VFEND (VORICONAZOLE) RISK MANAGEMENT PLAN

RMP Version number: 6.3

Data lock point for this RMP: 31 May 2023

Date of final sign off: 29 June 2023

Rationale for submitting an updated RMP:

- In May 2022, the MAH submitted a Type II variation including an updated EU RMP v 6.0, following the completion of the PASS A1501103 included in the pharmacovigilance plan. In addition, in line with PRAC PSUR assessment report (Procedure no.: EMEA/H/C/PSUSA/00003127/202102) dated October 2021, the RMP was updated to remove the important identified risk of "Peripheral neuropathy" and the missing information of "Resistance" from the list of the safety concerns.

- The MAH received a first RSI dated 01 September 2022 as part of procedure EMEA/H/C/WS2270 whereby the EMA requested the MAH continue to make the Patient Alert Card available for the important identified risks of Phototoxicity and Squamous cell carcinoma. An updated RMP v6.1 was submitted in November 2022 as part of this response.

- In March 2023, the MAH submitted an updated RMP version (6.2) to respond to a 2nd RSI dated 12 January 2023 as part of procedure EMEA/H/C/WS2270 whereby the EMA have indicated to:

    - remove the following important risks and missing information from the Summary of safety concerns: 'Hepatic toxicity', 'QTc prolongation', 'Visual events', 'Skin cancer (non-SCC)', 'Suicide-related events', 'Effects in pregnancy', 'Effects in paediatrics' and 'Off-label use'.

    - remove the statement in Part III.2. Additional Pharmacovigilance Activities.

    - add key elements of the Patient Alert Card in Annex 6.

- The MAH is submitting an updated RMP version (6.3) to respond to a 3rd RSI dated 12 May 2023 as part of procedure EMEA/H/C/WS2270 whereby the EMA have indicated to update, with additional text, the key elements of the Patient Alert Card in Annex 6.

Summary of significant changes in this RMP since version 6.0 (and including changes performed in version 6.1 and 6.2):

RMP Part/Module	RMP 6.0 and 6.1 Major Change (s)	RMP 6.2 Major Change (s)	RMP 6.3 Major Change (s)
PART I Product(s) Overview	Aligned to the current SmPC.	Aligned to the current SmPC.	Aligned to the current SmPC.
PART II Safety Specification			
PART II.Module SI Epidemiology of the Indication(s) and Target Population(s)	Updated with new references (RMP v 6.0).	No changes made.	No changes made.
PART II.Module SII Non-clinical Part of the Safety Specification	No changes made.	No changes made.	No changes made.
PART II.Module SIII Clinical Trial Exposure	No changes made on the CT exposure tables; a general statement on the cumulative exposure as of new DLP is included (28 February 2022, RMP v 6.0).	No changes made on the CT expo-sure tables; a general statement on the cumulative exposure as of new DLP is included (17 November 2022).	No changes made on the CT exposure tables; a general statement on the cumulative exposure as of new DLP is included (31 May 2023).
PART II.Module SIV Populations Not Studied in Clinical Trials	Minor Update.	No changes made.	No changes made.
PART II.Module SV Post-Authorisation Experience	Post-Authorisation Exposure updated as of new DLP (28 February 2022, RMP v 6.0).	Post-Authorisation Exposure updated as of new DLP (17 November 2022).	Post-Authorisation Exposure updated as of new DLP (31 May 2023).
PART II.Module SVI Additional EU Requirements for the Safety Specification	No changes made.	No changes made.	No changes made.
PART II.Module SVII Identified and Potential Risks	Overall module updated to reflect the removal of "Peripheral neuropathy" and "Resistance" from the list of the safety concerns (RMP v 6.0). Risks characterization updated as of new DLP (28 February 2022, RMP v 6.0).	Overall module updated to remove the following important risks and missing information: 'Hepatic toxicity', 'QTc prolongation', 'Visual events', 'Skin cancer (non-SCC)', 'Suicide-related events', 'Effects in pregnancy', 'Effects in paediatrics' and 'Off-label use' based on the 2nd RSI dated 12 January 2023. Risks characterization of remaining safety concerns updated as of new DLP (17 November 2022).	Risks characterization of remaining safety concerns updated as of new DLP (31 May 2023).

RMP Part/Module	RMP 6.0 and 6.1 Major Change (s)	RMP 6.2 Major Change (s)	RMP 6.3 Major Change (s)
PART II.Module SVIII Summary of the Safety Concerns	Updated to remove "Peripheral neuropathy" and "Resistance" from the list of the safety concerns (RMP v 6.0).	Updated as per changes in Module SVII based on the 2nd RSI dated 12 January 2023.	No changes made.
PART III Pharmacovigilance Plan (including post-authorisation safety studies)			
III.1 III.2 III.3	The DCA for SCC is no longer in place, so it is removed PASS A1501103 (included as Category 3) is completed (CSR dated 30 April 2022) and therefore removed from PART III.2 and PART III.3 (RMP v 6.0).	 The statement about the study A1501103 completion is removed.	No changes made.
PART IV Plans for Post-Authorisation Efficacy Studies	No changes made.	No changes made.	No changes made.
PART V Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)			
V.1 V.2 V.3	Updated to include the MAH proposal to remove aRMMs to address Phototoxicity, Squamous Cell Carcinoma and Hepatic toxicity (RMP v 6.0) Any reference to PASS 1501103 is removed Updated to reinclude Patient Alert Card to address the important identified risks of phototoxicity and SCC as per RSI received in September 2022 (RMP v 6.1).	Updated to reflect the EMA agreement on the removal of the HCP aRMMs as per updated assessment report dated 05 January 2023.	No changes made.
PART VI Summary of the Risk Management Plan	Updated as per changes in PART III and PART V	Updated as per changes in PART III and PART V.	No changes made.
PART VII Annexes			

RMP Part/Module	RMP 6.0 and 6.1 Major Change (s)	RMP 6.2 Major Change (s)	RMP 6.3 Major Change (s)
	Annex 2: Updated to include PASS 1501103 as completed. Annex 3: Updated to remove PASS 1501103. Annex 6: Updated to include rationale for the removal of RMMs (RMP v 6.0) and re-inclusion of Patient Alert Card (RMP v 6.1). Annex 7: Updated to remove data for Peripheral neuropathy. Annex 8: Updated to reflect the changes overtime.	Annex 6: updated to add key elements of Patient Alert Card as per the 2nd RSI dated 12 January 2023. Annex 7: Updated to remove CT exposure related to the safety concerns that are being removed: Hepatic toxicity', 'QTc prolongation', 'Visual events', 'Skin cancer (non-SCC)', 'Suicide-related events.' Annex 8: Updated to reflect the changes overtime.	Annex 6: the key elements of the Patient Alert Card updated with additional text provided by PRAC in the 3rd RSI dated 12 May 2023. Annex 8: Updated to reflect the changes overtime.

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 5.1

Approved with procedure: EMEA/H/C/000387/II/0121

Date of approval (opinion date): 27 January 2017

QPPV name[1]: Barbara De Bernardi

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.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

Abbreviation	Term
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANLL	Acute non-lymphocytic leukaemia
aRMM(s)	additional Risk Minimisation Measure(s)
ASD	Adult and Adolescent Spectrum of HIV Disease
AST	Aspartate aminotransferase
AUCτ	Area under the plasma concentration time curve within a dose interval
BCC	Basal cell carcinoma
BSI	Bloodstream infection
CDC	Centres for Disease Control and Prevention
Cmax	Maximum plasma concentration
CT	Clinical trial
CYP	Cytochrome P450
DHPC	Direct Healthcare Professional Communication
EC	Oesophageal candidiasis
ECG	Electrocardiogram
ECIL	European Conference on Infections in Leukaemia
ECMM	European Confederation of Medical Mycology
EORTC	European Organization for Research and Treatment of Cancer
ERG	Electroretinogram
EU	European Union
FHCRC	Fred Hutchinson Cancer Research Center
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte macrophage colony stimulating factor
GTT	Gamma glutamyl transpeptidase
GvHD	Graft vs. host disease
HCP	Health Care Professional
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HSCT	Haematopoietic stem cell transplant
IA	Invasive aspergillosis
ICC	Invasive candidiasis including candidaemia
ICD-9	International Classification of Diseases Code 9
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IFI	Invasive fungal infection
L-AMB	Liposomal amphotericin B (AmBisome®)
LFTs	Liver function tests
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MM	Multiple myeloma
MSG	National Institute of Allergy and Infectious Diseases Mycosis Study Group
NCHS	National Center for Health Statistics
NHDS	National Hospital Discharge Survey
NMSC	Non-melanoma skin cancer
NOAEL	No adverse effect level

Abbreviation	Term
OR	Odds ratio
PAM	Post Approval Measure
PASS	Post-authorisation safety study
PfAST	Pfizer Analytical and Statistical Tool
PIL	Patient Information Leaflet
PL	Package leaflet
PSUR	Periodic Safety Update Report
PT	Preferred term
Q12h	Treatment every 12 hours
Q&A	Question & Answer
RMC	Risk Management Committee
RMP	Risk Management Plan
SBECD	Sulphobutylether β cyclodextrin sodium
SCC	Squamous cell carcinoma
SGOT	Serum glutamic-oxaloacetic transaminase (ALT)
SGPT	Serum glutamic-pyruvic transaminase (AST)
SMQ	Standardized MedDRA Query
SMR	Standardized mortality ratio
SOP	Standard Operating Procedure
SOT	Solid organ transplant
SmPC	Summary of Product Characteristics
TME	Targeted medical event
TransNet	Transplant Associated Infections Surveillance Network
ULN	Upper limit of normal
US	United States
USRDS	US Renal Data System
UV	Ultra-violet
VOLD	Veno-occlusive liver disease

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Voriconazole
Pharmacotherapeutic group(s) (ATC Code)	J02AC03
Marketing Authorisation Holder Applicant	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	VFEND VORICONAZOLE PFIZER
Marketing authorisation procedure	Centralised Decentralised Procedure
Brief description of the product:	Chemical class: voriconazole is a broad-spectrum, triazole antifungal agent.
	Summary of mode of action: the primary mode of action is inhibition of fungal cytochrome P450-mediated 14α-lanosterol demethylation, an essential step in ergosterol biosynthesis.
	Important information about its composition: voriconazole is a synthetic drug.
Hyperlink to the Product Information:	Please refer to Module 1.3.1 of this submission.

Indication(s) in the EEA	Current: VFEND, is indicated in adults and children aged 2 years and above as follows: Treatment of invasive aspergillosis. Treatment of candidaemia in non-neutropenic patients. Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*). Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. VFEND should be administered primarily to patients with progressive, possibly life-threatening infections. Prophylaxis of invasive fungal infections in high-risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

Dosage in the EEA

Current:

Adults	Intravenous	Oral	
		Patients 40 kg and above*	Patients less than 40 kg*
Loading dose Regimen (first 24 hours)	6 mg/kg every 12 hours	400 mg every 12 hours	200 mg every 12 hours
Maintenance dose (after first 24 hours)	4 mg/kg twice daily	200 mg twice daily	100 mg twice daily

* This also applies to patients aged 15 years and older

Children (2 to <12 years) and young adolescents with low body weight (12 to 14 years and <50 kg)	**Intravenous**	**Oral**
Loading Dose Regimen (first 24 hours)	9 mg/kg every 12 hours	Not recommended
Maintenance Dose (after first 24 hours)	8 mg/kg twice daily	9 mg/kg twice daily (a maximum dose of 350 mg twice daily)

Note: Based on a population pharmacokinetic analysis in 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescents aged 12 to <17 years

All other adolescents (12 to 14 years and ≥50 kg; 15 to 17 years regardless of body weight): voriconazole should be dosed as adults.

Dosage adjustment (Children [2 to <12 years] and young adolescents with low body weight [12 to 14 years and <50 kg]) If patient response to treatment is inadequate, the dose may be increased by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially). If patient is unable to tolerate treatment, reduce the dose by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially).

Use in paediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied.

Prophylaxis in Adults and Children

Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. Prophylaxis should be as short as possible depending on the risk for developing invasive fungal infection (IFI) as defined by neutropenia or immunosuppression. It may only be continued up to 180 days after transplantation in case of continuing immunosuppression or graft versus host disease (GvHD)

Dosage

The recommended dosing regimen for prophylaxis is the same as for treatment in the respective age groups. Please refer to the treatment tables above.

Pharmaceutical form(s) and strengths	Current: VFEND 50 mg film-coated tablets VFEND 200 mg film-coated tablets VFEND[2] is also available as 200 mg powder for solution for infusion, and 40 mg/mL powder for oral suspension.
Is/will the product be subject to additional monitoring in the EU?	No

[2] A variation (EMEA/H/C//000387/IB/0146/G) has been submitted to EMA on 08 April 2022 to remove 200 mg powder and solvent for solution for infusion non marketed formulation from the EU Centralised Procedure MA.

PART II. SAFETY SPECIFICATION

Voriconazole is a broad-spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

- Treatment of invasive aspergillosis.
- Treatment of candidaemia in non-neutropenic patients.
- Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*).
- Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

Voriconazole should be administered primarily to patients with progressive, possibly life-threatening infections.

- Prophylaxis of invasive fungal infections in high-risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

Module SI. Epidemiology of the Indication(s) and Target Population (s)

SI.1. Invasive Aspergillosis (IA)

Aspergillosis is caused by an infection with an *Aspergillus fungus*. The incidence of IA has been increasing in recent decades corresponding with the increase in the number of immuno-compromised patients.

The section below summarizes the epidemiology of IA in the EU and US general population, and patient subpopulations.[3]

SI.1.1. Incidence

The data on the incidence of IA in the general population are scarce. The search identified one study that reported the incidence of IA in the US general population.

Europe
No study was found reporting incidence of IA in the general population from the EU region.

United States
In a review article, Pfaller, et al, reported the incidence of IA (from 1996 to 2003) in the US general population from the National Hospital Discharge Survey (NHDS). The NHDS is conducted annually by the National Center for Health Statistics (NCHS).

[3] Throughout the literature review, IA was represented by the following Boolean search terms: [(aspergillosis OR invasive aspergillosis OR IA OR fungaemia) AND epidemiology OR population-based OR incidence OR prevalence OR mortality)].

NHDS data serve as a basis for calculating statistics on hospital inpatient utilization in the US. The incidence of IA (per 100,000 population) was reported to be 3.4 in 1996, 4.1 in 2000 and 2.2 in 2003. [1]

In the US population, the MAH analysed the NHDS data using the same International Classification of Diseases Code 9 (ICD-9) for IA documented in the Pfaller, et al paper [1] and estimated the incidence of IA from 2004 to 2007 in the US general population.

Year	IA incidence (per 100,000 population)
1996	3.4
1997	2.8
1998	2.1
1999	2.4
2000	4.1
2001	3.0
2002	2.6
2003	2.2
2004	2.9
2005	2.3
2006	1.9
2007	3.6

Data from 1996 through 2003 from the study by Pfaller, et al, and from 2004 through 2007 calculated by the MAH.

In an analysis using the National Inpatient Sample[2], a hospital discharge database in the US, there were 169,110 IA-related hospitalizations during 2000-2013. The rate of IA-related hospitalizations per 1 million persons rose from 32.7 in 2000 to 45.7 in 2013.

Incidence of IA in selected patient subpopulations: As mentioned earlier, IA infections primarily occur in patients with immunocompromised status. Several studies were found that reported rates of IA in patients with hematologic malignancy, or HSCT recipients, or solid organ transplant (SOT).

The following table summarizes IA incidence estimates in selected patient subpopulations.

Selected Patient Population	IA incidence (%)
Haematology or HSCT	
Autologous HSCT	0.5-6
Allogeneic HSCT	2.7-23
Allogeneic HSCT from an HLA matched related donor	2.3
Transplantation from an HLA-mismatched related donor	3.2
Transplantation from an unrelated donor	3.9
Malignancies	
Acute myeloid leukaemia (AML)	5-24 (1.9*)
Acute lymphoblastic leukaemia (ALL)	3.8 (1.3*)
Non-Hodgkin's lymphoma	0.8
Hodgkin's disease	0.4
Multiple myeloma	2-3
SOT	
Lung	2.4-26
Heart	0.4-15
Liver	0.3-10
Kidney	0.1-1
Pancreas	1.1-2.9
Small bowel	0-11
HIV infection	2.1
	3.5**
ICU patients	4***

* per 1000 patient-day; ** per 1000 person-years; ***per 1000 ICU admissions

Below is a summary of a few studies.

Patients with haematologic malignancy or HSCT: Overall the incidence of IA in patients with haematologic malignancies was reported to be approximately 2.6%.[3] In patients with AML, the IA incidence ranged from 5% to 24% and in patients with ALL, it was 3.8%.[4] Among patients with HSCT, the IA incidence ranged from 0.5% in patients with autologous HSCT to 23% in patients with allogeneic HSCT. [4 5]

In addition, the rate of invasive fungal infection (IFI) in allogeneic HSCT recipients who underwent autopsy was reported to be 30% (99/327).[3]

Below are the details of studies reporting incidence of IA.

In a retrospective review of medical records of patients admitted to 18 hospitals in Italy between 1999 and 2003, Pagano and colleagues examined 11,802 patients with haematologic malignancies: among these patients, 310 patients with IA were identified, with an incidence of 2.6%.[6] In a study conducted at a large tertiary care hospital in France, Nicolle (2011) estimated IA incidence in patients with AML (n=2,078) and ALL (850) admitted between 2004 and 2009. The IA incidence rate was 1.9 (95% CI: 1.5, 2.3) per 1000 patient-day in patients with AML and 1.3 (95% CI: 0.8, 2.0) per 1000 patient-day in patients with ALL.[7]

In another study, Morgan, et al estimated the incidence of IA in 4,621 patients with HSCT at Transplant Associated Infections Surveillance Network (TransNet) sites across the US, during a 22-month period, from 01 March 2001 through 31 December 2002. Incidence of IA at 12 months was 0.5% after autologous HSCT, 2.3% after allogeneic HSCT from a human leukocyte antigen (HLA) matched related donor, 3.2% after transplantation from a HLA-mismatched related donor, and 3.9% after transplantation from an unrelated donor. [5]

In an updated analysis of TransNet data with a cohort of 16,200 HSCT recipients who received their first transplants between March 2001 and September 2005 and were followed up through March 2006, the 6-month and 12-month IA incidence were 1.3% and 1.6%, respectively.[8]

In a recent literature review, Herbrecht et al. (2012) summarized the rate of IA in patients with immunocompromised status. The rate of IA in patients with allogeneic HSCT ranged from 2.7% to 23%, and in patients with autologous HSCT ranged from 0.5% to 6%.[4]

Patients with SOT: The incidence of IA in patients with lung transplant ranged from 2.4% to 26%, heart 0.4% to 15%, liver 0.3% to 10% kidney 0.1% to 1%, pancreas 1.1% to 2.9%, and small bowel 0 to 11%.[4 5 9]

Below is the overview of studies summarizing the incidence of IA in patients with SOT.

A retrospective analysis of medical records of patients receiving SOT at the Cleveland Clinic Foundation to estimate the incidence of IA was conducted. Overall, a total of 33 cases of IA with an incidence of 4.8 per 1000 patient-years (33 per 6813 patient-year) were reported in patients with SOT. The incidence was higher for lung transplant recipients compared to other SOT recipients: lung 12.8% (24 cases per 188 patients) or 40.5 per 1000-patient year; heart 0.4% (3/686) or 1.4 per 1000 patient-year; liver 0.7% (3/439); 1 per 1000 patient year; and renal 0.4% (3/733) or 1.2 per 1000 patient-year. [9]

Morgan, et al using TransNet data described earlier, estimated the incidence of IA at 12 months as 2.4% after lung transplantation, 0.8% after heart transplantation, 0.3% after liver transplantation, and 0.1% after kidney transplantation. [5]

The review article by Herbrecht et al. (2012) also reported the incidence of IA in patients who had received SOT: 3% to 26% in patients with lung or heart-lung, 0.4% to 15% for heart, 0.7% to 10% for liver, 1.1% to 2.9% for pancreas, 0.2% to 1% for kidney and 0 to 11% in patients with small bowel transplant. [4]

Patients infected with HIV: IA has been reported to be rare in patients with HIV infection. It mainly occurs in HIV patients with neutropenia or those receiving corticosteroids, however in many patients with HIV no recognized risk factors have been identified.

In a retrospective study all HIV-infected patients hospitalized between January 1986 and April 1997 in 4 Italian Departments of Infectious Diseases in an area of high prevalence of HIV infection (Ferrara, Bologna, Reggio Emilia, and Venezia) were examined for IA.

Of 2,614 patients diagnosed with HIV/AIDS during the study period, 2.1% (54 total patients; 13 females and 41 males, average age 32 years) were identified with IA.

The mean interval between the diagnosis of HIV and the diagnosis of IA was 10.4 months (range 0 to 36 months).[10]

In a study conducted by Holding, et al, the authors analysed data collected from medical records of HIV-infected patients from the Adult and Adolescent Spectrum of HIV Disease project (ASD) from January 1990 through January 1998. In this study, HIV infected patients aged > 13 years from inpatient and outpatient facilities in 10 US cities, were selected at their first health care visit. Among 35,252 HIV-infected patients, there were 228 cases of aspergillosis, yielding an incidence of 3.5 cases per 1,000 person-years (95% CI: 3.0 to 4.0 per 1000 person-year). [11]

Patients admitted to an intensive care unit (ICU): In a review of medical charts of 8988 patients admitted to an ICU in a tertiary care hospital in Belgium between July 1997 and December 1999, 71 patients were identified with positive cultures for Aspergillus spp. A total of 37 cases were classified as either definite or probable IA, representing an incidence of 4 per 1000 ICU admissions.[12]

SI.1.2. Prevalence

No study reporting the prevalence of IA was found during the literature search.

SI.1.3. Demographics of the population, age, gender, racial and/or ethnic origin and risk factors for the disease

Age: age has been identified as an important risk factor for IA. The incidence in paediatric populations is reported to be lower than those in adult populations.[13]

Sex: IA is reported to be more common in males. In a systematic review by Lin, et al described earlier, information on sex was reported for 225 of the 373 patients with individual data. Of total 225 patients, 63 (28%) were female and 162 (72%) were male.[14]

Risk Factors for the Disease:

Potential health risk for Invasive Aspergillosis, Candidaemia in Non-Neutropenic Patients, Fluconazole-Resistant Serious Invasive Candida Infections (Including *C. krusei*), Serious Fungal Infections Caused by *Scedosporium* spp. and *Fusarium* spp.

SI.1.4. The main existing treatment options

For IA, although voriconazole is recommended as the first line treatment, liposomal amphotericin B is considered as an alternative by the Infectious Diseases Society of America (IDSA)[15] and by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID).[16]

The recommendations are graded by strength (from A- strongly supports a recommendation for use to C- poor evidence to support a recommendation) and ranked according to level of scientific evidence (I- strongest to III- weakest). Other available options are recommended as salvage therapy and consist of other lipid formulations of amphotericin (A-II), posaconazole (B-II), itraconazole (B-II), caspofungin (B-II), or micafungin (B-II). Primary therapy with amphotericin B deoxycholate is not recommended (A-I) unless the economic status in a given institution or country precludes the use of other compounds.

Prophylactic Indications: For primary antifungal prophylaxis in allogeneic HSCT patients, only fluconazole and voriconazole were graded as AI drugs during the initial neutropenic phase in the ECIL-3 guidelines, and only posaconazole and voriconazole[4] were graded as AI drugs during the GvHD phase.[17] Other antifungals are also recommended; those included are fluconazole, itraconazole, the echinocandins and the polyenes.

SI.1.5. Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Invasive aspergillosis mortality in the general population: In a review article by Pfaller and colleagues described above, the author also reported analysis from the multiple cause-of-death data and provided the mortality rates of IA in the US general population for the years 1991 through 2003. The IA mortality rates (per 100,000 population) were approximately 0.42 in 1997 and 0.25 in 2003.[1]

Invasive aspergillosis mortality in patient subpopulations: Lin, et al systematically pooled the mortality data from clinical trials, cohort or case control studies, and case series of > 10 patients (77 studies in total) with definite or probable IA and reported the mortality rate for IA by underlying conditions. The overall mortality rate in patients with IA was reported to be 58%. The mortality was highest in patients with HSCT recipients (86.7%).

The mortality rate for male patients is reported to be slightly higher than that for female patients (56.8% vs. 47.6%). The rate did not vary significantly by age. Below is a description of studies reporting IA mortality rate in patient subpopulations.

Invasive aspergillosis mortality in patients with haematologic malignancy or HSCT: In a registry-based study that collected data (2004-2007) from 21 tertiary care centres in Italy, Pagano et al (2009) reported the overall mortality rate in patients with AML. Among 140 AML patients diagnosed with IA, overall mortality rate at day 120 of infection was 33%.[18] In another study conducted at a large tertiary care hospital in France, described earlier, all-cause mortality rate was 14% at 1 month and 38% at 3 months in patients with AML, and 6% at 1 month and 53% at 3 months in patients with ALL. [7]

[4] Provisional grading pending the publication of the full paper. Note since the ECIL-3 issue, the study was published, Marks 2011 (Marks DI, Pagliuca A, Kibbler CC, et al. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. Br J Haematol 2011;(Aug): 155:318–327)

In a study in TransNet sites in the US described above, after HSCT, mortality at 3 months following diagnosis of IA ranged from 53.8% in autologous transplants to 84.6% in unrelated-donor transplants. In an updated analysis, Kontoyiannis, et al reported an overall mortality of patients with HSCT at 1-year of 74.6%.[8] In a review article by Denning DW et al., the mean mortality rate in patients with HSCT (including recipients of autologous, allogeneic, and peripheral stern cell transplants) developing IA was 90% and ranged from 33% to 100%.[19]

Invasive aspergillosis mortality in patients with SOT: In the TransNet data in the US, mortality at 3 months after diagnosis of IA ranged from 20% in lung transplant patients to 66.7% in heart and kidney transplant patients.

Invasive aspergillosis mortality in patients co-infected with HIV: The prognosis is reported to be poor in patients co-infected with HIV and IA. In a study in Italy described earlier, the mean survival time was 2 to 4 months in patients co-infected with IA and HIV. Cause of death was directly related to aspergillosis in 62.9% (34/54) patients. [10] In the ASD study described before, the median survival was 3 months after the diagnosis of aspergillosis in 228 patients co-infected with aspergillosis and HIV. The percentage of patients alive 1 year after diagnosis of aspergillosis was 26% (95% CI: 20, 32).[20]

Invasive aspergillosis mortality in patients admitted to an ICU: In a review of medical charts of ICU patients in a tertiary care hospital in Belgium between July 1997 and December 1999, 75.7% (28/37) patients died during their stay in ICU. [12]

Summary: The following table summarizes IA mortality in selected patient subpopulations.

Patient population	Mortality (%)
Autologous HSCT	53.8
Unrelated donor HSCT	84.6 33
Acute myeloid leukaemia	14* 38** 33***
Acute lymphoblastic leukaemia	6* 53**
HSCT recipients	Mean 90% (ranged 33% - 100%)
Lung transplant patients	20
Heart and kidney transplant patients	66.7
Co-infected with HIV	62.9
ICU patients	75.7

*At 1 month of IA diagnosis, **At 3 months of IA diagnosis, ***At 4 months of IA diagnosis.

SI.1.6. Important co-morbidities

Following are the important co-morbid conditions reported in patients with IA.

- Haematologic malignancies/HSCT/cancer patients
- Solid organ transplant (SOT) (i.e., renal, heart, liver, lung or multi-organ transplant)

- HIV infection

Table 1. Co-morbidity in the Target Population – Patients with Invasive Aspergillosis

Hematologic malignancies or HSCT
The risk of IA among patients with HSCT is a function of neutropenia and/or immunodeficiency which makes them susceptible to infections including IA. Estimates from the TransNet Database, which enrolled HSCT recipients with proven or probable invasive fungal infections between 2001 and 2006, suggest that IA remains the most common of all IFIs following HSCT. [8] The search identified one study that reported the proportion of patients with haematologic malignancy among patients diagnosed with IA. In a retrospective study, conducted at the University Hospital Leuven, Belgium between January 1, 2000, and January 1, 2003, among 127 adult ICU patients with IA, 30% (38/127) patients had hematologic malignancy.[21]
Mortality: Mortality estimates in haematologic malignancy or HSCT patients infected with IA have been presented in Section SI.1.5 **Co-prescribed medications:** Persons with haematological malignancy have complex medication regimens that vary according to the lesion type, stage, and symptomatology. Immunosuppression-causing cytotoxic agents are at the core of curative chemotherapy. These patients also take antineoplastic agents for palliation along with an array of analgesics, sedatives, antidepressants, corticosteroids, and other anti-nausea drugs. Following are some of the co-prescribed medications. **Acute myelogenous leukaemia patients:** Daunorubicin, mitroxantrone, idarubicin, cytarabine, imatinib. **Acute lymphocytic leukaemia patients:** Cyclophosphamide, daunorubicin, vincristine, steroids, mercaptopurine. **Bone Marrow Transplant patients:** Busulfan, cyclophosphamide, etoposide, carmustine, cisplatin, cytarabine, melphalan, lomustine, antithymocyte globulin.
SOT
Patients with SOT are at much higher risk for IA infection than the general population. It has been well established that the state of immunosuppression and the intensity of immunosuppressive regimen is a major determinant of the development of IA in these high-risk patients. In a systematic review of published data that included 1,941 patients with a diagnosis of aspergillosis, 252 (13%) of patients were SOT recipients.[22] **Mortality:** Mortality estimates in SOT patients infected with IA have been presented in Section SI.1.5 **Co-prescribed medications:** SOT recipients require aggressive immunosuppressive therapy to prevent graft rejection. As a result, transplant patients commonly take calcineurin inhibitors (e.g., ciclosporin), antiproliferative agents (e.g., azathioprine), corticosteroids (e.g., prednisone), and various therapeutic antibodies.[23] Because they are immunosuppressed, transplant recipients often require prophylactic anti-infective agents to prevent and treat opportunistic infections: antibacterial, antifungal, and antiviral agents.
HIV infection
The search did not identify any study that reported the proportion of patients with HIV among patients diagnosed with IA. **Mortality:** Mortality estimates in HIV infected patients have been presented in Section SI.1.5 **Co-prescribed medications:** Patients with HIV, especially symptomatic disease, take aggressive multidrug antiretroviral regimens consisting of reverse transcriptase inhibitors, protease inhibitors, and fusion inhibitors.[24] Other drugs commonly used by this population include various anti-infective agents for prevention of opportunistic infections, antidepressants and anxiolytics, and drugs for treatment-induced dyslipidaemia. In a study conducted in Canada, 71% (10/14) of patients were neutropenic or on steroids including megestrol. Eight (8) patients were on ganciclovir at the time of diagnosis of aspergillosis.

SI.2. Candidaemia in Non-Neutropenic Patients

Candidiasis is caused by a group of microscopic fungi or yeast and is associated with substantial morbidity and mortality, prolongation of hospital stay, and increased healthcare cost worldwide.

The section below summarizes summary of studies reporting candidaemia incidence, prevalence and mortality estimates from published literature. Search terms to identify relevant papers are mentioned below.[5]

Indication/target population

No study was found that reported the incidence of candidaemia in specifically "non neutropenic" patients. Below is a summary of studies reporting incidence of candidaemia in the general population in the EU and US, and specific patient subpopulations.

Europe

The incidence (per 100,000 population) of candidaemia in the general population ranged from 1.4 to 4.9 in Iceland,[25] 3.5 in Spain,[26] 1.7 to 2.86 in Finland,[27] 2.4 in Norway[28] and 2.96 to 4.20 in Switzerland[29]. A meta-analysis[30] of 25 population-based studies conducted in European population from January 2000 to February 2019 reported a pooled incidence of 3.88 per 100,000 persons per year.

In a nationwide study in Iceland, all patients infected with *Candida* spp. were identified by a nationwide search in microbiology databases from 01 January 1980 to 31 December 1999. During the 20-year period, annual incidence (per 100,000 population) of candidaemia increased 3.5-fold, from 1.4 between 1980 and 1984 to 4.9 between 1995 and 1999.[25] In another study in Spain, mean annual incidence of candidaemia was 3.5 per 100,000 population between September 1997 and August 1999 were reported. In this study, the cases of candidaemia were identified from 19 hospitals across Spain. [26] Using data from the laboratory-based surveillance program on candidaemia from June 2008 to June 2009 in 40 medical centres across Spain, an overall incidence of approximately 100 cases per 100,000 hospital admissions was reported. Poikonen, et al analysed the laboratory-based surveillance data from the National Infectious Disease Register in Finland and reported the annual incidence (per 100,000 population) of 1.7 in 1995 and 2.2 in 1999.[27] In a large study in Norway, collecting data on cases of candidaemia from all microbiological laboratories across Norway, the average annual incidence between 1991 to 2003 was 2.4 per 100,000 population. [28] Data from the nation-wide Swiss Antibiotic Resistance Surveillance System from 2009 to 2018 suggested that the population-based incidence of candidemia (per 100,000 persons) increased from 2.96 in 2009–2013 to 4.20 in 2014–2018.[29]

United States

In a population-based surveillance program for candidaemia by the Centres for Disease Control and Prevention (CDC) in affiliation with academic medical intuitions, reported the incidence of candidaemia in Atlanta and San Francisco. A total of 837 incident cases of candidaemia were identified between January 1992 and December 1993.

[5] Throughout the literature review, Candidemia was represented by the following Boolean search terms: [(candidemia OR invasive candidiasis OR blood Candida OR fungaemia) AND epidemiology OR population-based OR incidence OR prevalence OR rates OR mortality)].

The average annual incidence (per 100,000 population) in Atlanta was 8.7 and in San Francisco was 7.1 during the study period.[31]

In a review paper by Pfaller, et al described earlier, estimates of candidaemia incidence from NHDS data were reported.

The incidences of candidaemia were reported to be 23 per 100,000 population in 1996 and 29 per 100,000 population in 2003 in the US general population. [1] Additionally, the MAH analysed the NHDS data using the same ICD-9 and estimated the incidence of candidaemia from 2004 through 2007.

The following table summarizes the incidence of candidaemia in the US from 1996 through 2007.

Year	Incidence of Candidaemia (per 100,000 population)
1996	23
1997	22
1998	22
1999	24
2000	23
2001	22
2002	23
2003	29
2004	22
2005	23
2006	24
2007	24

Estimates from 1996 through 2003 were reported by Pfaller et al and estimates for 2004 through 2007 were calculated by the MAH

In 2017, in a population-based surveillance study for candidemia conducted by CDC[32] encompassing 5% of the US population, 1,226 candidemia cases were identified with an estimated incidence of 7 cases per 100,000 persons. Incidence rates were higher in adults aged ≥ 65 years old (20.1/100,000), males (7.9/100,000), and those of black race (12.3/100,000).

SI.2.1. Incidence

Global

In a population-based surveillance in the Calgary Health Region of Canada, candidaemia incidence (per 100,000 population) of 2.9 during a 5-year period from 1 July 1999 and 30 June 2004 was estimated. Higher incidence observed in the latter 3 years of the study (3.7) compared to the first 2 years (1.6).[33]

Incidence of candidaemia in patient subpopulations: A higher incidence of candidaemia in patients with immunocompromised status compared to general population status has been reported.

Patients with SOT: *Candida* species are a common cause of invasive fungal infections in patients with SOT. In the TransNet data, described earlier, the incidence of candidaemia in patients with SOT was reported to be approximately 1.9% at 12 month follow up.[34] In a review paper based on the literature, Paya, et al. reported that 32% of patients with heart transplant, 60% to 100% with heart-lung transplant, 77% to 80% with lung transplant, and 60% with kidney transplant patients had candidaemia infection.[35]

Patients with HIV infection: While anti-retroviral therapy reduces the risk of acquiring an opportunistic infection, candidiasis is a common cause of invasive fungal infections among patients with HIV/AIDS.[36] In a retrospective study conducted over an 8-year period (1990–1997) in a large hospital in Rome, Italy, 39 (1.2%) patients were diagnosed among 3292 HIV-infected patients during the study period. The overall incidence of candidaemia was 1.1 episodes per 100 persons per year in the study period. The incidence decreased from 1.4 episodes in the 1990 to 1996 period to 0.8 in 1997.[37] In another population-based surveillance study in Barcelona, Spain 4% of patients with candidaemia had underlying HIV infection.[38] Similarly, in Northern Italy, 6% of patients infected with candidaemia had underlying HIV infection. [36]

In an analysis of medical records of 400 HIV-positive patients at 2 institutions in Argentina, between 1985 and 1995, 1.25% (5/400) patients developed candidaemia.[39]

Patients with haematologic malignancy or HSCT: Candidiasis is a common infection in patients with haematological malignancy or HSCT recipients. Below are a few studies reporting the incidence of candidaemia in patients with haematologic malignancies.

In a retrospective study, the authors reviewed the medical records including microbiologic data of adult patients with haematologic malignancy with candidaemia at the University of Texas M. D. Anderson Cancer Center from March 2001 to February 2007. Over the 7-year period, 173 episodes of candidaemia were identified in 170 patients with haematologic malignancy. The incidence (per 100,000 inpatient days) of candidaemia was reported to be 13.9 in 2001 and 23.2 in 2004. In the discussion section the author reported that these rates are higher than those reported from European surveys (2.6 to 7.3 per 100,000 inpatient days) and surveillance-based studies in the US.[40] In a population-based survey of public and private microbiology laboratories in Australia, a total of 1095 incident cases of candidaemia were identified; 288 (26%) episodes occurred in 288 adults with cancer. Among them, 138 had haematological malignancies. [40]

Patients with Diabetes: Patients with diabetes are susceptible to systemic infection caused by *Candida* species. In a study conducted in the US, the average incidence of candidaemia was 28 per 100,000 population among adults (> 18 years) with diabetes. [31]

The following table summarizes the incidence of candidaemia reported in the general population in the EU and US.

Region	Year/ Time period	Incidence (per 100,000)
Europe		
Finland	1995	1.7
Finland	1999	2.2
Norway	1991–2003	2.4
Iceland	1980-1984	1.4
Iceland	1995–1999	4.9
Spain	1997-1999	3.5
Switzerland	2014-2018	4.2
United States		
Iowa	1998-2001	6.0
San Francisco, CA	1992-1993	7.1
Atlanta, GA	1992-1993	8.7
Connecticut	1998-2000	7.1
Baltimore, MD	1998-2000	24.0
NHDS data (US overall)	2007	24.0
CDC	2013-2017	7.0

The following table summarizes the rates of candidaemia in patient subpopulations.

Patient population	Incidence(%)
Solid organ transplant Heart transplant, Heart-lung transplant, Lung transplant, Kidney transplant	1.9 32 60-100 77-80 80
HIV infection	1.2-6.0
Haematologic malignancy or HSCT	13.9 (year 2001)* 23.2 (year 2004*
Diabetes	0.028

* per 100,000 inpatient days

SI.2.2. Prevalence

No study was found reporting prevalence of candidaemia.

SI.2.3. Demographics of the population in the authorised indication, age, gender, racial and/or ethnic origin and risk factors for the disease

Age: In the majority of the population-based surveillance studies, the highest incidence of candidaemia occurs at the extremes of the age spectrum. For example, in a study in Spain, the age-specific incidence (per 100,000 population) was highest in infants (38.8) compared to those aged > 65 years (12.0).[41] In a study in Norway, the average annual incidences vary substantially between the various age groups. The incidence (candidaemia episodes per 100,000 population) was reported to be the highest in patients aged ≤ 1 year (10.3), and very low (from 0.5 to 1.3) in the age group between >1 and 39 years. Thereafter, there is a gradual increase with age from 1.7 in patients aged 40 to 49 years to 7.4 in patients aged 70 to 79 years and 8.4 in patients aged ≥ 80 years.

Similarly, in the CDC study in Atlanta and San Francisco, California described before, the incidence (per 100,000 population) was highest in children < 1 year and elderly aged ≥ 65 years compared to other age group. [31] In another study in Iowa, 67% of the cases with candidaemia were aged 50 or above.

Sex: The majority of studies reported higher candidaemia incidence (or proportion of cases among all candidaemia patients) among males than females.

In a study in Spain described earlier, the majority of cases of candidaemia were in males (65%).[26] In a nationwide study in Norway, of the 1381 candidaemia episodes with adequate patient information, 58% of the patients were in males and 42% were in females.

In the CDC study in Atlanta, Georgia and San Francisco, California US, the incidence per 100,000 was higher among males than females (9 vs. 6).[31] Similarly, in the study in Iowa, more males than females (59% vs. 41%) were reported. However, no significant difference in candidaemia rate between males and females was found in a study in Baltimore, Maryland and Connecticut.

Race: Estimates on the incidence of candidaemia by race are limited in the published literature. In the CDC study described above, overall incidence (per 100,000 population) was twice as high among Blacks as Whites (12 vs. 6) in all age groups, and 4 folds higher among Black infants (0 to 12 months) than among White infants (165 vs. 41).[31]

Diagnosis of candidaemia (in-patient vs. outpatient setting): The majority of patients with candidaemia reported in the reviewed studies were diagnosed in an inpatient setting.

In the study in Iowa, 56% of candidaemia cases in a general medicine ward, 40% in an ICU and only 4% were diagnosed in an outpatient setting. [31]

Risk Factors for the Disease

Potential health risk for Invasive Aspergillosis, Candidaemia in Non-Neutropenic Patients, Fluconazole-Resistant Serious Invasive Candida Infections (Including *C. krusei*), Serious Fungal Infections Caused by *Scedosporium* spp. and *Fusarium* spp.

SI.2.4. The main existing treatment options summarise the standard of care, with the view of the expected safety profile and outcome in the absence of treatment with the medicinal product

There are multiple treatment options for invasive candidiasis and candidaemia in non-neutropenic adult patients. Available therapies have been recently reviewed by a panel of European experts and published.[42]

The recommendations are graded by strength (from A- strongly supports a recommendation to use to D- supports a recommendation against use) and ranked according to level of scientific evidence (I- strongest to III- weakest).

Voriconazole has been granted a BI recommendation. Echinocandins (anidulafungin (Ecalta®, Pfizer), caspofungin (Cancidas®, Merck and Co.) and micafungin (Mycamine®, Astellas Pharma Europe) were recommended with AI level for initial targeted treatment of candidaemia and invasive candidiasis in adult patients. Other options for the treatment of invasive candidiasis and candidaemia in non-neutropenic adult patients include amphotericin B liposomal (BI), fluconazole (CI) and amphotericin B lipid complex (CII). Amphotericin B deoxycholate (alone or in combination with fluconazole or flucytosine) and efungumab plus lipid-associated amphotericin B, amphotericin B colloidal dispersion and itraconazole were granted a recommendation against use (DI for the 2 first and DII others). Posaconazole was ranked DIII because of lack of data reported by the authors of the guidelines.

SI.2.5. Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Discuss the possible stages of disease progression to be treated and applied to the natural history of the indication in the (untreated) population. This section should also describe concisely the relevant adverse events to be anticipated in the (untreated) targeted population in EU, their frequency and their characteristics.

A few studies reported the mortality rate in patients with candidaemia.

Europe

Three (3) studies were identified that reported the mortality rate of candidaemia in the EU. In a study in Barcelona Spain, 44% (150/341) patients died within 30 days; 74 (22%) died within 7 days of the diagnosis of candidaemia. In another study in Spain, the crude candidaemia mortality rate was 40.6%: 41.4% in adults and 32.5% in infants.[26] In a nationwide study in Spain, the crude mortality associated with candidaemia was 20.20%.

In the European Confederation of Medical Mycology (ECMM) survey, the crude mortality in patients with candidaemia was approximately 35%.[43]

United States

Using the multiple cause-of-death and the US general population estimate from the Bureau of Census, Pfaller, et al reported candidaemia mortality rates (per 100,000 population) of about 0.7 in 1991 and 0.4 in 1997 and 2003.[1]

In the CDC study in Atlanta and San Francisco described above, of 837 cases of candidaemia, 88.5% (741/837) patients had the outcome information. Of these 741 patients, 29% (240/837) died. [31] In another study in Baltimore and Connecticut (October 1998 to September 2000), 409 patients from a total of 1143 patients died within 30 days of the diagnosis of candidaemia, for an overall crude mortality rate of about 36%.

The MSG[6] study, a prospective observational study in 34 tertiary care medical centres in the US conducted from February 1995 through November 1997 among hospitalized patients (n = 1447), reported higher mortality among adults than children (47% vs. 29%).[44]

The following table summarizes the mortality rates in patients with candidaemia.

Region	Mortality (%)
Europe	
Spain	44
Spain	40.6
Spain	20.2
Italy	38
Finland	35
US	
Atlanta, Georgia	29
Baltimore, MD and Connecticut	36
US overall Adults Children	 47 29
US overall (TransNet)	66.4

Candidaemia mortality rate in patient subpopulations: Mortality rates of candidaemia vary by patients underlying conditions. The ECMM hospital based surveillance survey indicated the highest 30-day mortality rates of candidaemia occurred in patients with solid tumours (49.2%), haematological malignancy (44.5%) or in patients treated in ICUs (42.4%).[43] In the TransNet data in the US described earlier, the overall 1-year mortality among HSCT patients with candidaemia was 66.4%.[8]

In a 2-year prospective study of candidaemia in Sweden, the 30-day mortality rate was 39% in surgical patients and 32% in ICU patients.[45]

Similar rates were reported from the ECMM hospital-based surveillance survey; the 30-day mortality rate of candidaemia was 42.4% in ICU-treated patients and 35.3% in surgical patients. [43] A higher rate was reported from Spain where the 30-day mortality rate was 50% in adult ICU patients with candidaemia. [26]

The ECMM hospital-based surveillance survey indicated the 30-day mortality rate of candidaemia was 23.4% in patients with HIV infection. [43] In the Highly Active Antiretroviral Therapy study, the overall mortality rate in patients co-infected with candidaemia and HIV was 59%. In another retrospective chart review of all patients diagnosed with candidaemia among HIV infected patients in Saint Michael's Medical Center, New Jersey, US described before, 36% (4/11) patients co-infected with candidaemia and HIV died.[46]

[6] National Institute of Allergy and Infectious Diseases Mycosis Study Group

In a study in the US, on 87 patients with diabetes mellitus and candidaemia, the overall mortality was 39% (34/87); nosocomial candidaemia was an independent risk factor of mortality [OR = 10.2 (95% CI: 1.1, 97.9)].[47]

Factors associated with candidaemia mortality: Independent risk factors of death from candidaemia include older age (> 65 years), procedures associated with intensive care (e.g., central venous catheters, total parenteral nutrition), and severity of underlying illness.[48] Delays in initiation of treatment and inappropriate (or inadequate) treatment of fungal infections in patients with candidaemia also have a significant impact on mortality.[49]

SI.2.6. Important co-morbidities:

Generally, candidiasis is not a disease seen in normal healthy hosts; rather, there is a large number of reasonably well-characterized risk factors.

Some of the risk factors are other diseases or the degree of severity of the underlying illness, while others are induced by various therapies. Major predisposing factors (i.e., disease/conditions or risk factors) of candidaemia are listed below. [68] [69] [50]

Disease/conditions

- Haematological malignancy / HSCT
- HIV infection / AIDS
- SOT
- Diabetes mellitus
- Surgery

In the section below, the epidemiology of selected important candidaemia co-morbidities are presented.[7]

[7] Throughout the literature review, serious fungal infections caused by candidemia. was represented by the following Boolean search terms: [(candidemia OR invasive candidiasis OR blood Candida OR fungaemia) AND SOT OR lung transplant OR heart transplant OR liver transplant OR multiorgan transplant OR haematologic malignancy OR HSCT OR HIV OR human immunodeficiency virus OR AIDS OR acquired immune deficiency syndrome OR Diabetes OR DM OR surgery OR surgical procedure)]

Table 2. Co-morbidity in the Target Population – Patients with Candidaemia

Indication/target population
Haematologic malignancies or HSCT
The search identified two studies that reported the proportion of patients with haematologic malignancy among patients diagnosed with candidaemia. In a study in adult patients admitted to the ICUs in Dijon University Hospital in France between 1990 and 2000, of 51 patients identified with candidaemia, haematological malignancy was the underlying condition in 43.1% (22/51) of patients. [43] In another study in Virgen del Rocío University Hospital in Spain from January 2004 to June 2009, 35.39% (80/226) of the patients with candidaemia had active malignancy. **Mortality:** Section SI.2.5 summarizes studies that reported mortality estimates of candidaemia in patients haematologic malignancy or HSCT.
Surgery
The combination of surgical procedures along with a prolonged hospital stay and use of invasive devices place the patient at risk for invasive fungal infections including candidaemia. A few studies were identified that reported the rate of candidaemia in patients underwent surgical procedure(s). Below is a summary of studies that reported proportion of candidaemia patients that had surgeries. In a study in the Dijon University Hospital in France, described earlier, 51 ICU patients were identified with candidaemia. Of 51 patients, 60.8% (31/51) were considered as surgical patients and 39.2% (20/51) were considered as medical patients. [43] In a study in the US, medical records were examined for all surgical patients having cultures positive for *Candida* spp. between 1973 and 1980. Of the 159 patients identified, 29.5% (47/159) patients were in surgical wards.[51] Similarly, in a study in Virgen del Rocío University Hospital in Spain described earlier, 42.9% of the patients with candidaemia had a surgery. [53] **Mortality:** Refer to Section SI.2.5 **Co-prescribed medications:** Overall, surgical patients receive multiple medications: analgesics, and antibiotics. Treatment resistant pathogens are increasingly common requiring more aggressive medical therapy, which often results in combination anti-infective regimens.
SOT
The search identified one study that reported the proportion of patients with SOT among patients diagnosed with candidaemia: in the study in Virgen del Rocío University Hospital, Spain described earlier, 2.65% of the patients with candidaemia infection were in SOT recipients. **Mortality:** Refer to Section SI.2.5
HIV infection
The search did not identify any study that reported the proportion of patients with HIV infected among candidaemia patients. **Mortality:** Refer to Section SI.2.5
Diabetes
A higher rate of candidaemia in patients with diabetes has been reported compared to the general population. In a retrospective review of invasive fungal infections among university hospitals in France, 8% of patients with candidiasis had underlying diabetes mellitus.[52] **Mortality:** Refer to Section SI.2.5 **Co-prescribed medications:** Patients with diabetes use many medications, both to treat hyperglycaemia and for the prevention and treatment of diseases (as a consequence of diabetes) like cardiovascular and kidney disease. Most commonly, persons with diabetes take oral antihyperglycemics, insulin, HMG CoA-reductase inhibitors (statins), antiplatelet agents (e.g., aspirin), and antihypertensives, especially angiotensin converting enzyme inhibitors and angiotensin receptor blockers.

SI.3. Fluconazole-Resistant Serious Invasive *Candida* Infections (Including *C. krusei*)

Fluconazole is an important antifungal compound in the treatment of candidiasis. With increasing use of broad spectrum antibacterial in recent decades, there has been an increase in rates of resistance to azoles antibiotics including fluconazole.

Important risk factors for fluconazole resistant *Candida* spp. include prior treatment with azole (particularly fluconazole), recent gastrointestinal tract surgery and neutropenia.[53]

Below is the epidemiology of fluconazole-resistant *Candida* infections. Search terms to identify relevant papers are mentioned below.[8]

Indication/target population

No study was found that reported the population-based incidence of fluconazole resistant candidiasis in the EU and US general population. A few studies reported the proportion of patients infected with decreased fluconazole susceptibility and/or fluconazole resistant *Candida* spp. in all patients with candidiasis in the EU and US.

SI.3.1. Incidence

Europe

Two studies were identified reporting the proportion of patients with fluconazole resistance in all patients with candidiasis in the EU.

A study conducted in Virgen del Rocío University Hospital, a large urban hospital with teaching accreditation in Spain from January 2004 to June 2009, reported the proportion of patients with fluconazole resistance *Candida* infection. During the study period, 229 episodes of candidaemia were identified. Of 226 episodes of candidaemia, 13.27% (30/266) isolates showed fluconazole resistance. The species isolated from the fluconazole resistance *Candida* spp. were *C. glabrata* (n = 14), *C. krusei* (n = 14), and *C. tropicalis* (n = 2).[53] In a nationwide study in Spain described before, overall, decreased susceptibility to fluconazole was reported in 7.01% isolates of candidaemia.

In a surveillance program for fungaemia in Denmark, fungal isolates were tested for antimicrobial susceptibility during 2004 and 2006. About 32% of the isolates tested showed decreased susceptibility to fluconazole and/or itraconazole (defined as a minimum inhibitory concentration (MIC) of > 8 mg⁄L and > 0.125 mg⁄L, respectively). Separate estimate for fluconazole resistant isolates was not reported.[54]

[8] Throughout the literature review, fluconazole-resistant serious invasive Candida infections (including C. krusei) was represented by the following Boolean search terms: [(resistant candidemia OR fluconazole-resistant fungaemia OR fluconazole-resistant fungal infection) AND epidemiology OR population-based OR incidence OR prevalence OR rates OR mortality)]

United States

In the SENTRY Antimicrobial Resistance Surveillance Program, which was designed to monitor the predominant pathogens and antimicrobial resistance for both nosocomial and community-acquired infections worldwide in 1997, in vitro susceptibility testing of 203 isolates of *Candida* spp. against fluconazole from the US showed that 2.5 % were resistant to fluconazole at the published National Committee for Clinical Laboratory Standards MIC interpretive breakpoint concentrations (i.e., MIC ≥ 64 mg/mL).[55]

A higher rate of fluconazole resistant Candida spp. has been reported in patients with haematologic malignancy. Of the 168 Candida isolates tested in a retrospective study among haematologic malignancy patients with candidaemia at The University of Texas MD. Anderson Cancer Center from March 2001 to February 2007, 48 (29%) were resistant or susceptible-dose–dependent in vitro to fluconazole.[56]

Global

Among 13,338 bloodstream infections (BSI) attributable to *Candida* spp. (12 species from > 200 institutions worldwide) tested at the University of Iowa between 1992 and 2004, < 3% showed resistance to fluconazole (MIC > 64 g/mL) in all *Candida* spp., with the exception of *C. glabrata* (9%) and *C. krusei* (40%).[1]

The longitudinal nature of the ARTEMIS DISK Surveillance Program in 127 medical centres in 39 countries also provides trends over a 6.5-year period (from 1997 through 2003) in fluconazole resistance among clinical isolates of *Candida* spp. (e.g., blood, sterile sites, etc.) all tested by a single standardized agar disk diffusion method. Among the 10 *Candida* spp., the fluconazole resistance across various centres ranged among isolates of *C. albicans* (0.8% to 1.5%), *C. tropicalis* (3.0% to 6.6%), *C. parapsilosis* (2.0% to 4.2%), *C. lusitaniae* (1.6% to 6.6%), and *C. kefyr* (0.0% to 5.7%).

Additionally, elevated rates of resistance were observed among isolates of *C. glabrata* (14.3% to 22.8%), *C. guilliermondii* (6.3% to 26.1%), *C. rugosa* (14.3% to 66.0%), and *C. famata* (9.8% to 47.4%) during the study period. [1]

In the SENTRY Program described above, 1.6% BSI *Candida* isolates tested in Canada and 2.4% in South America, showed resistance to fluconazole at MIC ≥ 64 mg/ml. [55]

In another population-based surveillance program of candidiasis in Calgary Health Region, Canada about 30% (56/184) of isolates demonstrated reduced susceptibility to fluconazole. Of them, 43 were susceptible dose-dependent and 13 were resistant. [33]

The following table summarizes the proportion of patients with fluconazole resistant *Candida* infection.

Region	Proportion of patients with fluconazole resistant *Candida* infection (%)
EU	
Spain	13.27
Denmark	32
US	2.5-2.9
Canada	7.1

SI.3.2. Prevalence

No study was found reporting the prevalence of fluconazole resistant candidiasis.

SI.3.3. Demographics of the population in the authorised indication, age, gender, racial and/or ethnic origin and risk factors for the disease

Age: Fluconazole resistant candidiasis is reported to be higher in adult patients compared to children. In a study conducted in Virgen del Rocío University Hospital in Spain from January 2004 to June 2009 described earlier, median age of patients with fluconazole resistant *Candida* spp. was 58 years. [53]

Sex: A higher proportion of male patients than females with fluconazole resistant *Candida* infection have been reported. In a study in Spain described above, 60% of patients with fluconazole resistant *Candida* infection were males. [53]

Race: A higher rate of fluconazole resistant *Candida* infection in Blacks has been found in one study. In an active laboratory-based surveillance study conducted from October 1998 through September 2000 in 2 areas of the US (Baltimore, MD., and Connecticut; combined population, 4.7 million), Black race was identified a risk factor for fluconazole resistant *Candida* spp. in the univariate analysis. Of 35 patients with fluconazole resistant *Candida* infection, 60% (21/35) were black.

SI.3.4. The main existing treatment options

Refer to the main existing treatment options for Candidaemia in Non-Neutropenic Patients

SI.3.5. Natural history of the indicated condition in the <untreated> population, including mortality and morbidity:

A high mortality rate in patients with fluconazole resistant candidiasis has been observed in studies. In a nationwide candidaemia study in Australia, of the 39 patients with a fluconazole-resistant isolate, 19 were initially treated with fluconazole and 6 (32%) died by day 30. Additional 15 patients received other antifungal agents (9 amphotericin B-based products, 3 caspofungin, 2 itraconazole, and 1 voriconazole) and 8/15 (53%) died by day 30.[40]

SI.3.6. Important co-morbidities:

Co-morbid conditions associated with fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*) are similar to those in patient with *Candida* infection.

- Haematologic malignancies/HSCT

- SOT
- Surgery
- HIV infection

Below is the epidemiology of co-morbid conditions of fluconazole-resistant *Candida* spp.[9]

Table 3. Co-morbidity in the Target Population – Patients with Fluconazole-Resistant Serious Invasive *Candida* Infections

Indication/target population
Haematologic malignancies or HSCT
The search identified one study that reported the proportion of patients with active malignancy or HSCT among patients with fluconazole resistant *Candida* infection. In a study in Virgen del Rocío University Hospital Spain, described before, 30% (9/30) of the patients with fluconazole resistant *Candida* infection had active malignancy and about 10% (3/9) of them had received bone marrow transplantation. [53] **Mortality:** Refer to Section SI.3.5
SOT
In the same study described above, 6.7% (2/30) of the patients with fluconazole resistant *Candida* infection were SOT recipients. [53]
HIV infection
In the same study described above, 10% (3/30) of the patients with fluconazole resistant *Candida* infection were infected in patients with HIV. [53]
Surgery
In the same study described above, 36.7% (11/30) of the patients with fluconazole resistant *Candida* infection had surgery. [53]

SI.4. Serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp

Scedosporium spp. and *Fusarium* spp. are rare fungal infections in humans. Below are studies reporting rates of *Scedosporium* spp. and *Fusarium* spp. Search terms used to identify relevant papers are mentioned below.[10]

SI.4.1. Incidence

Scedosporium spp

The majority of the published literature on *Scedosporium* spp. consists of single case reports and small case series. No study was identified reporting incidence of *Scedosporium* in the general population in the EU and US. Additionally, the analysis of US NHDS data by the

[9] Throughout the literature review, serious fungal infections caused by fluconazole-resistant serious invasive Candida infections was represented by the following Boolean search terms: [(candidaemia OR invasive candidiasis OR blood Candida OR fungaemia) AND SOT OR lung transplant OR heart transplant OR liver transplant OR multiorgan transplant OR haematologic malignancy OR HSCT OR HIV OR human immunodeficiency virus OR AIDS OR acquired immune deficiency syndrome OR surgery OR surgical procedure)].

[10] Throughout the literature review, Serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. was represented by the following Boolean search terms: [(Scedosporium spp. OR Scedosporium apiospermum OR monosporium apiospermum OR Fusarium spp) AND epidemiology OR rates OR population-based)]

MAH described earlier revealed only one case of *Scedosporium* reported between 2004 and 2007.

Global
In a survey including 49 laboratories across Australia, 180 cases with 118 (65.6%) cases of colonization and 62 (34.4%) cases of invasive infection with *Scedosporium* spp. in a 3-year (2003 to 2005) time period were identified.[57]

***Scedosporium* infection in patient subpopulations:** A few papers were found that reported proportion of patients infected with *Scedosporium* spp. in all fungal isolates in patient sub-populations.

***Scedosporium* infection in patients with haematological malignancy or HSCT**: In a retrospectively review of all new cases of mould infections in patients with acute leukaemia, a total of 8,633 patients with a newly diagnosed acute leukaemia (6,303 myeloid and 2,330 lymphoid) were identified in Italy between 1998 and 2003 (expect 1998).[58] In 542 patients with proven or probable mould infections, only 0.9% (5/542 or approximately 900 per 100,000) cases of proven scedosporiosis were diagnosed.

In a study conducted at the MD. Anderson Cancer Center, Houston, Texas, incidence (per 100,000 patient-inpatient days) of *Scedosporium* infection of 0.82 from 1993 to 1998, and of 1.33 from 1999 to 2005 among patients with cancer was reported.[59]

In another study from the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, Washington, 9 HSCT recipients developed invasive fungal infection due to the *Scedosporium* spp. over 15 years from 1985 to 1999.[60]

Scedosporium infection in patients with SOT: In a retrospective review of the literature in SOT recipients between 1976 and 1999 in Pittsburgh, PA, Castiglioni, et al reported 23 cases of *S. apiospermum* infections with an overall incidence of 100 cases per 100,000 patients. The median time to diagnosis of infection was 4 months (range, 0.4 to 156 months) following transplant.[61]

In another review of lung and heart-lung transplant patients between 1986 and 1999 in Australia, 7 of 330 (2.3%) had pulmonary scedosporiosis. [60]

The following table summarizes the rate of *Scedosporium* infection in patient subpopulations.

Patient Population	Rate (per 100,000)
Haematological malignancy	91
Acute leukaemia	900
SOT	100

Serious fungal infections caused by *Fusarium* spp.

The majority of the published literature on *Fusarium* spp. consists of case reports, small case series and reports in patient subpopulations. The search did not identify any paper reporting the incidence of *Fusarium* infection in the general population of EU.

The analysis of US NHDS by the MAH showed that the incidence (per 100,000 population) of *Fusarium* was 0.03 in 2004 and 0.09 in 2007.

The following table summarizes the incidence of *Fusarium* infection in the US (NHDS data).

Year	Incidence of *Fusarium* (per 100,000 population)
2004	0.03
2005	0.08
2006	0.05
2007	0.09

***Fusarium* infection in patient subpopulations**: Immunocompromised patients are at high risk for *Fusarium* spp. particularly those with prolonged neutropenia and/or severe T-cell immunodeficiency. A few papers were found that reported proportion of patients infected with *Fusarium* spp. in patient subpopulations.

Fusarium infection in patients with haematological malignancy or HSCT: fusariosis has been considered an emerging infection in patients with haematological malignancies. In a multicentre retrospective study on fungal infections from 14 haematology departments over a period of 10 years (from 1988 to 1997) in Italy, the incidence of *Fusarium* infections in patients with haematological malignancy was 0.06% (60 cases per 100,000).[62] In a study in HSCT recipients from 9 hospitals (2 in the US and 7 in Brazil), the overall incidence (per 100,000 population) of fusariosis was reported to be ~ 597 patients; the incidence was lowest (~ 150 to 200) in autologous recipients, intermediate (~ 250 to 500) in matched related and matched unrelated allogeneic recipients, and highest (2000) among recipients of mismatched related donor allogeneic HSCTs.

In a review of medical records of patients at MD. Anderson Cancer Center, at the University of Texas, 43 patients with positive cultures for *Fusarium* spp. between January 1986 and December 1995 were identified. All patients were immunocompromised.[63]

In another study at the same institute, Campo and colleagues reviewed records (1998 to 2009) of patients with haematologic malignancy and found that 44 patients were infected with *Fusarium* spp. Of the 44 patients, 37/44 (84%) had acute leukaemia/myelodysplastic syndrome, with the remaining 7/44 (16%) of patients with lymphoma or chronic leukaemia as their underlying disease.[64]

***Fusarium* infection in patients with SOT:** No study was identified reporting the rates of *Fusarium* infection in patients with SOT. The majority of the literature on *Fusarium* infection in humans consists of single case reports.

The following table summarizes the incidence of *Fusarium* infection in patient subpopulations.

Patient population	Incidence of *Fusarium* (per 100,000 population)
Autologous HSCT recipients	150 to 200
Matched related and matched unrelated allogeneic HSCT recipients	250 to 500
Mismatched related donor allogeneic HSCTs	2000
Autologous HSCT recipients	150 to 200

SI.4.2. Prevalence

No study reporting prevalence of *Scedosporium* spp. was identified.

No study was found reporting prevalence of *Fusarium* in the general population or patient subpopulations.

SI.4.3. Demographics of the population in the authorised indication, age, gender, racial and/or ethnic origin and risk factors for the disease

Serious fungal infections caused by *Scedosporium* spp.

Age: In the study described earlier, Caira and colleagues performed a literature search and summarized demographic characteristics of 52 cases of patients infected with *Scedosporium* spp. from 29 reports in patients with acute leukaemia over the last 30 years. Mean age of the patients was 47 years (range 3 to 79 years).

In a literature review of 162 cases of *Scedosporium*, the median age of patients was 45 years (ranging from a few months to 81 years).[65]

Sex: Much higher rates of *Scedosporium* infection among males than females have been reported.

In the study by Caira and colleagues described above, male/female ratio was 1.9:1.[13]

In a literature review of 162 cases of *Scedosporium* described above, 102 (63%) infections were diagnosed in males.

Serious fungal infections caused by *Fusarium* spp.

Age: In a study in Israel, the mean age of the patients with *Fusarium* was 57 years (range 0 to 92 years.[66] In a study in HSCT recipients from US and Brazil, the median age of patients infected with *Fusarium* was 34 years (range 2 to 67 years).[67]

Sex: In a study in HSCT recipients from 9 hospitals (2 in the US and 7 in Brazil) described above, 55.7% (34/61) of patients infected with *Fusarium* were males and 44.24% (27/61) were females.[68]

Similarly, in a study conducted in a large tertiary care hospital in Israel described above, a total of 89 patients were identified with *Fusarium* infection. About 52% (47/89) of patients were male patients.[69]

SI.4.4. The main existing treatment options summarise the standard of care, with the view of the expected safety profile and outcome in the absence of treatment with the medicinal product

The antifungal armamentarium for the treatment of fusariosis is more restricted and the data more scarse, as no randomized study has been conducted.[70] Voriconazole is considered as the drug of choice and alternatives consist of amphotericin B (deoxycholate and lipid formulations) and posaconazole.

The treatment of scedosporiosis is very difficult due to the resistance of the *Scedosporium* spp. to many antifungal agents. Besides voriconazole, there are reports of successful treatment with combinations including terbinafine and another antifungal agents.[71]

SI.4.5. Natural history of the indicated condition in the untreated population, including mortality and morbidity:

A high mortality rate in patients infected with *Scedosporium* spp. has been observed in studies.

In a study at the University of Texas MD. Anderson Cancer Center, Houston, TX, the 12-week mortality rates were 70% and 100% for *S. apiospermum* and *S. prolificans* infection, respectively. [59]

In a study from the FHCRC in Seattle, WA, described before, all 9 HSCT recipient patients died within 1 month following the diagnosis of *Scedosporium* infection. In another study, the mortality rate in patients infected with *Scedosporium* among SOTs was 54% (31/57): 77.8% for patients with *S. prolificans* infection, and 54.5% for patients with *S. apiospermum* infections.[72]

In a literature review of 162 cases of *Scedosporium*, the overall mortality was 46.9%; the mortality rate was 87.5% in patients with disseminated disease.

Serious fungal infections caused by *Fusarium* spp.

In a retrospective review of medical charts by Campo, et al, the crude mortality rate in patients with fusariosis at 12 weeks was 66%.[64] In the TransNet data in the US described earlier, the overall 1-year mortality among HSCT patients with *Fusarium* infections was 93.7%.[8] In another retrospective cohort study conducted between January 1999 and December 2003 in Italy, the attributable mortality rates associated with fusariosis was 53%.[6]

SI.4.6. Important co-morbidities:

Co-morbidities in patients infected with *Scedosporium* spp.: Following are the important co-morbid conditions reported in patients with *Scedosporium* spp. [11]

- Haematologic malignancies or HSCT
- SOT
- Surgery

Table 4. Co-morbidity in the Target Population – Patients with Serious Fungal Infections Caused by *Scedosporium* spp.

Indication/target population
Haematologic malignancies or HSCT
The search identified two studies that reported the proportion of patients with malignancy or HSCT among patients with *Scedosporium* spp. infection. In a literature review of 162 cases of patients infected with *Scedosporium*, 45.7% (74/162) had malignancy. In a study conducted at the MD. Anderson Cancer Center, Houston, Texas, described earlier, all 25 patients that met criteria for probable or definite *Scedosporium* infection had a diagnosis of haematologic malignancy, and 12 were BMT recipients. [59]
SOT
The search identified one study that reported the proportion of patients with SOT among patients with *Scedosporium* spp. infection. Hussain, et al identified a total of 80 transplant recipients with *Scedosporium* infections (13 from University of Pittsburgh Medical Center, PA, University of Maryland, Baltimore, Duke University Medical Center, Durham, NC, Emory University, Atlanta, GA, and Hospital Gregorio Maran˜o´n, Madrid, Spain and 67 reported in the literature). Of 80 transplant recipients with *Scedosporium* infections, 71.25% (57/80) were in SOTs.
Mortality: Refer to Section SI.4.5 **Co-prescribed medications:** Alemtuzumab is being increasingly used for the prevention and/or treatment of acute allograft rejection in organ transplant recipients.[73] In a study in SOT described earlier, 50% of the patients had received cyclosporine A, 36% had received tacrolimus. [72]

Co-morbidities in patients infected with *Fusarium* spp.: Following are the important co morbid conditions reported in patients with *Fusarium* spp.[12]

- Hematologic malignancies/HSCT

[11] Throughout the literature review, serious fungal infections caused by *Scedosporium* spp. was represented by the following Boolean search terms: : [(Scedosporium OR scedosporiosis) AND SOT OR lung transplant OR heart transplant OR liver transplant OR multiorgan transplant OR haematologic malignancy OR HSCT OR HIV OR human immunodeficiency virus OR AIDS OR acquired immune deficiency syndrome OR surgery OR surgical procedure)]

[12] Throughout the literature review, serious fungal infections caused by Fusarium spp. was represented by the following Boolean search terms: [(Fusarium OR furosis OR fungaemia) AND SOT OR lung transplant OR heart transplant OR liver transplant OR multiorgan transplant OR haematologic malignancy OR HSCT OR HIV OR human immunodeficiency virus OR AIDS OR acquired immune deficiency syndrome OR surgery OR surgical procedure)]

- SOT
- Surgery

Table 5. Co-morbidity in the Target Population – Patients with Serious Fungal Infections Caused by *Fusarium* spp.

Indication/target population
Hematologic malignancies or HSCT
The search did not identify any study that reported the proportion of patients with haematologic malignancy or HSCT among patients with *Fusarium* spp. **Mortality:** Refer to Section SI.4.5
SOT
The search did not identify any study that reported the proportion of patients with SOT among patients infected with *Fusarium* spp. **Mortality:** Refer to Section SI.4.5
Surgery
The search did not identify any study that reported the proportion of patients had surgery among patients infected with *Fusarium* spp. **Mortality:** Refer to Section SI.4.5

Module SII. Non-Clinical Part of the Safety Specification

Table 6. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Reproductive Toxicity: Studies in animals have shown reproductive toxicity at high doses of voriconazole.	No adequate information on the use of voriconazole in pregnant women is available. The potential risk to humans is unknown. Effects in pregnancy is a missing information (see 0); SmPC provides information to the prescriber in Section 4.6 Pregnancy and lactation and Section 5.3 Preclinical safety data.
Developmental toxicity: In reproduction studies, voriconazole was shown to be teratogenic in rats and embryotoxic in rabbits at systemic exposures equal to those obtained in humans with therapeutic doses. In the pre and postnatal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labor and produced dystocia with consequent maternal mortality and reduced perinatal survival of pups. The effects on parturition are probably mediated by species-specific mechanisms, involving reduction of oestradiol levels, and are consistent with those observed with other azole antifungal agents	Voriconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential must always use effective contraception during treatment. Effects in pregnancy is a missing information (see 0.)
Hepatotoxicity: Functional and adaptive changes to the liver were seen in repeat dose rodent and non-rodent studies with voriconazole.	Hepatotoxicity occurred at exposure levels several times higher than those observed in human patients at the standard maintenance dose of 200 mg oral bid (AUC (0-12) 13.7 µg•h/mL; protocol # A1501092). In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with voriconazole which were noted in patients with serious underlying medical conditions (predominantly haematological malignancy). Hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been revisable upon discontinuation of therapy. Hepatic toxicity is an important identified risk (see Module SVII).
Cardiovascular Changes in QTc interval and heart rate have been observed in dogs following voriconazole administration. Arrhythmias have occurred in the presence of high plasma voriconazole concentrations. All cardiovascular effects of voriconazole were reversible.	A clinical study to assess the cardiovascular risk of voriconazole in humans has been conducted at high oral voriconazole doses (up to 1600 mg). Arrhythmias have not been observed in humans at rates greater than those seen in clinical studies with other approved antifungals, consistent with results from nonclinical studies that suggest a safety margin for this effect exists. QTc prolongation is an important identified risk (see Module SVII).

Table 6. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Visual Effects In anaesthetised dogs voriconazole had a distinct effect on ERG (dose-related reductions in the amplitude and implicit time of the a-wave and reductions in the amplitude and slope of the b-wave) at plasma concentrations of 4.5, 9.5, and 16 µg/ml. These results confirm the retina as the site of action of voriconazole and are consistent with effects observed in humans	A transient visual disturbance may occur shortly after administration of voriconazole. The mechanism is unknown, but functional effects occur at the level of retina and involve reversible decreases in the amplitude of the ERG waveform and colour discrimination. The symptoms usually diminish on repeated dosing and may be of clinical significance in ambulatory patients, who should be advised not to drive or operate machinery while affected. There is no long-term structural effect to the eye in long term animal toxicology studies and the visual disturbance results in few discontinuations in clinical studies. Overall, the visual effects are not considered to represent an issue for long-term use of voriconazole. Visual events is an important identified risk (see Module SVII).
Phototoxicity: voriconazole N-oxide, the major circulating metabolite in humans and preclinical species was shown to absorb UV light at 310 nm indicting the potential to be a mediator of phototoxicity if it were to reach sites exposed to sunlight. An in vitro 3T3 neutral red uptake assay to determine the phototoxic potential of voriconazole and its N-oxide metabolite has been completed. Neither cytotoxicity nor phototoxicity was observed for either voriconazole or voriconazole N-oxide indicating a lack of phototoxicity potential when tested to the limits of solubility or the maximum recommended concentration of 1000 mg/L.	Although phototoxicity has been observed in humans, in the non-clinical 3T3 neutral red uptake assay neither voriconazole nor N-oxide voriconazole were shown to be phototoxic. Phototoxicity is an important identified risk (see Module SVII).

Module SIII. Clinical Trial Exposure

Populations for Analysis of Clinical Trial Data in this RMP

The clinical trial exposure data were obtained from 42 phase 1, 2, and 3 voriconazole studies conducted by Pfizer clinical research. These 42 studies were grouped into seven main categories on the basis of study design. The studies included in each of the seven categories are summarized in Table 7.

Table 7. Summary of Clinical Studies Pooled for Analysis

Study Category	Study Numbers
Therapeutic Use* (Adults)[a]	A1500303, A1500304, A1500305, A1500307, A1500309, A1500602, A1500603, A1500604, A1500608
Therapeutic Use (Paediatrics)	A1501080, A1501085, A150303, A150304, A150305, A150307, A150309, A150602, A150603, A150604, A150608
Prophylaxis use (Adults)	A1501073[b] A1501038
Prophylaxis Use (Paediatrics) including paediatrics clinical pharmacology studies)	A1500249, A1501007, A1505037, A1501073[c], A1501081, A1501088, A1501096
Compassionate Use (Adults and Paediatrics)	A1500301, 1500303A[c], 1500304A[c], A1500311, A1500312, A1500606, A1500607
Clinical Pharmacology (Adults)	A1501005, A1501092, A1500205, A1500209, A1500210, A1500214, A1500222, A1500224, A1500230, A1500232, A1500245, A1500248, A1500250, 95CK39-0673, A1501001
Other	A1500302[d]

a. During the initial clinical development of voriconazole, 52 adolescents were included in the adult therapeutic studies.
b. Study A1501073, an adult prophylaxis study, included 9 paediatric patients.
c. The extension studies 303A and 304A enrolled subjects who had previously participated in studies 303 and 304, respectively, as well as "new compassionate use patients" who had not previously participated in those studies. Only the "new compassionate use patients" are included in the Compassionate Use group of studies. Those previously enrolled in Studies 150-303 and 150-304 are, as indicated above, included in the Therapeutic studies group.
d. Study 150-302 was a dose-ranging study in HIV-infected patients with oropharyngeal candidiasis.
Source: Tables 1.1-1.4.

Exposure data in voriconazole clinical studies are summarized below for the 1,603 adult subjects and the 105 paediatric subjects who received voriconazole for the therapeutic studies, the 270 adult subjects and the 183 paediatric subjects who received voriconazole for the prophylactic studies, and for all the 3,749 subjects who received voriconazole in any of the 42 phase 1, 2, and 3 voriconazole studies (extension studies 303A and 304A are considered part of studies 303 and 304 and have not been added to this total). These 42 studies are included in the "All Studies" category in Tables 8 through 11 below.

Of note, voriconazole was also being utilized in another Pfizer clinical development program (anidulafungin: A885) where 226 subjects were exposed to voriconazole with placebo and 400 subjects received voriconazole in association with the following drugs: anidulafungin (378), anidulafungin/placebo (20), caspofungin/placebo (2).

As of 31 May 2023, cumulatively, it is estimated that 6017 subjects have participated in the voriconazole clinical development program where 4034 subjects were exposed to voriconazole alone.

Table 8. Duration of Exposure

Therapeutic Use (Adults)		
Duration of Exposure [a, b]	**Persons**	**Person Time (days)**
Cumulative up to 1 month	1,079	12,916
Cumulative up to 3 months	1,313	27,208
Cumulative up to 6 months	1,582	60,282
Cumulative up to 12 months [c]	1,603	65,229
Therapeutic Use (Paediatrics)		
Duration of Exposure [a, b]	**Persons**	**Person Time (days)**
Cumulative up to 1 month	54	686
Cumulative up to 3 months	90	2,904
Cumulative up to 6 months	105	4,724
Cumulative up to 12 months [c]	105	4,724
Prophylactic Use (Adults)		
Duration of Exposure [a, b]	**Persons**	**Person Time (days)**
Cumulative up to 1 month	70	1,118
Cumulative up to 3 months	124	4,027
Cumulative up to 6 months	240	17,487
Cumulative up to 12 months [c]	270	23,369
Prophylactic Use (Paediatrics)		
Duration of Exposure [a, b]	**Persons**	**Person Time (days)**
Cumulative up to 1 month	151	2,476
Cumulative up to 3 months	178	3,537
Cumulative up to 6 months	182	4,098
Cumulative up to 12 months [c]	183	4,281
All Studies		
Duration of Exposure [a, b]	**Persons**	**Person Time (days)**
Cumulative up to 1 month	2,210	27,396
Cumulative up to 3 months	2,827	63,954
Cumulative up to 6 months	3,411	136,182
Cumulative up to 12 months	3,641	193,366
Cumulative to > 12 months	3,749	256,452 [d]

a. One month is considered to be thirty (30) days, for 12 months up to 364 days has been used.
b. "Cumulative" means from time 0 to the time described.
c. No patients in these studies received treatment for >12 months.
d. This number represents total person time (days).
Source: Table 1.2 N

Table 9. Duration of Exposure (By Formulation)

Therapeutic Use (Adults)		
Formulation	**Persons**	**Person Time (days)**
IV Voriconazole (Commercial)	1,084	13,696
IV Voriconazole (304 Formulation)[a]	133	1,379
Oral Voriconazole (304 Formulation)[b]	101	8,003
Oral Voriconazole (Commercial)	869	42,120
Missing information	3	96
Therapeutic Use (Paediatrics)		
Formulation	**Persons**	**Person Time (days)**
IV Voriconazole (Commercial)	94	1,439
IV Voriconazole (304 Formulation)[a]	3	26
Oral Voriconazole (304 Formulation)[b]	3	93
Oral Voriconazole (Commercial)	67	3,216
Missing Information	1	29
Prophylactic Use (Adults)		
Formulation	**Persons**	**Person Time (days)**
IV Voriconazole (Commercial)	250	1,969
Oral Voriconazole (Commercial)	254	21,400
Prophylactic Use (Paediatrics)		
Formulation	**Persons**	**Person Time (days)**
IV Voriconazole (Commercial)	183	2,896
Oral Voriconazole (Commercial)	126	1,728
All Studies		
Formulation	**Persons**	**Person Time (days)**
IV Voriconazole (Commercial)	2,511	46,182
IV Voriconazole (304 Formulation)[a]	136	1,405
Oral Voriconazole (304 Formulation)[a]	104	8,096
Oral Voriconazole (Commercial)	2,556	200,833
Not available	9	423

a. Dosing with voriconazole was to commence by the intravenous route every 12 hours. The first 2 doses, on Day 1, were to be 6 mg/kg body weight and subsequent doses, from Day 2 onward, were 3 mg/kg body weight twice daily. Intravenous dosing could continue for a maximum of 28 days.
b. After between 7 and 28 days of intravenous dosing, it was recommended that subjects switch to oral administration at a dose of 200 mg twice daily.
Source: Table 1.2.1N

Table 10. By Age Group and Gender

Therapeutic Use (Adults)				
	Persons		**Person Time (days)**	
Age Group	**Male**	**Female**	**Male**	**Female**
≥18 to ≤65 years	860	529	3,6843	20,640
>65 to ≤75 years	108	49	4,345	2,141
>75 years	32	25	646	614
Total	**1,000**	**603**	**41,834**	**23,395**
Therapeutic Use (Paediatrics)				
	Persons		**Person Time (days)**	
Age Group	**Male**	**Female**	**Male**	**Female**
< 18 years	54	51	2,772	1,952
Prophylactic Use (Adults)				
	Persons		**Person Time (days)**	
Age Group	**Male**	**Female**	**Male**	**Female**
≥18 to ≤65 years	148	105	13,343	9,443
>65 to ≤75 years	12	5	542	41
>75 years	--	--	--	--
Total	**160**	**110**	**13,885**	**9,484**
Prophylactic Use (Paediatrics)				
	Persons		**Person Time (days)**	
Age Group	**Male**	**Female**	**Male**	**Female**
< 18 years	106	77	2,615	1,666
All Studies				
	Persons		**Person Time (days)**	
Age Group	**Male**	**Female**	**Male**	**Female**
<18 years	362	247	41,845	20,223
≥18 to ≤65 years	1,880	892	112,694	62,685
>65 to ≤75 years	185	91	11,152	5,034
>75 years	54	38	1,670	1,149
Total	**2,481**	**1,268**	**167,361**	**89,091**

Source: Table 1.2.2N

Table 11. By Ethnic or Racial Origin

Therapeutic Use (Adults)		
Ethnic/Racial Origin	**Persons**	**Person Time (days)**
Asian	111	2,519
Black	161	4,452
Other	70	2,538
White	1,261	55,720
Total	**1,603**	**65,229**
Therapeutic Use (Paediatrics)		
Ethnic/Racial Origin	**Person**	**Person Time (days)**
Asian	30	1,487
Black	5	248
Other	13	347
White	57	2,642
Total	**105**	**4,724**
Prophylactic Use (Adults)		
Ethnic/Racial Origin	**Persons**	**Person Time (days)**
Asian	2	84
Black	-	-
Other	13	1,536
White	210	18,211
Missing	45	3,538
Total	**270**	**23,369**
Prophylactic Use (Paediatrics)		
Ethnic/Racial Origin	**Person**	**Person Time (days)**
Asian	27	422
Black	19	449
Other	23	742
White	114	2,668
Total	**183**	**4,281**
All Studies		
Ethnic/Racial Origin	**Persons**	**Person Time (days)**
Asian	307	13,554
Black	263	18,045
Other	187	13,731
White	2,947	207,584
Not available	45	3,538
Total	**3,749**	**256,452**

Source: Table 1.2.3N

Module SIV. Populations Not Studied in Clinical Trials

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

Table 12. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for exclusion	Missing information (Yes/No)	Rationale (if not included as missing information)
Pregnant or lactating females	To minimise the potential risk of reproductive toxicity.	Yes	
Subjects with the following abnormalities of liver function tests (LFTs): • Aspartate transaminase (AST), • Alanine transaminase (ALT) > 5 x upper limit of normal (ULN), • Alkaline phosphatase (ALP), or total bilirubin > 5 x ULN	To minimise the potential risk of hepatic events or worsening hepatic function.	No	Clinical studies have shown that there was greater than 3-fold increase in voriconazole total exposure in subjects with mild or moderate hepatic impairment (Child Pugh class A or B) compared to healthy subjects receiving the same single oral dose. In addition, subjects with moderate hepatic impairment receiving half the recommended oral maintenance dose had similar steady-state voriconazole exposure to those in healthy subjects receiving the full dose, but their exposures on day 1 receiving half the recommended oral loading dose was lower than those in healthy subjects receiving the standard loading dose. Therefore, it is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole. Voriconazole has not been studied in patients with severe hepatic cirrhosis (Child-Pugh Class C) or in patients with chronic hepatitis B or chronic hepatitis C. There is limited data on the safety of voriconazole in patients with abnormal liver function tests AST, ALT, ALP, or total bilirubin >5 times the upper limit of normal). Voriconazole has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and should only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk.

Table 12. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for exclusion	Missing information (Yes/No)	Rationale (if not included as missing information)
Subjects with renal insufficiency (Creatinine Clearance < 50 mL/min)	To minimise the risk of accumulation of the intravenous vehicle, sulphobutylether-beta-cyclodextrin (SBECD), in patients with moderate or severe renal impairment.	No	In patients with moderate to severe renal dysfunction (creatinine clearance < 50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients unless an assessment of the benefit-risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral voriconazole therapy. There are limited safety data with SBECD in human subjects.

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

Table 13. Limitations to Detect of ADRs

<table>
<tr><th>Ability to Detect Adverse Reactions</th><th>Limitation of Trial Programme</th><th>Discussion of Implications for Target Population</th></tr>
<tr><td>Which are rare</td><td>Overall, 2,161 adult and paediatric subjects were exposed to voriconazole in clinical studies for invasive fungal infections (including pharmacokinetic studies). The number of all subjects in the clinical studies for therapeutic use is 1,708 (1,603 adults + 105 paediatrics) and the number of all subjects in clinical studies for the prophylaxis use is 453 (270 adults + 185 paediatrics).</td><td>Rare and very rare events may not have been observed.

With 2,161 exposed subjects, there is a <50% chance of detecting rare ADRs with a frequency of ≤0.03%.

<table>
<tr><th>Frequency category</th><th>Frequency/ Prevalence of ADR</th><th>Probability of detecting at least 1 patient experiencing this ADR</th></tr>
<tr><td rowspan="5">Rare</td><td>0.1%</td><td>88.49%</td></tr>
<tr><td>0.05%</td><td>66.07%</td></tr>
<tr><td>0.04%</td><td>57.88%</td></tr>
<tr><td>0.03%</td><td>47.71%</td></tr>
<tr><td>0.01%</td><td>19.43%</td></tr>
<tr><td rowspan="2">Very Rare</td><td>0.005%</td><td>10.24%</td></tr>
<tr><td>0.001%</td><td>2.14%</td></tr>
</table>

Voriconazole was approved in 2002. Since then, several events have been added to the SmPC [including hyponatremia, peripheral neuropathy, periostitis and squamous cell carcinoma (SCC)].</td></tr>
<tr><td>Due to prolonged exposure</td><td>A limited number of subjects in the Phase 3 clinical studies for treatment and prophylaxis of invasive fungal infections received voriconazole for long-term defined as greater than 180 days (6 months). Please refer to Table 8.</td><td>SCC and periostitis were adverse events potentially associated with prolonged exposure to voriconazole reported in post-marketing.</td></tr>
<tr><td>Which have a long latency</td><td>The period of observation for subjects treated with voriconazole has been limited in the therapeutic and prophylaxis trials.</td><td>The adverse events with long latency (i.e. SCC) were not detected in clinical trials.</td></tr>
</table>

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Children

The safety and efficacy of voriconazole in children below 2 years has not been established.

Overall, a total of 105 paediatric subjects (2 to < 18 years) received voriconazole in the therapeutic clinical studies. During the initial clinical development of voriconazole, no dedicated controlled clinical studies were conducted in the paediatric population. Safety and efficacy data in the paediatric population for the treatment of IA, ICC and EC, were available for a limited number of adolescents (12 to <18 years) who were included in the adult therapeutic studies (n=52 from Studies 150-303, 304, 305, 307, 309, 602, 603, 604, and 608). The median duration of treatment in adults (N=1,603) in these studies was 16 days (range: 1-326 days). The median duration of treatment in paediatrics (N=52) was 41 days (range: 1-180 days). Clinical data from these 52 subjects demonstrated that the safety and efficacy of voriconazole in the paediatric population were generally similar to those observed in adult subjects enrolled in those studies.

An additional 53 paediatric subjects (25 subjects aged 2 to <12 years and, 28 subjects aged 12 to <18 years), were included in two recently completed studies [A1501080 (subjects with IA) and A1501085 (subjects with ICC or EC)] for voriconazole therapeutic use. The median duration of treatment in studies A1501080 and A1501085 was 41 days (range: 3-95) and 15.5 days (range: 2-62), respectively. The overall safety profile of paediatric subjects in these studies was similar to that of adults except for a higher frequency of subjects with liver-related AEs observed in both studies (29% in Study A1501080 and 36.4% in Study A1501085) compared to that reported in the adult therapeutic studies (24.1%). The nature and severity of hepatic-related AEs in the paediatric patients in these 2 studies were consistent with the known safety profile of voriconazole as observed in the adult therapeutic studies. No fatal outcome was reported for any of the hepatic related AEs. No cases of liver failure were reported.

The safety profile of 158 paediatric subjects aged 2 to <12 years were also evaluated in voriconazole compassionate use program for treatment in invasive fungal infections. The safety profile of paediatric subjects was similar to adults.

A total of 183 paediatric subjects (143 subjects aged 2 to <12 years and 40 subjects aged 12 to <18 years) received voriconazole in the clinical studies for prophylaxis of invasive fungal infections. One hundred and seventy-four (174) paediatric subjects received voriconazole for prophylaxis in six pharmacokinetic studies, as reported in Table 14. Additional nine paediatric subjects (aged 12 to <18 years) were included in adult prophylaxis study (A1501073).

Table 14. Pharmacokinetic Paediatric Studies

Study	Age Range	Number of subjects exposed
150-249	2 < 12 years old	11
A1501007	2 < 12 years old	28
A1501037	2 < 12 years old	48
A1501088	2 < 12 years old	40
A1501081	12 < 18 years old	26
A1501096	2 < 15 years old	21

An integrated pooled population pharmacokinetic analysis of four of the paediatric PK studies (A1501007, A1501037, A1501081 and A1501088), together with a pharmacokinetic study in 35 healthy adults (A1501092 provided adult comparison data) enabled further optimization of the voriconazole paediatric dosing regimen, which supported a variation for a dosing update in paediatric subjects (EMEA/H/C/387/II/83, 2011).

A pooled analysis of the safety data of paediatric subjects included in clinical trials (n= 288; 105 from therapeutic use and 183 from prophylaxis use) was also performed by the MAH. The frequency and severity of all-causality AEs and important identified and potential risks associated with voriconazole (refer to Module SVIII Summary of the Safety Concerns) for the pooled paediatric populations were reviewed and compared to adults (n=1,873; 1,603 from therapeutic use and 270 from prophylaxis use). No new safety information was identified. The adverse event profile in these 288 paediatric subjects was in general similar to that in adults. However, similar to studies A1501080 and A1501085, a higher frequency of liver-related AEs[13] mainly associated to elevated liver enzymes (increased ALT, AST and GGT) was observed in paediatrics (21.9% vs 16.1% in adults). The nature and severity of liver-related AEs in the paediatric subjects were similar to those observed in adults. No case of hepatic failure was observed. The majority of the cases was mild to moderate and reported outcome as recovered.

Post-marketing data suggest there may be a higher reporting rate of skin reactions (especially erythema) in the paediatric population with respect to adults. Similarly, a higher reporting proportion of cases reporting phototoxicity among children with respect to adults (12% vs. 2.7%) was observed. There have been more frequently reported post-marketing cases of pancreatitis in paediatric patients than in adults.

Elderly

In an oral multiple dose study Cmax and AUCτ in healthy elderly males (≥65 years) were 61% and 86% higher, respectively, than in healthy younger males (18-45 years). No significant differences in Cmax and AUCτ were observed between healthy elderly females (≥ 65 years) and healthy younger females (18- 45 years).

[13] As per Drug related hepatic disorders, comprehensive search (SMQ)

In the therapeutic studies no dosage adjustment was made on the basis of age. A relationship between plasma concentrations and age was observed.

However, the safety profile of voriconazole in young and elderly subjects was similar and, therefore, no dosage adjustment is necessary for the elderly.

Pregnant or Breast-Feeding Women

Studies in animals have shown reproductive toxicity, however the potential risk for humans remains unknown.

Patients with Hepatic Impairment

Subjects with some degree of hepatic impairment were treated in the voriconazole clinical program. Although there are some pharmacokinetic effects associated with hepatic cirrhosis no significant differences in the overall safety profile have been found between subjects with and without hepatic impairment.

After an oral single-dose (200 mg), AUCτ was 233% higher in subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared with subjects with normal hepatic function. Plasma protein binding of voriconazole was not affected by impaired hepatic function.

In an oral multiple-dose study, AUCτ was similar in subjects with moderate hepatic cirrhosis (Child-Pugh B) given a maintenance dose of 100 mg twice daily and subjects with normal hepatic function given 200 mg twice daily. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C).

Patients with Renal Impairment

Subjects with some degree of renal impairment were treated in the voriconazole clinical program and no significant differences in the overall safety profile have been found between subjects with and without renal impairment.

In an oral single-dose (200 mg) study in subjects with normal renal function and mild (creatinine clearance 41-60 ml/min) to severe (creatinine clearance < 20 ml/min) renal impairment, the pharmacokinetics of voriconazole were not significantly affected by renal impairment. The plasma protein binding of voriconazole was similar in subjects with different degrees of renal impairment.

Patients with Other Relevant Co-Morbidity

None were specifically studied in the clinical trial program.

Patients of Different Racial and/or Ethnic Origin

In vivo studies indicated that CYP2C19 plays a key role in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism.

For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%.

Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, a 4-fold higher voriconazole exposure (AUCτ) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have on average 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts. Nonetheless, no significant differences in the overall safety profile have been found among CYP2C19 homozygous extensive metabolizers, heterozygous extensive metabolizers and poor metabolizers.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma. This metabolite has minimal antifungal activity and does not contribute to the overall efficacy of voriconazole.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

Cumulatively through 31 May 2023, approximately 36,588 Kg of Pfizer voriconazole has been sold worldwide, which equates to an estimated exposure of approximately 250,432 patient-years and 91,470 patient-days.

SV.1.1. Method Used to Calculate Exposure

Since the treatment duration depends upon patients' clinical and mycological response it is not possible to estimate the number of patients exposed based on a fixed length of treatment; the number of patient-years/days is used to estimate exposure. The patient exposure, expressed as patient-years and patient days, was estimated based on the total amount of Kg of Pfizer voriconazole that has been sold worldwide provided by IQVIA from fourth quarter of 2010 through the fourth quarter of 2022 and extrapolated till 31 May 2023, divided by the voriconazole WHO DDD (equal to 0.4 g) for patient days, and further divided by 365.25 for patient years.

36,588 KG / 0.0004 KG / 365.25 = 250,432 patient-years.

36,588 KG / 0.0004 KG = 91,470 patient-days

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

There is low potential for misuse for illegal purposes with voriconazole. Voriconazole does not have characteristics that would make it attractive for use for illegal purposes.

Module SVII. Identified and Potential Risks

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

Not applicable as this is not an initial version of the RMP.

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

Important Identified Risk: Phototoxicity

Risk-benefit impact: Phototoxicity reactions are frequent in patients with immunocompromised status and with exposure to direct sunlight.

Important Identified Risk: Squamous cell carcinoma (SCC)

Risk-benefit impact: Immunocompromised patients, including patients who have received organ transplant, are at a greater risk of SCC of the skin compared to the immunocompetent population.

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

“Peripheral Neuropathy” “Hepatic toxicity”, “QTc prolongation”, and “Visual events” previously classified as important identified risk were reclassified as “not important” and removed from the list of safety concerns.

“Skin cancer (non-SCC)” and “Suicide-related events” previously classified as important potential risks were reclassified as “not important” and removed from the list of safety concerns.

“Resistance” Effects in pregnancy”, “Effects in paediatrics” and “Off-label use” previously classified as missing information were reclassified as not important and therefore removed from the list of safety concerns.

The rationales for the changes to the list of safety concerns are presented below. Further details on the safety concerns will be provided in SVII.3.

Important Identified Risks Removed from the List of Safety Concerns

The risk of ‘peripheral neuropathy’ is not likely to have an impact on the risk-benefit balance of the product. Peripheral neuropathy is therefore removed from the RMP as requested by the PRAC Rapporteur in the final assessment report (EMEA/H/C/PSUSA/00003127/201802).

“Hepatic toxicity”, “QTc prolongation”, “Visual events”, “Skin cancer (non-SCC)” and “Suicide-related events” are no longer considered important risks per GVP Mod V (rev 2); according to the RSI dated 12 January 2023, routine PV and routine RMM are considered sufficient to identify and/or minimize these risks. Therefore, these important risks are removed from the list of the RMP safety concerns.

Missing Information Removed from the List of Safety Concerns

Regarding resistance, currently available data suggest that overall resistance to voriconazole among clinical isolates of Aspergillus spp. (among which A. fumigatus predominates) remains below 10%. Based on these evaluations, the MAH commitment to continue monitoring resistance in PSURs, acknowledging a potential increase in resistance of environmental fungi, was endorsed by the PRAC Rapporteur (Procedure no.: EMEA/H/C/PSUSA/00003127/202102) and the proposal to remove resistance from the RMP as a safety concern, was also accepted.

Effects in pregnancy", "Effects in paediatrics" and "Off-label use" are removed from the list of the safety concerns in line with GVP Module V (Rev. 2) as requested in the RSI dated 12 January 2023

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

Important identified risks included in this RMP are: phototoxicity and SCC.

There are no important potential risks for voriconazole.

During the initial clinical development of voriconazole, 52 adolescents were included in the adult therapeutic studies. Safety data from the 52 adolescents were originally combined with the data for the adults (N=1,603) and the safety data from the pooled population (N=1,655) were presented in Module SVII of RMP version 2.0.

Safety data (N=53) from paediatric studies (A1501080 and A1501085) were pooled with the 52 paediatrics patients described above (N=105) and presented in Part II.SIV.3.1

Safety data of paediatric patients from prophylaxis use studies (N=183; Studies 249, A1501007, A1501037, A1501081, A1501088, A1501096, A1501073, and A1501038) were also pooled and presented in Part II.SIV.3.1.

Safety data from the 52 adolescent subjects were removed from the data for the 1,655 patients (N=1,603 adults only subjects). Safety data from 1,603 adults from therapeutic studies were pooled with the adult only prophylaxis studies (N=270; Studies A1501038 and A1501073). Therefore, current Part II.SVII.3 presents adult only safety data [N=1,873; therapeutic (A1500303, A1500304, A1500305, A1500307, A1500309, A1500602, A1500603, A1500604, A1500608) and prophylactic (A1501038 and A1501073) studies].

Clinical data including adult and paediatric populations are presented in Annex 7 and are unchanged since last RMP version 5.1.

Cumulative post-marketing data through 17 November 2022 are presented in the sections below (MedDRA version 25.1).

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

Important Identified Risks

Table 15. Phototoxicity

Potential mechanisms
The major circulating metabolite, voriconazole N-oxide, in humans and preclinical species was shown to absorb UV light at 310 nm, indicating the potential to be a mediator of phototoxicity if it were to reach sites exposed to sunlight. An in vitro study to evaluate the phototoxicity potential of voriconazole and its N-oxide metabolite in Balb/c 3T3 mouse fibroblasts has been completed.
Neither cytotoxicity nor phototoxicity was observed for either voriconazole or voriconazole N-oxide indicating a lack of phototoxicity potential when tested to the limits of solubility or the maximum recommended concentration of 1000 mg/L.

Evidence source
Clinical studies, post-marketing experience.

Characterisation of the risk

Clinical

Frequency with 95% CI:

All-causality squamous cell carcinoma (SCC) AEs occurred with a frequency of 0.9% (one case of Bowen's disease) as per Table 17.

Table 16. Summary of Treatment-Emergent Risk Events (All-Causality) - Pooled Therapeutic and Prophylaxis Studies - Adult Subjects[a, b]

Frequency (%)	n/N	95% Confidence Interval (%)
0.9	17/1,873	0.5%, 1.4%

a. Therapeutic study protocols included are 303, 304, 305, 307, 309, 602, 603, 604, 608.
b. Prophylaxis study protocols included are A1501038 and A1501073.
n = number of subjects reporting at least one event in the risk category; N = total subjects in the studies

The overall frequency of phototoxicity in therapeutic and prophylaxis studies is similar: 0.9% vs 1.1%, respectively (see Annex 7, Table 1 and 2).

Seriousness/outcomes
One subject (0.1%) experienced a SAE suggestive of phototoxicity (Photosensitivity reaction). There were no subjects with phototoxicity-related SAEs in the prophylaxis studies (refer to Annex 7, Table 3 and 4).

The most frequently observed AE in pooled adult data was photosensitivity reaction (12), with most subjects (8) having recovered at the time of last follow-up. Of the 4 cases of sunburn reported, 2 patients recovered and the other 2 had not recovered at the last follow-up. One episode of Actinic keratosis with outcome recovered was also observed. Outcomes of treatment-emergent AEs suggestive of phototoxicity in adult population for the therapeutic and prophylaxis studies can be found in Annex 7, Table 5 and 6, respectively.

Severity and nature of risk
The majority of phototoxicity- related AEs (for a total of 15 occurrences) for the combined studies were mild (9) to moderate (6) in severity. In addition, there were 2 episodes of Photosensitivity reaction considered severe. Treatment-emergent phototoxicity-related events in the adult population are summarised in Annex 7, Table 7 and 8, for the therapeutic and prophylaxis studies, respectively.

Table 15. Phototoxicity

Safety

Cumulative Safety Database Experience (non-CT Cases)

In the post-marketing experience, since first approval and through 31 May 2023, 826 cases were received by the MAH corresponding to a 3.1% proportional reporting rate. Distribution of event by seriousness and clinical outcome is provided below:

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Events by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	893 (100)	327 (36.6)	61 (6.8)	5 (0.6)	363 (40.6)	14 (1.6)	134 (15.0)	378 (42.3)
Photosensitivity reaction	741 (83.0)	252 (34.0)	51 (6.9)	1 (0.1)	310 (41.8)	12 (1.6)	108 (14.6)	311 (42)
Actinic keratosis	87 (9.7)	55 (63.2)	7 (8.0)	4 (4.6)	32 (36.8)	2 (2.3)	15 (17.2)	34 (39.1)
Sunburn	51 (5.7)	12 (23.5)	2 (3.9)	0	11 (21.6)	0	9 (17.6)	31 (60.8)
Photodermatosis	14 (1.6)	8 (57.1)	1 (7.1)	0	10 (71.4)	0	2 (14.3)	2 (14.3)

Cumulative Safety Database Experience (CT Cases)

In the cumulative period through 31 May 2023, a total of 6 CT case reports (0.14%) were received by the MAH. Distribution of event by seriousness and clinical outcome is provided below:

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Events by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	6 (100)	6 (100)	2 (33.3)	0	5 (83.3)	0	0	1 (16.7)
Photosensitivity reaction	6 (100)	6 (100)	2 (33.3)	0	5 (83.3)	0	0	1 (16.7)

Background incidence/prevalence:[14] Photosensitivity is an adverse cutaneous reaction that results when a certain chemical or drug is applied topically or taken systemically at the same time a person is exposed to ultraviolet (UV) or visible light.

The literature search did not identify papers reporting incidence and/or prevalence of phototoxicity in patients with fungal infections. Some studies reported frequency of skin reactions in patients using specific medications, which are summarised below.

In a retrospective study of 151 patients with acute non-lymphocytic leukaemia (ANLL), the incidence of drug-induced skin reactions was estimated and compared to the general population. About 60% (91/151) of

[14] Relevant papers were identified using the following Boolean search terms: [(papilloedema OR phototoxicity) AND SOT OR lung transplant OR heart transplant OR liver transplant OR multiorgan transplant OR haematologic malignancy OR HSCT OR HIV OR human immunodeficiency virus OR AIDS OR acquired immune deficiency syndrome OR surgery OR surgical procedure)]

Table 15. Phototoxicity

patients developed a drug-related reaction to one or more drugs during remission, induction, and maintenance therapy. Overall, the incidence of drug-associated rash was significantly higher than the general population. The incidence of drug-associated rashes in patients with ANLL for allopurinol was (16%), co-trimoxazole (14%), miconazole (28%), and ketoconazole (18%).[74] An analysis using the Japanese Adverse Drug Event Report database (2004 – 2016) revealed that 0.08% (330 out of 430,587) of all adverse drug event reports concerned photosensitive reactions.[75] However, Drug-induced photosensitivity is likely significantly under-reported due to the difficulty in clinical diagnosis and lack of documentation in public databases.[76]
Risk factors and risk groups Phototoxicity reactions are frequent in patients with immunocompromised status and with exposure to direct sunlight. A higher reporting proportion of phototoxicity reactions in the paediatric population compared to that of adult population was observed in the post-marketing experience.
Preventability It is recommended that all patients, including children, avoid exposure to direct sunlight during voriconazole treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF). If phototoxic reactions occur, multidisciplinary advice should be sought, and the patient should be referred to a dermatologist. Voriconazole discontinuation and use of alternative antifungal agents should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. Voriconazole should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified.
Impact on the risk-benefit balance of the product While generally, drug-induced phototoxicity is not a severe medical condition, patients may experience exaggerated sunburn reaction with erythema and oedema that occurs within minutes to hours of sunlight exposure. Vesicles and bullae may develop with severe reactions. A less common manifestation of phototoxicity includes pigment changes of the skin. In severe cases, patients may exhibit cutaneous lupus erythematosus or pseudoporphyria.[77] Sun avoidance and the use of sun protection are expected to prevent this risk. Discontinuation of voriconazole is expected to relieve the symptoms. Therefore, the impact on individual patients is minimal.
Public health impact Most phototoxic reactions result from the systemic administration of drugs. Although mortality is rare, drug-induced photosensitivity can cause significant morbidity in some individuals, who must severely limit their exposure to natural or artificial light. Phototoxicity is expected to be managed via sun avoidance, use of sun protection and discontinuation of voriconazole. Because of the extensive education to make prescribers and patients aware of this risk, as well as how to prevent and manage it, the potential impact of this risk from voriconazole treatment on public health is expected to be minimal.
MedDRA Preferred Terms: Actinic keratosis, Photodermatosis, Photosensitivity reaction, Sunburn.

Table 17. Squamous Cell Carcinoma

Potential mechanisms
The mechanism is not known.

Evidence source
Clinical studies, post-marketing experience and literature.

Literature Evidence
Incidence of squamous cell carcinoma in patients receiving voriconazole for prophylaxis or treatment

A literature search did not identify published articles describing incidence of SCC of the skin in the overall voriconazole treated patient population. Eight studies using retrospective data were identified that reported SCC of the skin or NMSC incidence in patients with lung or lung-heart transplant receiving voriconazole for prophylaxis or treatment in the US. The incidence of SCC of the skin ranged from 3.1% to 46%.

Summary of studies reporting SCC or NMSC incidence in patients with lung or lung-heart transplant or HSCT receiving voriconazole

Reference	Location/setting	SCC (or NMSC) Incidence
Vadnerkar et al[78]	University of Pittsburgh Medical Center, Pennsylvania, US	3.1% (17/543) developed SCC (all patients were exposed to voriconazole in this study).
Feist et al[79]	California Medical Center, San Diego, US	39.5% (17/43) in the voriconazole group compared to 19.5% (15/77) in the non-voriconazole group developed SCC.
Zwald et al[80]	Emory University, Georgia, US	26.6% (16/60) developed NMSC in the voriconazole group, defined as ≥3 months of voriconazole exposure. 39% (12/31) developed NMSC who were not exposed to voriconazole, defined as no or less than 3 months of voriconazole use.
McLaughlin et al[81]	US (MarketScan™ Database)	At crude level, 19% patients with any claim for voriconazole in the database developed NMSC. At crude level, 12% patients without any claim for voriconazole in the database developed NMSC.
Mansh et al[82]	University of California, San Francisco, US	Incidence of SCC with any exposure to voriconazole was 1% at year 1, 25% at year 5 and 43% at year 10 post-lung transplant.
Wojenski et al[83]	Mayo Clinic, Rochester, Minnesota US (HSCT recipients)	Cumulative SCC incidence at 1 year was 3%, at 2 years was 8%, at 3 years was 13%, at 4 years was 14%, and at 5 years was 19%.
Rashtak et al[84].	Mayo Clinic, Rochester, Minnesota, US	At 5- and 10-years post-lung transplantation, the cumulative incidence of SCC of the skin was 28% and 42% respectively.
Singer et al[85]	University of California, San Francisco, US	At 5 years post-lung transplantation, 46% of patients ever exposed to voriconazole developed SCC in the extrapolated analysis predicting the incidence estimate.

Characterisation of the risk

Frequency with 95% CI

All-causality squamous cell carcinoma (SCC) AEs occurred with a frequency of 0.1% (one case of Bowen's disease) as per Table 18.

Table 18. Summary of Treatment-Emergent Risk Events (All-Causality) - Pooled Therapeutic and Prophylaxis Studies[a, b] - Adult Subjects (SCC)

Frequency (%)	n/N	95% Confidence Interval (%)
0.1	1/1873	0.0, 0.3%

a. Therapeutic study protocols included are 303, 304, 305, 307, 309, 602, 603, 604, 608.
b. Prophylaxis study protocols included are A1501038 and A1501073.
n = number of subjects reporting at least one event in the risk category; N = total subjects in the studies

There were no adult subjects with SCC in the prophylaxis studies and 1 case (Bowen's disease) from the therapeutic studies was reported (refer to Annex 7, Table 9 and 10).

Seriousness/outcomes
There were no serious SCC-related AEs in the pooled adult's data. The outcome of the single case of Bowen's disease was reported as ongoing at the time of last follow-up. Additional details can be found in Annex 7, Table 11 and 12 (SAEs), and Table 13 and 14 (Outcomes) for the therapeutic and prophylaxis studies, respectively.

Severity and nature of risk
There was one treatment-emergent SCC AE (Bowen's disease) for the pooled adults data, which was categorized as mild in severity. Details can be found in Annex 7, Table 15 for the therapeutic studies. There were no SCC AEs in adults from the prophylaxis studies (Table 16).
Squamous cell carcinomas that are detected at an early stage and removed promptly are almost always curable and cause minimal damage. However, left untreated, they eventually penetrate the underlying tissues and can become disfiguring. A small percentage can metastasize to distant tissues and organs and can become fatal.[86]

Safety
Cumulative Safety Database Experience (non-CT Cases)

In the post-marketing experience, since first approval and through 31 May 2023, 177 cases were received by the MAH corresponding to a 0.7% proportional reporting rate. Distribution of event by seriousness and clinical outcome is provided below:

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Events by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	195 (100)	195 (100)	32 (16.4)	20 (10.3)	54 (27.7)	7 (3.6)	31 (15.9)	83 (42.6)
Squamous cell carcinoma of skin	101 (51.8)	101 (100)	19 (18.8)	9 (8.9)	28 (27.7)	3 (3.0)	16 (15.8)	45 (44.6)
Squamous cell carcinoma	68 (34.9)	68 (100)	10 (14.7)	7 (10.3)	16 (23.5)	3 (4.4)	11 (16.2)	31 (45.6)
Bowen's disease	26 (13.3	26 (100)	3 (11.5)	4 (15.4)	10 (38.5)	1 (3.8)	4 (15.4)	7 (26.9)

Cumulative Safety Database Experience (CT Cases)

In the cumulative period through 31 May 2023, a total of 3 CT case reports of SCC (0.07%) was received by the MAH. Distribution of event by seriousness and clinical outcome is provided below:

PT	# of Events (% of Total PTs)	# Serious Events (% of PT)	# Events with Criterion of Hospitalization (% of PT)	Distribution of Events by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	3 (100)	3 (100)	1 (33.3)	0	0	1 (33.3)	2 (66.7)	0
Squamous cell carcinoma of skin	1 (33.3)	1 (100)	0	0	0	0	1 (100)	0
Squamous cell carcinoma	2 (66.7)	2 (100)	1 (50)	0	0	1 (50)	1 (50)	0

Background incidence/prevalence[15]

The following summarizes the published data on the incidence of SCC of the skin in 1) the general population by age group (i.e., paediatric, adult, and elderly), and 2) in patients exposed to voriconazole for prophylaxis or treatment by the same age group, when available.

Results from A1501097 PASS are summarized below in the subsection "Epidemiology of SCC in immunocompromised patients".

SCC incidence in the general population

The literature search identified a few studies that described the incidence of SCC of the skin or non-melanoma skin cancer (NMSC) in the general population. Using data from the Swedish Cancer Registry, Wassberg C et al.,[87] reported that the age-standardized SCC incidence (per 100,000 population) in Sweden in 1995 was 23.1 in men and 10.1 in women. In another population-based study using data from the Cancer Registry (2004-2008) in the Netherlands, Hollestein LM et al.[88] estimated the age-standardized SCC incidence (per 100,000 persons years) of 32.4 in men and 17.2 in women. In an updated analysis using data from the Cancer Registry (1989-2017) in the Netherlands, the estimated age-standardized SCC incidence (per 100,000 person-years) in male was 40.0 in 1989 and 107.6 in 2017; for female patients, 13.9 in 1989 and 68.7 in 2017.[89]

The incidence of SCC of the skin increases with increasing age. Old age has been identified as an important risk factor for developing the SCC of the skin. In a comprehensive review article by Alam M et al.,[90] the age-adjusted incidence of SCC (per 100,000 persons per year) among Whites was reported to range from 100 to 150, and the age-specific incidence among individuals aged >75 years was about 10 times that incidence. [90]

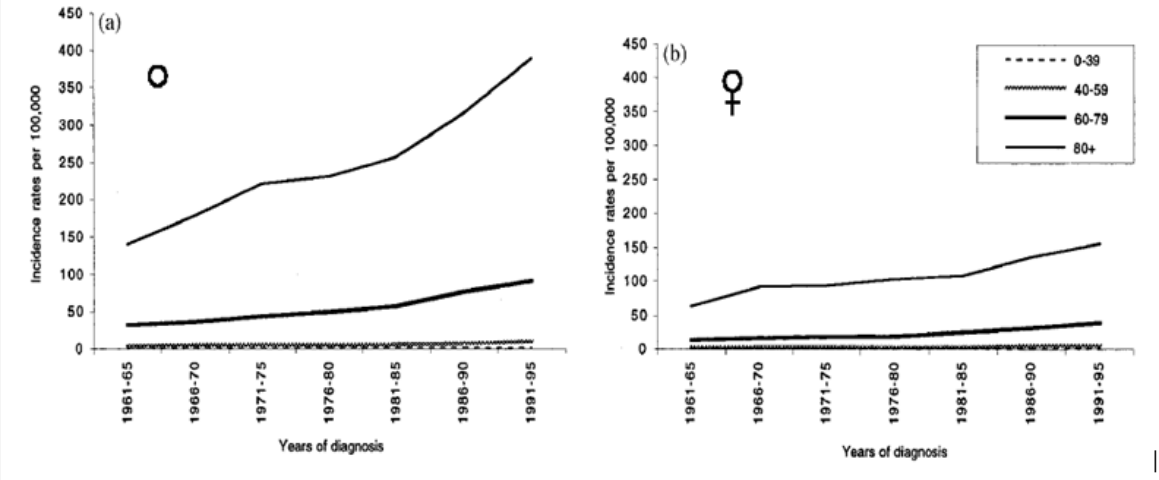
In the Swedish study, described above, [87] SCC incidence (per 100,000 population) among males was approximately 15 in aged <59 years, 75 in aged 60-79 years and 400 in aged ≥80 years between 1991 and 1995. The age-specific SCC incidence during the same time period in females was approximately 10 or less in aged <59 years, 25 in aged 60-79 years and 140 in aged 80 and above[16] (Figure 1 a and b).

Figure 1. Age-Specific Incidence of SCC of the Skin in Sweden in (a) Men and (b) Women by Year of Diagnosis

[15] Relevant papers were identified using the following Boolean search terms: [(squamous cell carcinoma SCC OR basal carcinoma OR BCC OR melanoma OR malignant melanoma) AND SOT OR lung transplant OR heart transplant OR liver transplant OR multiorgan transplant OR haematologic malignancy OR HSCT OR HIV OR human immunodeficiency virus OR AIDS OR acquired immune deficiency syndrome OR surgery OR surgical procedure)]

[16] Approximated from Figure 1 a & b

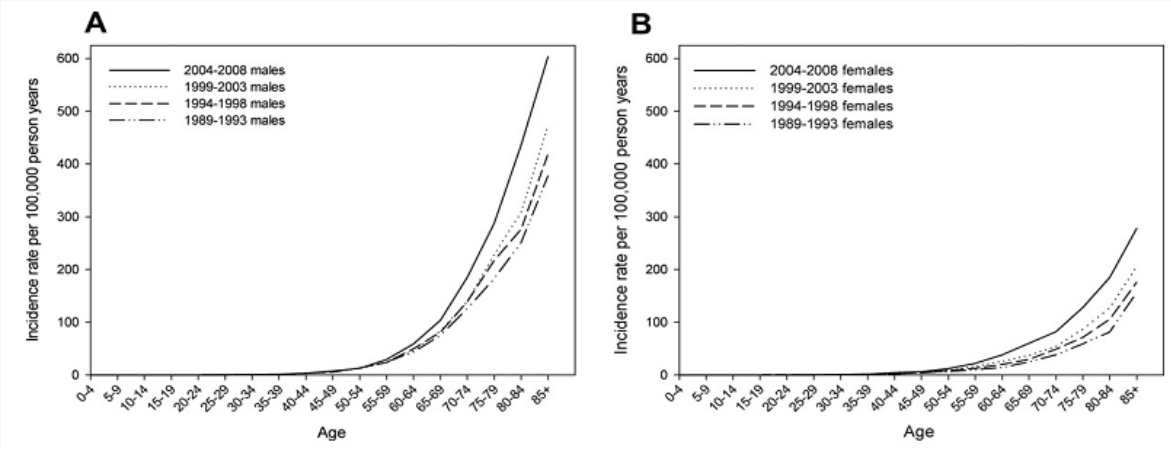
Table 17. Squamous Cell Carcinoma



Source: Wassberg C et al. [87]

Similar to the study in Sweden, the incidence of SCC increased with age in both males and females in the Netherlands (Figure 2, A and B).

Figure 2. Age-specific incidence rates of SCC of the skin in males (A) and (B) females in the Netherlands by period of diagnosis



Source: Hollestein LM. [88]

The literature search did not identify papers describing incidence or prevalence estimates of SCC in patients with fungal infections. Alternatively, the MAH summarised the rates in patient populations similar to the target population.
It has been well documented that immunocompromised patients, including patients who have received organ transplant, have an increased risk of cutaneous SCC compared to the immunocompetent population. Overall, the incidence of SCC in transplant recipients is 40 to 250 times that of the general population.

Epidemiology of SCC in immunocompromised patients: Renal transplant patients receiving long-term immunosuppressive therapy are at increased risk of developing skin cancers compared to the general population, with SCC being the most common post-transplantation cutaneous malignancy.
The search identified six studies that reported SCC incidence in renal transplant patients in different geographical locations, as well as studies in heart transplant, multi-organ transplant, and HIV-infected patients.
In a retrospective analysis of medical records (1972 to 2004) at the Organ Transplant Center in Kuwait, investigators reviewed the records of more than 1500 kidney recipients. A total of seven cases of SCC were identified reporting an incidence of 5.97 per 1000 patients.[91]
Falsarella, et al conducted a retrospective analysis of medical records (January 1984 to December 2006) of post-transplant patients with biopsy-proven skin cancer. Among 1300 renal transplant recipients from January 1984 to December 2006, 33 (2.5%) had skin malignancies during a mean follow up of 42 months (range 1 to 213 months).[92]
Ramsay and colleagues conducted a prospective study and estimated an incidence of NMSC in the renal transplant recipients in the UK. A total of 244 (91% enrolled) renal transplant recipients were screened for skin cancers between 1998 and 2006. The mean incidence per 1000 patients was 78.2 for NMSC, 34.5 for SCC and 35.8 for BCC during a mean follow up of 7.3 years.[93]
In a prospective study by Fuente, et al,[94] 174 patients who received renal transplant were followed from January 1989 to October 1999 at 6-month intervals in the Hospital Universitari Germans Triasi Pujol, Badalona, Spain. The median follow-up time was 72 months (range 12 to 140 months). Twenty-two (22) patients developed SCC during the study period with an incidence of 126.43 per 1,000 patients.[95]
Using the data from the University Hospital Leiden, The Netherlands, Hartevelt, et al. estimated the overall incidence of SCC was 7.6 per 1000 person-year and the incidence of BCC was 3.3 per 1000 person-year.[96]
Bordea and colleagues carried out a comprehensive analysis of all skin cancer cases occurring in patients receiving renal transplants in Oxford, UK over a 21-year period. From 1975 to 1996, 1115 patients received 1360 kidney grafts. Total follow-up time was 7559 patient-year at risk, which individually ranged from 2 to 23 years. Data on skin cancers were collected by review of the clinical notes and histopathology records. Of

the 980 transplant patients, 187 (19.1%) patients developed at least 1 skin cancer. Overall, the rate of any skin cancer was reported to be 141 per 1000 person-year. The rates (per 1000 person-year) of individual tumour types were SCC 71.4, BCC 22.4, and Merkel cell tumour 0.13.[97]

Heart Transplant patients: Only one study was identified that reported rate of SCC in heart transplant recipients.

Fortina and colleagues enrolled 230 heart transplant recipients aged 18 years or older at the time of transplantation who were followed for at least 3 years in Padua, Italy. The patients were treated with cyclosporine and azathioprine (double therapy; n = 37), or with cyclosporine, azathioprine, and oral prednisone (triple therapy; n = 193). Among the 230 heart transplant recipients entered into the study, 20.8% (48/230) developed NMSC after transplantation: 26 patients had invasive or in situ SCCs, 13 had BCCs, and 9 had both tumours. The overall incidence of SCC was 152.17 per 1,000 patients (35/230).[98]

Liver Transplant patients: Data on the rates of SCC in liver transplant recipients are sparse. The search identified only one study that reported the rate of SCC in liver transplant patients. In a survey, 182 liver transplant recipients, who received liver transplant at the Division of Transplantation, New England Medical Center Tufts University School of Medicine, Boston, Massachusetts, United States, between 1991 and 2000 were inquired about the development of cutaneous malignancies. Of 182 recipients, 15 l responded to survey questionnaire. Twenty-three (23) patients reported SCC with a rate (per 1,000 patients) of 126.37 compared to 16 patients who developed BCC with an incidence of 87.91.

The authors concluded that the incidence estimate observed in the survey may be an underestimation of the actual incidence of SCC in liver transplant patients because of the limitations of voluntary reporting of skin cancers in this study.[99]

Multi-organ transplant patients: A total of three studies were identified that reported rates of SCC in renal, liver, heart, lung or multi-organ transplant patients. Lindelöf, et al used the data from the Swedish Organ Transplant cohort, which is composed of 5931 patients who underwent renal transplantation (n = 5139), liver (n = 397), or other organ (heart, lung, and pancreas) (n = 395) from January 1, 1970, through December 31, 1997. A total of 273 patients with SCC were identified from the national Swedish Cancer Registry reporting an incidence of 46.0 per 1000 patients.[100]

In another study, Jensen, et al. linked the records of all patients in Norway who received their first kidney (from 1963) or heart transplant (from 1983) through 1992 with the Cancer Registry of Norway and estimated the incidence of skin cancers. All transplant recipients were followed up from date of the first transplantation to the date of cancer diagnosis, death, emigration, or end of the study, whichever occurred first.

The overall incidence (per 1000 patient-year) of cutaneous SCC was estimated to be 6.47 (7.23 in males and 5.19 in females) and lip SCC was 0.66 (0.74 in males and 0.53 in females) in renal or heart transplant patients.[101]

In another retrospective cohort study, a total of 1329 patients who received their first kidney (1062 patients) or heart allograft (267 patients) were included from May 1969 to December 1998 at the transplantation units of Bergamo, Padua, Rome, and Verona, Italy. The median age at transplantation was 37.5 years for the renal transplant recipients and 54 years for the heart transplant recipients, respectively.

The median follow-up time up was 4 years (range 3 months to 26 years) for the renal transplant patients and 2.5 years (range 2 months to 10 years) for the heart transplant patients. Overall, the incidence rate of SCC was 3.5 per 1000 persons-year (95% CI: 2.2, 4.5).[102]

HIV infected patients: In a prospective study, Crum-Cianflone estimated the incidence of cutaneous malignancies among HIV-infected persons enrolled in a large HIV study.

Age-adjusted incidence rate (per 1000-person year) of SCC was reported for the following time periods: 1991 to 1995 was 0.85 (95% CI: 0.0-18.0), 1996 to 2000 was 0.24 (95% CI: 0.0-5.80), and 2001 to 2006 was 0.49 (95% CI: 0.0, 10.4).[103]

PASS A1501097 - Evaluating the risk of SCC of the skin with voriconazole exposure in patients with lung/heart-lung transplant:

The MAH conducted a retrospective observational study to assess the potential association between voriconazole use and the development of SCC of the skin in patients with lung or heart/lung transplant (LT).

A total of 900 patients aged ≥ 18 years undergoing consecutive LT were included from 14 transplant centers in EU(440), North America (430) and Australia (30).

Overall, the crude incidence rate (per 1,000 person-years) of SCC of the skin was 33.4 in the exposure to voriconazole alone category, 10.4 in the exposure to other azoles alone category, 21.7 in the exposure to voriconazole and other azole(s) category, and 13.1 in the unexposed category.

Table 17. Squamous Cell Carcinoma

In a multivariable Cox regression model analysing voriconazole, other azoles and immunosuppressive agents as time-dependent variables, exposure to voriconazole alone (adjusted HR=2.39, 95% CI: 1.31-4.37) and exposure to voriconazole and other azole(s) (adjusted HR=3.45, 95% CI: 1.07-11.06) were associated with SCC of the skin as compared with the unexposed category after controlling for the confounding variables.

SCC in patients with haematologic malignancy: In a cohort of 24,011 patients who underwent allogeneic or syngeneic HSCT reported to the Center for International Blood and Marrow Transplant Research (n = 18 488; transplantations from 1964 through 1994, followed up through 1995) or at Fred Hutchinson Cancer Research Center in Seattle (n = 5523; transplantations from 1969 through 1996, followed up through 1997). Using data from the cohort, the authors estimate the cumulative incidence of SCC was 1.1% (or 11 per 1000 patients) at 20 years (95% CI: -0.7, 1.7) in analyses adjusting for the competing risk for death.[104]
The following table presents the incidence of SCC in patient subpopulations.

Reference	Country	Incidence (per 1000 patients)
Renal transplant patients		
Samhan, et al [91]	Kuwait	3.41
Falsarella, et al [92]	Brazil	12.30
Ramsay, et al [93]	United Kingdom	34.5
Fuente, et al [94]	Spain	126.43
Heart Transplant patients		
Fortina, et al [98]	Italy	152.17
Multi-organ transplant patients		
Lindelöf, et al [100]	Sweden	46.0
Jensen, et al [101]	Norway	6.47 [a]
Naldi, et al [102]	Italy	3.5 [a]
HIV infected patients		
Crum-Cianflone, et al [103]	US 1991 -1995 1996-2000 2001-2006	 0.85 [a] 0.24 [a] 0.49 [a]
Haematologic malignancy or HSCT	US	11

a. per 1000 person-years.

Risk factors and risk groups

In general, skin type, advanced age, sun exposure, genetic predisposition as well as exposure to ionizing radiation, arsenic, or industrial chemicals; pre-existing burns and scars; and immunosuppression [86] are the risk factors for SCC of the skin.

Immunocompromised patients, including patients who have received organ transplant, are at a greater risk of SCC of the skin compared to the immunocompetent population.

The risk of SCC in organ transplant recipients has been associated with the following risk factors in epidemiologic investigations: older age, prolonged occupational sunlight exposure, long duration of immunosuppressive therapy, intense immunosuppressive therapy, significant prior exposure to ultraviolet radiation; infection with human papillomavirus, lower CD4 cell counts, and certain hosts factors (eye or hair colour, complexion, White race, patients with Fitzpatrick skin types I, II, or III).[105 106 107]

Squamous cell carcinoma of the skin has been reported with long-term exposure to voriconazole in patients with immunosuppressed status.

Table 17. Squamous Cell Carcinoma

Preventability Voriconazole should be discontinued if premalignant skin lesions or SCC are identified
Impact on the risk-benefit balance of the product Squamous cell carcinomas that are detected at an early stage and removed promptly are almost always curable and cause minimal damage. However, left untreated, they eventually penetrate the underlying tissues and can become disfiguring. A small percentage can metastasize to distant tissues and organs and can become fatal. [86]
Public health impact In general, despite increased knowledge and public education regarding the causes of skin cancer and modes of prevention, the incidence of SCC continues to rise worldwide.[108] The speculated causes for the rise include an aging population, improved detection, and environmental factors, such as depletion of the ozone layer. Although cutaneous SCC is not often fatal, it can cause significant morbidity. Most SCCs are located in the head and neck region, where surgery for advanced-stage disease can be disfiguring. Furthermore, the cost of treatment has been shown to pose a significant public health burden. In a study of the US Medicare population, the treatment of NMSCs ranked fifth among the most expensive cancers to treat because, although NMSC has a low mortality, its incidence is more common than all other cancers combined.[109] Although the potential impact of SCC on public health is expected to be high in general, the potential impact of SCC from voriconazole use on public health is expected to be minimal.
MedDRA Preferred Terms: Adenosquamous cell carcinoma, Basosquamous carcinoma, Basosquamous carcinoma of skin, Bowen's disease, Squamous cell carcinoma, Squamous cell carcinoma of skin.

SVII.3.2. Presentation of the Missing Information

There are no missing information for voriconazole.

Module SVIII. Summary of the Safety Concerns

Table 19. Summary of Safety Concerns

Important identified risks	Phototoxicity Squamous cell carcinoma (SCC)
Important potential risks	None
Missing information	None

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

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

None.

Other forms of routine pharmacovigilance activities for safety concerns

None.

III.2. Additional Pharmacovigilance Activities

None.

III.3. Summary Table of Additional Pharmacovigilance Activities

None.

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

None.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

There are no post-authorization efficacy studies (PAES) that are a specific obligation by the competent authorities and/or condition of the MA.

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

V.1. Routine Risk Minimisation Measures

Table 20. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important identified risk	
Phototoxicity	Routine risk communication: Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for Dermatological adverse reactions monitoring are included SmPC section 4.4.
Squamous Cell Carcinoma (SCC)	Routine risk communication: Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for Dermatological adverse reactions monitoring are included SmPC section 4.4.
Important potential risk	
None	
Missing information	
None	

V.2. Additional Risk Minimisation Measures

The additional risk minimisation measures to address Phototoxicity, and Squamous Cell Carcinoma comprised of educational/communication materials for patients, as per Table 21.

Table 21. Additional Risk Minimisation Measures by safety concern

Safety Concern	Additional Risk Minimisation Measures
Important Identified Risk	
Phototoxicity	Educational/communication program including a Patient Alert Card
Objectives:	To ensure that patients are aware of the potential for phototoxicity associated with voriconazole use, as well as precautionary measures to help mitigate this risk.
Rationale for the additional risk minimisation activity:	This education program was implemented to counsel patients appropriately regarding the precautions to help mitigate this risk (i.e. sun-avoidance behaviours).
Target audience and planned distribution path:	Patients
Plans to evaluate the effectiveness of the interventions and criteria for success:	PASS A1501102, a non-interventional study using a cross-sectional survey to evaluate the effectiveness of the aRMMs to mitigate the risks of phototoxicity, SCC of the skin, and hepatic toxicity in patients using voriconazole.
Squamous Cell Carcinoma (SCC)	Educational/communication program including a Patient Alert Card
Objectives:	To ensure that patients are aware of the potential for SCC associated with voriconazole use, and precautionary measures to help mitigate this risk
Rationale for the additional risk minimisation activity:	This education program was implemented to counsel patients appropriately regarding the precautions to help mitigate this risk (i.e., sun-avoidance behaviours).
Target audience and planned distribution path:	Patients
Plans to evaluate the effectiveness of the interventions and criteria for success:	PASS A1501102, a non-interventional study using a cross-sectional survey to evaluate the effectiveness of the aRMMs to mitigate the risks of phototoxicity, SCC of the skin, and hepatic toxicity in patients using voriconazole.

Removal of additional risk minimisation activities

To ensure that the risks of phototoxicity, hepatic toxicity and SCC of the skin are adequate-ly managed, further risk minimisation activities were performed beginning in April 2014. These activities included aRMMs which had the following components: HCP Checklist, HCP Question & Answer Brochure, and Patient Alert Card. However, no clear conclusion could be drawn on the effectiveness of these aRMMs.

Available data from PASS A1501102 which evaluated the effectiveness of additional RMMs aimed at reducing the risks of phototoxicity, SCC of the skin and hepatic toxicity in patients receiving voriconazole suggested that the source for HCPs knowledge about the risks with voriconazole is not clearly linked to the aRMM. Further, study A1501103, a non-interventional, retrospective PASS designed to monitor selected safety risks in patients re-ceiving voriconazole in the real-world setting, particularly with long-term use (i.e., ⩾180 days), did not show increased risk of hepatic disorders, phototoxicity, SCC of the skin, vis-ual disorders and periostitis with voriconazole use or other information that would necessi-tate continued implementation of the educational materials.

Moreover, after an extensive literature review of relevant publications, guidelines and other resources, there is evidence that the most important recommendations included in both the routine and additional RMMs for voriconazole in relation to hepatic toxicity, SCC and phototoxicity have been integrated into routine clinical practice, in particular in the European region.

Since the SmPC remains the most important routine RMM, it currently clearly communicates all relevant pieces of safety information to prescribers and therefore HCP-focused aRMMs are not expected to provide further significant awareness to the prescribers regarding these well-known risks.

The MAH therefore proposed to remove the HCP educational materials from the RMP and keep the Patient Alert Card as proposed by EMA in the RSI received in September 2022 (Procedure No. EMEA/H/C/WS2270). This proposal was accepted by EMA in the Updated Assessment Report dated 05 January 2023 as part of the same procedure.

V.3. Summary of Risk Minimisation Measures

Table 22. Summary Table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Phototoxicity	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. Additional risk minimisation measures: Patient Alert Card.	Routine pharmacovigilance Additional Pharmacovigilance: None.
Squamous Cell Carcinoma (SCC)	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8. Additional risk minimisation measures: Patient Alert Card.	Routine pharmacovigilance Additional Pharmacovigilance: None.
Important Potential Risk		
None		
Missing information		
None		

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Vfend (voriconazole)

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

Vfend's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vfend should be used.

This summary of the RMP for Vfend 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 Vfend's RMP.

I. The Medicine and What It Is Used For

Vfend is authorised for:

- Treatment of invasive aspergillosis.
- Treatment of candidaemia in non-neutropenic patients.
- Treatment of fluconazole-resistant serious invasive Candida infections (including *C. krusei*).
- Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

Voriconazole should be administered primarily to patients with progressive, possibly life-threatening infections.

- Prophylaxis of invasive fungal infections in high-risk allogeneic haematopoietic stem cell transplant (HSCT) recipients.

It contains voriconazole as the active substance and it is given by intravenous and oral route of administration.

Further information about the evaluation of Vfend's benefits can be found in Vfend's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's https://www.ema.europa.eu/en/medicines/human/EPAR/vfend#:~:text=Vfend%20%3A%20EPAR%20%2D%20All%20Authorised%20presentations%20(PDF%2F37.18%20KB)&text=treatment%20of%20in%20candidaemianon%2Dneutropenic,infections%20caused%20by%20Scedosporium%20spp.

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

Important risks of Vfend, together with measures to minimise such risks and the proposed studies for learning more about Vfend'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 Vfend, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse events 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 Vfend is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Vfend 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 Vfend. 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 23. List of important risks and missing information

Important identified risks	Phototoxicity Squamous cell carcinoma (SCC)
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 24. Important Identified Risk: Phototoxicity

Evidence for linking the risk to the medicine	Clinical studies, post-marketing safety database.
Risk factors and risk groups	Phototoxicity reactions are frequent in patients with immunocompromised status and with exposure to direct sunlight. A higher reporting proportion of phototoxicity reactions in the paediatric population compared to that of adult population was observed in the post-marketing experience.
Risk minimisation measures	Routine: SmPC section 4.4 and 4.8 Additional: Patient Alert Card.

Table 25. Important Identified Risk: Squamous cell carcinoma (SCC)

Evidence for linking the risk to the medicine	Clinical studies, post-marketing safety database and literature.
Risk factors and risk groups	In general, skin type, advanced age, sun exposure, genetic predisposition as well as exposure to ionizing radiation, arsenic, or industrial chemicals; pre-existing burns and scars; and immunosuppression [86] are the risk factors for SCC of the skin. Immunocompromised patients, including patients who have received organ transplant, are at a greater risk of SCC of the skin compared to the immuno-competent population. The risk of SCC in organ transplant recipients has been associated with the following risk factors in epidemiologic investigations: older age, prolonged occupational sunlight exposure, long duration of immunosuppressive therapy, intense immunosuppressive therapy, significant prior exposure to ultraviolet radiation; infection with human papillomavirus, lower CD4 cell counts, and certain hosts factors (eye or hair colour, complexion, White race, patients with Fitzpatrick skin types I, II, or III). [105] [106] [107] Squamous cell carcinoma of the skin has been reported with long-term exposure to voriconazole in patients with immunosuppressed status.
Risk minimisation measures	Routine: SmPC section 4.2, 4.4 and 4.8 Additional: Patient Alert Card.

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 Vfend.

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

None.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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

The following risk minimisation tools were distributed:

- Health Care Professional Checklist for phototoxicity, squamous cell carcinoma (SCC) and hepatotoxicity.

- Health Care Professional Question and Answer Brochure for phototoxicity, SCC and hepatotoxicity.

- Patient Alert Card for phototoxicity and SCC.

Specifications for the Additional Risk Minimisation Tools

The three components of the RM tools are the HCP/Prescriber Checklist, HCP Question & Answer (Q&A) Brochure and Patient Alert Card.

The content and layout of the RM tools were non promotional in nature. User testing of the RM tools was conducted in October 2013 with a sample of HCPs in the UK and France prior to the finalization of RM tools and subsequent distribution in April 2014. Specifically, prototypes of each tool (i.e., HCP Checklist, HCP Q&A Brochure, and Patient Alert Card) were reviewed in a one on one, moderator guided interview for clarity and comprehension of the content and purpose of each piece. Findings from this user testing allowed for the improvement of the tools' content and format to enhance comprehension of the product's risks and how to manage them.

- **HCP/Prescriber checklist:**

What is it?	**A checklist to be completed by HCPs at the initiation of voriconazole treatment**
What is its purpose?	To remind HCPs about the risks of phototoxicity, hepatotoxicity and Skin SCC. To remind HCPs about monitoring liver function (particularly useful for the out-patient setting, since hospitalised patients are already closely monitored) and dermatological evaluation on a systematic and regular basis whenever Vfend is continued despite the occurrence of phototoxicity-related lesions, as described in the SmPC. To remind HCPs about appropriate usage of voriconazole and management of patients with underlying hepatic impairment and those developing hepatic injury. To encourage HCPs to discuss/educate the patient/care giver regarding the risks of phototoxicity, hepatotoxicity and SCC, as well as the need for monitoring liver function and dermatological consultation at regular intervals as described in the SmPC. To remind HCPs to provide a Patient Alert Card to the patient.
Target audience	HCPs in hospitals and the outpatient setting involved in treating patients with voriconazole.
Format(s) of the tool	Hard copy.
Distribution channel(s)	Hard copy distribution to HCPs.

- **Guide for healthcare professionals (HCP Q&A Brochure):**

What is it?	A detailed document in Question & Answer (Q&A) format to provide key information for HCPs pertaining to the use of voriconazole and phototoxicity, hepatotoxicity and SCC risks.
What is its purpose?	To advise HCPs on the risks of phototoxicity, hepatotoxicity and SCC with voriconazole. To educate and remind HCPs to conduct liver function and refer for dermatological evaluation on a regular basis as described in the SmPC. To educate HCPs about other risk minimisation measures i.e. the HCP Checklist and the Patient Alert Card. To remind HCPs to report any suspected adverse reactions.
Target audience	HCPs in hospitals and the outpatient setting who are potentially involved in the treatment with voriconazole.
Format(s) of the tool	Hard copy brochure.
Distribution channel(s)	Hard copy distribution.

- **Patient alert card:**

What is it?	**A small card to be carried by patients, predominately for the outpatient setting.**
What is its purpose?	To remind patients to avoid prolonged exposure to direct sunlight during voriconazole treatment and to inform HCPs if experiencing relevant skin abnormalities. To provide contact information of patient, treating physician and treatment centre.
Target audience	Patients and care givers.
Format(s) of the tool	Hard copy version of the Patient Alert Card.
Distribution channel(s)	Hard copy.

Implementation of the Additional Risk Minimisation Activities

These additional risk minimisation activities were designed to take into account the different clinical practice settings (inpatient and outpatient). The distribution of the materials started in April 2014 across 33 countries* (Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway,

* Including the ex 28 EU member states

Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, and UK.) Once local Health Authority approval was obtained, the RM tools were mailed to the country within 4 weeks. Additionally, in some of the countries, depending on local rules and regulations, the RM tools were posted to various webpages, including local Pfizer country offices and local National Health Authorities.

Table 1 below presents aRMM tools distribution metrics including the date when the aRMM tools where distributed to the local Health Authority for approval, when the aRMM tools were mailed, number of HCPs who were mailed the tools and the number and proportion of returned envelopes as well as the date when the evaluation survey started in the 10 countries where the evaluation survey was conducted: UK, France, Austria, Ireland, Denmark, Germany, Spain, Italy, Netherlands and Hungary.

Table 1. RM Tools Distribution and Study Country Timelines

Study Country	Date RM Tools Submitted to Local Health Authority	Date RM Tools Mailed to HCPs	HCPs Mailed RM tools (n)	Returned Envelopes with RM tools n (%)	Survey Open Date*
UK	January 2014	April 2014	4,852	76 (1.6)	September 2015
France	January 2014	April 2014	6,253	30 (0.5)	September 2015
Austria	June 2014	August 2014	377	6 (1.6)	October 2015
Ireland	June 2014	August 2014	317	13 (4.1)	October 2015
Denmark	June 2014	December 2014	886	24 (2.7)	December 2015
Germany	June 2014	November 2014	3,154	10 (0.3)	December 2015
Spain	June 2014	December 2014	4,857	34 (0.7)	December 2015
Italy	June 2014	October 2014	10,545	127 (1.2)	December 2015
Netherlands	June 2014	November 2014	3,624	10 (0.3)	December 2015
Hungary	June 2014	September 2014	889	3 (0.3)	December 2015

**Due to the varying start dates for data collection, the actual duration of the survey window in each country varied but was a minimum of 60 days.*

Core Development of the HCP Checklist and the Other Risk Minimisation Tools

The risk minimisation tools were designed to be primarily available to HCPs via a paper-based distribution system. In addition several Health Authorities (EMA, MHRA, and ANSM) have included PDF copies of the materials on their websites for download.

The risk minimisation tools were designed to be useful and easy to use, to encourage high uptake of the voluntary tools. The HCP Checklist served as a core tool functioning as an educational tool and a reminder of the screening and prescribing process for prescribers.

Finalisation and Local Adaptation of the Tools and Other Materials

The voriconazole risk minimisation tool prototypes were submitted to local Heath Authorities for review and tailored for any local rules and regulations. The tools have been available in the local languages of the countries in which they have been distributed.

Removal of additional risk minimisation activities

To ensure that the risks of phototoxicity, hepatic toxicity and SCC of the skin are adequately managed, further risk minimisation activities were performed beginning in April 2014. These activities included aRMMs which had the following components: HCP Checklist, HCP Question & Answer Brochure, and Patient Alert Card. However, no clear conclusion could be drawn on the effectiveness of these aRMMs.

Available data from PASS A1501102 which evaluated the effectiveness of additional risk minimisation measure aimed at reducing the risks of phototoxicity, SCC of the skin and hepatic toxicity in patients receiving voriconazole suggested that the source for HCPs knowledge about the risks with voriconazole is not clearly linked to the aRMM. Furthermore, study A1501103, a non-interventional, retrospective PASS designed to monitor selected safety risks in patients receiving voriconazole in the real-world setting, particularly with long-term use (i.e. ≥180 days), did not show increased risk of hepatic disorders, phototoxicity, SCC of the skin, visual disorders and periostitis with voriconazole use or other information that would necessitate continued implementation of the educational materials.

Moreover, after an extensive literature review of relevant publications, guidelines and other resources, there is evidence that the most important recommendations included in both the routine and additional RMMs for voriconazole in relation to hepatic toxicity, SCC and phototoxicity have been integrated into routine clinical practice, in particular in the European region. Since the SmPC remains the most important routine RMM, it currently clearly communicates all relevant pieces of safety information to prescribers and therefore HCP-focused aRMMs are not expected to provide further significant awareness to the prescribers regarding these well-known risks.

The MAH therefore proposed to remove the HCP educational materials from the RMP and keep the Patient Alert Card as proposed by EMA in the RSI received in September 2022 (Procedure No. EMEA/H/C/WS2270). This proposal was accepted by EMA in the Updated Assessment Report dated 05 January 2023 as part of the same procedure.

Current Additional Risk Minimisation Measures

Patient Alert Card for Phototoxicity and SCC

- Reminds patients of the risk of phototoxicity and skin SCC during voriconazole treatment.

- Reminds patients when and how to report relevant signs and symptoms of phototoxicity and skin cancer.

- Reminds patients to take steps to minimize the risk of skin reactions and skin SCC (by avoiding exposure to direct sunlight, use of a sunscreen and protective clothing) during voriconazole treatment and inform HCPs if they experience relevant skin abnormalities.