specify: ☐ No ☐ Unknown
Does the patient have (a history of) hyperlipidaemia? *If yes, specify onset, nature/severity of event and outcome.*	☐ Yes. Specify: ☐ No ☐ Unknown
Does the patient smoke or have a smoking history? *If yes, specify age, duration and extent of smoking.*	☐ Yes. Specify: ☐ No ☐ Unknown
Other causes / risk factors	
Does the patient have (a history of) any atrial fibrillation? *If yes, specify onset, nature/severity of event and outcome.*	☐ Yes. Specify: ☐ No ☐ Unknown
Does the patient have or have any signs of bacterial endocarditis? *If yes, specify onset, nature/severity of event and outcome.*	☐ Yes. Specify: ☐ No ☐ Unknown
Does the patient have ventricular hypertrophy? *If yes, specify onset, nature/severity of event and outcome.*	☐ Yes. Specify:
Does the patient have arteritis? *If yes, specify onset, nature/severity of event and outcome.*	☐ Yes. Specify:
Is the patient obese? *If yes, specify weight and BMI.*	☐ Yes. Specify: ☐ No ☐ Unknown
Does the patient consume alcohol? *If yes, specify amount.*	☐ Yes. Specify the amount: ☐ No ☐ Unknown
Does the patient have a history of drug abuse (e.g. cocaine, prescription)? *If yes, specify age, duration and extent of abuse.*	☐ Yes. Specify: ☐ No ☐ Unknown

MERCK

MYOCARDIAL INFARCTION

MARRS #:_____ Product: _____

EVENT DETAILS:	
Date of first symptoms of the event:	
Description of the event:	
What were the presenting symptoms and signs, and what was their chronological order?	
How was the event diagnosed? Which tests/procedures were used and what were the results?	
Which (sequence of) treatments were given, and by whom? On which dates?	
What was the course of the illness following treatment?	
Did the myocardial infarction result in any complications such as cardiac failure, arrhythmias, valvular and septal abnormalities? *If yes, specify onset, nature/severity of event and outcome.*	
What was the outcome of the event over time, in terms of residual disability?	
Is there any other relevant information about the event?	

LAB/DIAGNOSTIC DATA: *Please provide baseline, highest, last on drug and newest values.*		
TEST(S)	**DATE(S)**	**RESULTS**
Investigations		
ECG		
Coronary angiography		
Chest X-ray		

MERCK

MYOCARDIAL INFARCTION

MARRS #:_____ Product: _____

LAB/DIAGNOSTIC DATA: *Please provide baseline, highest, last on drug and newest values.*		
TEST(S)	**DATE(S)**	**RESULTS**
Others		
Blood tests		
CK level		
CK-MB level		
Myoglobin level		
Troponin I and Troponin T level		
Any other relevant test/laboratory data available?		

GLOBAL SAFETY COMMENTS:

PLEASE RETURN VIA FAX TO:

Brazil 55 11 51810773 ext. 7998
Spain 34 91 571 6466
Germany 49 89 4561 1352
France 01 80 46 46 47
Canada 800-369-3090
All other including United States 215 661 6229

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

A one-time DHPC regarding the potential risk of Medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension (PFS)) will be disseminated to Healthcare providers (HCP) identified as potential prescribers of Noxafil Gastro-Resistant Powder and Solvent for Oral Suspension and Noxafil oral suspension such as paediatricians, haematologists, oncologists, and infectious disease specialists, as well as hospital pharmacists (the final list is to be confirmed by the NCA), in the EEA countries that market both the oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension at the time of launch of the new PFS formulation, in agreement with the NCA.

Direct Healthcare Professional Communication

<Date>

NOXAFIL® (posaconazole) new Gastro-Resistant Powder and Solvent for Oral Suspension, and existing oral suspension including generics not interchangeable – risk of medication error

Dear Healthcare professional,

Merck Sharp & Dohme, B.V (MSD) in agreement with the European Medicines Agency and the <National Competent Authority > would like to inform you of the following:

Summary

- A new formulation of Noxafil, gastro-resistant powder and solvent for oral suspension (PFS) has been approved for use in children 2 years of age and older
- The newly available Noxafil PFS and the existing oral suspension (OS) formulation including generics are not interchangeable
- Substitution between the two formulations can potentially result in over or underdosing, and risks of serious adverse drug reactions or lack of efficacy
- Prescribers should always specify the formulation and dosage for posaconazole on each prescription
- Pharmacists should ensure correct formulation and dosing are dispensed to patients.
- As a reminder, posaconazole tablets and oral suspension (OS) are not interchangeable either

Background on the safety concern

Posaconazole (POS) is a broad-spectrum tri-azole antifungal compound indicated for the treatment of fungal infections and the prophylaxis of invasive fungal infections (IFIs).

Posaconazole is available in the following formulations:

- oral suspension (OS, 40 mg/mL) for adults,
- gastro-resistant tablet (100 mg) for adults and paediatric population from 2 years old (weighing more than 40 kg),

- gastro-resistant powder and solvent for oral suspension (PFS, 300 mg powder sachet) for paediatric population from 2 years old,

- concentrate for solution for infusion (IV, 18 mg/mL) for adults and paediatric population from 2 years old.

The oral suspension (OS) is not interchangeable with gastro-resistant powder and solvent for oral suspension (PFS) due to the differences between these formulations in dosages, dosing schedules, and plasma drug concentrations. The dose for PFS also differs from the dose of IV formulation in paediatric patients.

Medication errors related to substitutions between Noxafil and generics OS formulation and Noxafil PFS could result in dosing errors potentially leading to adverse events in cases of overdosing or lack of efficacy in cases of under-dosing.

Please refer to the SmPC for formulation specific dosing recommendations.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*

This letter is not intended as a complete description of the benefits and risks related to the use of NOXAFIL. Please refer to the Summary of Product Characteristics for full prescribing advice.

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Annexes (if applicable)

<Link/reference to other available relevant information, such as information on the website of a competent authority>