EU RISK MANAGEMENT PLAN FOR CRESEMBA

(ISAVUCONAZOLE)

Document version:	11.0
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RMP version

RMP Version number:	11.0
Data lock point for this RMP:	31 July 2023
Date of final sign off:	14 June 2024
Procedure number:	EMEA/H/C/002734/X/0042/G

Rationale for submitting an updated RMP

During procedure EMEA/H/C/002734/X/0042/G, the PRAC Rapporteur requested an update to Part VI, which has accordingly now also been updated to include the indication for paediatric patients. At Day 195 of the procedure, the Rapporteur requested reduction of the dose for paediatric patients aged 1 to < 3 years to 5.4 mg/kg, and provision of a better-tailored dosage advice for paediatric patients aged 6 years and older with a bodyweight of 32 to 36 kg treated with oral isavuconazole. The revised dosing scheme is reflected in PART I. It remains the case that no additional risk minimisation measures or activities are planned.

Summary of significant changes in this RMP

A summary of the significant changes implemented in Version 11.0 of this EU RMP is provided in the table below:

Part **Part / Module**	**Changes made in the EU-RMP from Version 10.0 to Version 11.0**
PART I: Product(s) overview	For intravenous administration: Reduced dosing recommendation for paediatric patients aged 1 year to less than 3 years. For oral administration: Addition of dosage advice for paediatric patients aged 6 years and older with a bodyweight of 32 to 36 kg.
PART II: Module SI: Epidemiology of the Indications and target populations	No changes.
PART II: Module SII: Non-Clinical part of the Safety Specification	No changes.
PART II: Module SIII: Clinical trial exposure	No changes.
PART II: Module SIV: Populations not studied in clinical trials	No changes.
PART II: Module SV: Post-authorisation experience	No changes.
PART II: Module SVI: Additional EU requirements for the safety specification	No changes.

Part **Part / Module**	**Changes made in the EU-RMP from Version 10.0 to Version 11.0**
PART II: Module SVII: Identified and Potential Risks	No changes.
PART II: Module SVIII: Summary of Safety Concerns	No changes.
PART III: Pharmacovigilance Plan (including post-authorisation safety studies)	No changes.
PART IV: Plans for post-authorisation efficacy studies	No changes.
PART V: Risk-minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	No changes.
PART VI: Summary of RMP	No changes.

Other RMP versions under evaluation:

No other RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number:	9.0
Approved with procedure:	EMEA/H/C/002734/II/0035/G
CHMP opinion date:	8 July 2021

QPPV name:

PrimeVigilance GmbH
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60528 Frankfurt
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QPPV signature: The content of this RMP has been reviewed and approved by the Marketing Authorisation Holder's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
AFT	Antifungal therapy
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
AmB	Amphotericin B
AML	Acute myeloid leukaemia
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATG	Antithymocyte Globulin
BCSH	British Committee for Standards in Haematology
BEACOPP	Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone
CFR	Case-fatality rates
CHMP	Committee for Medicinal Products Human Use
CI	Confidence interval
CLcr	Creatinine clearance
CLL	Chronic Lymphocytic Leukaemia
CYP	Cytochrome P450
DIBD	Development International Birth Date
DLP	Data lock point
DRV	Darunavir
EACS	European AIDS Clinical Society
EEA	European Economic Area
EFV	Efavirenz
EPAR	European Public Assessment Report
ESRA	End-stage renal disease
EU	European Union
FCR	Fludarabine
FDA	Food and Drug Administration
FTC	Emtricitabine

G-CSF	Granulocyte Colony-Stimulating Factor
GITMO	Gruppo Italiano Trapianto Midollo Osseo
GVHD	Graft Versus Host Disease
HHS	US Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
HLA	Human Leukocyte Antigen
HSCT	Haematopoietic Stem Cell Transplant
IA	Invasive aspergillosis
ICU	Intensive care unit
IEC	Independent Ethics Committee
IFD	Invasive fungal disease
IFI	Invasive fungal infections
IMD	Invasive mould disease
IMI	Invasive mould infections
INN	International Non-Proprietary Name
IV	Intravenous
MAA	Marketing authorisation application
MIC	Minimum inhibitory concentration
N/A	Not applicable
NIS	Nationwide Inpatient Sample
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleos(t)ide Reverse Transcriptase Inhibitor
OR	Odds ratio
PATH	Prospective Antifungal Therapy (Alliance)
PK	Pharmacokinetic
PL	Package Leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible for Pharmacovigilance
QTcF	QT interval corrected by Fridericia's Correction Formula
RAL	Raltegravir
RMP	Risk Management Plan
RPV	Rilpivirine

RT	Radiotherapy
SCAR	Severe cutaneous adverse reaction
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SOT	Solid organ transplant
TDF	Tenofovir
TdP	Torsades de pointes
TEAE	Treatment-emergent adverse event
UK	United Kingdom
US/USA	United States of America

PART I: PRODUCT OVERVIEW

Active substance(s) (INN or common name)	Isavuconazole (as isavuconazonium sulfate)
Pharmacotherapeutic group(s) (ATC Code)	Antimycotics for systemic use, triazole- and tetrazole derivative (ATC code: J02AC05).
Marketing Authorisation Holder	Basilea Pharmaceutica Deutschland GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Cresemba
Marketing authorisation procedure	Centralized Procedure
Brief description of the product:	**Chemical class:** Isavuconazonium sulfate (BAL8557) is the water-soluble prodrug of the active triazole isavuconazole **Summary of mode of action:** After administration, the prodrug isavuconazonium sulfate is rapidly converted by plasma esterases into the active moiety isavuconazole (BAL4815) and the inactive cleavage product (BAL8728). Isavuconazole demonstrates a fungicidal effect by blocking the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450-dependent enzyme lanosterol 14-alpha-demethylase, responsible for the conversion of lanosterol to ergosterol. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane, thus weakening the structure and function of the fungal cell membrane. **Important information about its composition:** None
Hyperlink to the Product Information:	https://www.ema.europa.eu/en/medicines/human/EPAR/cresemba

<table>
<tr><td>Indication(s) in the EEA</td><td><u>Current</u>:
Cresemba is indicated in adults for the treatment of:
• Invasive aspergillosis
• Mucormycosis in patients for whom amphotericin B is inappropriate
<u>Proposed</u>:
Cresemba is indicated in adults and paediatric patients 1 year of age and older for the treatment of:
• Invasive aspergillosis
• Mucormycosis in patients for whom amphotericin B is inappropriate</td></tr>
<tr><td>Dosage in the EEA</td><td><u>Current</u>:
Loading dose: Therapy must be initiated with the specified loading dose regimen of either intravenous or oral isavuconazonium sulfate. The recommended loading dose is 1 vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) or 2 capsules every 8 hours for the first 48 hours (6 administrations in total).
Maintenance dose: The recommended maintenance dose is or 1 vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) or 2 capsules once daily, starting 12 to 24 hours after the last loading dose.
<u>Proposed</u>:
<u>Intravenous dosing</u> - Detailed information on dosage recommendations is provided in the following table:
<table>
<tr><td></td><td>Loading dose (every 8 hours for the first 48 hours)[1]</td><td>Maintenance dose (once daily)[2]</td></tr>
<tr><td colspan="3">Paediatric patients aged from 1 year to less than 18 years</td></tr>
<tr><td>Bodyweight < 37 kg</td><td>5.4 mg/kg isavuconazole</td><td>5.4 mg/kg isavuconazole</td></tr>
<tr><td>Bodyweight ≥ 37 kg</td><td>200 mg isavuconazole</td><td>200 mg isavuconazole</td></tr>
<tr><td>Adults</td><td>200 mg isavuconazole</td><td>200 mg isavuconazole</td></tr>
<tr><td colspan="3">[1] Six administrations in total.
[2] Maintenance dose: Starting 12 to 24 hours after the last loading dose.</td></tr>
</table>
<u>Oral dosing</u> – Adults:
Loading dose: The recommended loading dose is two 100 mg capsules (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours (6 administrations in total).
Maintenance dose: The recommended maintenance dose is two 100 mg capsules (equivalent to 200 mg of isavuconazole) once daily, starting 12 to 24 hours after the last loading dose.
<u>Oral dosing</u> - Detailed information on dosage recommendations in children from 6 years up to 18 years is provided in the following table:</td></tr>
</table>

	<table><tr><th>Bodyweight (kg)</th><th>Loading dose (every 8 hours for the first 48 hours)</th><th>Maintenance dose (once daily)[1]</th></tr><tr><td>16 kg to < 18 kg</td><td>Two 40 mg capsules</td><td>Two 40 mg capsules</td></tr><tr><td>18 kg to < 25 kg</td><td>Three 40 mg capsules</td><td>Three 40 mg capsules</td></tr><tr><td>25 kg to < 32 kg</td><td>Four 40 mg capsules</td><td>Four 40 mg capsules</td></tr><tr><td>32 kg to < 37 kg</td><td>One 100 mg capsule and two 40 mg capsules</td><td>One 100 mg capsule and two 40 mg capsules</td></tr><tr><td>≥ 37 kg</td><td>Five 40 mg capsules or two 100 mg capsules</td><td>Five 40 mg capsules or two 100 mg capsules</td></tr><tr><td colspan="3">[1] Maintenance dose: Starting 12 to 24 hours after the last loading dose.</td></tr></table> The maximum of any individual loading or daily maintenance dose to be administered to any paediatric patient is 200 mg isavuconazole.
Pharmaceutical form(s) and strengths	**<u>Current:</u>** Isavuconazole is available as: • Powder for concentrate for solution for infusion; each vial containing 200 mg of isavuconazole (as 372.6 mg of isavuconazonium sulfate). • Hard capsules containing 100 mg of isavuconazole (as 186.3 mg of isavuconazonium sulfate). **<u>Proposed</u>:** Isavuconazole is available as: • Powder for concentrate for solution for infusion; each vial containing 200 mg of isavuconazole (as 372.6 mg of isavuconazonium sulfate). • Hard capsules containing 100 mg of isavuconazole (as 186.3 mg of isavuconazonium sulfate). • Hard capsules containing 40 mg of isavuconazole (as 74.5 mg of isavuconazonium sulfate).
Is/will the product be subject to additional monitoring in the EU?	No

ATC = Anatomical Therapeutic Chemical; EEA = European Economic Area; EU = European Union; INN = International Non-Proprietary Name; N/A = Not Applicable; RMP = Risk Management Plan

PART II: SAFETY SPECIFICATION

In this Risk Management Plan (RMP), isavuconazonium sulfate (BAL8557,) refers to the prodrug for the active moiety isavuconazole (BAL4815). Throughout this RMP, the *in vivo* administered compound is referred to as "isavuconazole," with the knowledge that isavuconazole is the active moiety, and dosages are expressed in mg equivalents of the active drug isavuconazole. *In vitro* studies, unless otherwise indicated, and plasma concentrations refer to the active moiety, isavuconazole, and not to isavuconazonium sulfate.

The isavuconazole development programme was designed to support the use of intravenous (IV) and oral administration of the water-soluble prodrug of the active moiety isavuconazole.

PART II: MODULE SI – EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

Invasive fungal infections (IFIs) are a cause of morbidity and mortality in critically ill patients (**Sipsas 2012, Labner 2019, Holzheimer 2002, Jorda-Marcos 2007, Pfaller 2007, Mahfouz 2003**). Factors that influence the incidence and severity of IFIs include immunosuppressive agents, broad-spectrum antibiotics, and antineoplastic agents (**Badiee 2014**). The population at risk includes solid organ transplant and haematopoietic stem cell transplant recipients, intensive care unit (ICU) and surgical patients (**Holzheimer 2002, Mahfouz 2003, Dimopoulos 2003, Meersseman 2007, Peres-Bota 2004**). Historically, *Candida* species have been the most common IFI pathogen in critically ill patients; however, in recent years the *Aspergillus* species have become increasingly important pathogens (**Lass-Florl 2009**).

SI.1 Indication: Invasive aspergillosis

The sections below summarise the incidence and prevalence, demographic profile, main treatment options, mortality and morbidity, and co-morbidities for the target population of invasive aspergillosis (IA).

Incidence

Europe

There are limited data from Europe on the incidence of IA. Overall, the incidence of IA varies according to underlying diseases, pathogen, and geographic location (**Perkhofer 2010**, **Lortholary 2011**, **Pagano 2006**).

Lortholary and colleagues conducted a prospective surveillance programme (2005–2007) to assess the incidence of IA at 12 French academic hospitals. The study included patients of all ages, regardless of underlying diagnosis. Admissions per hospital and transplantation procedures were obtained. The diagnostic investigations and therapeutic management followed local practices. Only proven and probable IA according to 2002 European Organisation for Research and Treatment of Cancer/Mycoses Study Group criteria were considered. With 424 case-patients included, the median incidence per hospital was

0.271 per 1000 admissions (range 0.072–0.910). The study reported no significant alteration of incidence and seasonality over time (**Lortholary 2011**).

Perkhofer *et al* conducted a prospective, observational, multicentre study to assess the incidence, diagnosis, epidemiology, and outcome of invasive mould infections (IMIs) reported to the Nationwide Austrian *Aspergillus* Registry. In total, 186 cases were recorded, corresponding to an annual incidence of 42 cases per 1000 patients at risk (i.e., critically ill patients, e.g., those admitted for acute myeloid leukaemia [AML], organ transplant, etc.) or 2.36 cases per 100,000 inhabitants. Patients with AML (34%) and lung transplant recipients (17%) were at highest risk of IMI, followed by a mixed population with impaired immunity (14%). In total, out of 186 cases, 34%, 30% and 36% were proven, probable and possible cases of IMI. Predominant pathogens were *Aspergillus* spp. (67%) (**Perkhofer 2010**). In a retrospective cohort study of 11,802 cases in Italy with haematologic malignancies between 1999 and 2003, Pagano *et al* reported an incidence of IFI of 4.6% (538 cases); of which, 346 were caused by moulds (incidence of 2.9%) and 192 cases were caused by yeasts (incidence of 1.6%). Of those cases caused by moulds, 90% (310/346) were due to *Aspergillus* species (incidence 2.6%) (**Pagano 2006**).

United States

Webb *et al* used all available records in the Intermountain Healthcare Enterprise Data Warehouse from 2006 to 2015 to assess the incidence of IFI. A total of 3374 IFI episodes occurred in 3154 patients. The mean incidence was 27.2 cases/100 000 patients per year, with a mean annual increase of 0.24 cases/100 000 patients. IA accounted for 8.9% of all fungal infections. The median age was 55 years, and paediatric cases accounted for 13%; 26.1% of patients were on immunosuppression, 14.9% had autoimmunity or immunodeficiency, 13.3% had active malignancy, and 5.9% were transplant recipients (**Webb 2018**).

Neofytos *et al* conducted a retrospective observational study to evaluate the incidence of proven and probable IMIs among all adult Haematopoietic Stem Cell Transplant (HSCT; n = 1983) and solid organ transplant recipients (n = 2,557) from 2000 to 2009. In total, 106 patients with one IMI were identified. Of those with IMI, the most common IMI was IA (69/106; 65.1%). Among HSCT patients, the overall proportion of IMI was 0.2% (2/874) and 3.8% (42/1,109) in autologous and allogeneic HSCT recipients, respectively; the overall proportion of IA among allogeneic HSCT recipients was 2.5%. The overall incidence rate of IMI among lung, kidney, liver, and heart transplant recipients was 49, 2, 11, and 10 per 1000 person-years, respectively. The observed rate of IMI among human leukocyte antigen (HLA)-matched unrelated and haploidentical HSCT recipients increased from 0.6% annually to 3.0% after bronchoscopy initiation ($P < 0.05$) (**Neofytos 2013**).

The Prospective Antifungal Therapy Alliance (PATH Alliance®) performed prospective surveillance of IFIs among patients hospitalised at 25 medical centres in North America between 2004 and 2008, collecting information on the epidemiology, diagnosis, treatment, and mortality rates of IFIs. In total, 7526 IFIs were identified in 6845 patients. *Candida* spp. (73.4%) were the most common pathogens, followed by *Aspergillus* spp. (13.3%), and other yeasts (6.2%) (**Azie 2012**).

Tong *et al* reported on hospital discharge data for patients with a primary or secondary diagnosis of aspergillosis extracted from the 2003 Nationwide Inpatient Sample (NIS) and the fiscal year 2003 Medicare Provider Analysis and Review file. The data on patient demographics, length of stay, hospital charges, estimated costs, and reimbursement levels were reported. The NIS contains a total of over 38 million projected hospital discharges. From these, 10,400 aspergillosis cases were identified resulting in a United States (US) incidence rate of 36 per million per year (**Tong 2009**).

Warnock reported on a number of retrospective analyses of large databases from US hospital discharge and death records. These analyses showed that the incidence of IA as a hospital discharge diagnosis has increased since 1976. By 1996, there was an estimated 10,190 aspergillosis-related hospitalisations annually in the US resulting in 1,970 deaths. These cases represented 38 hospitalisations per million of all hospital discharges (**Warnock 2007**).

Marr *et al* examined the medical records of 5,589 patients who underwent HSCT at the Fred Hutchinson Cancer Research Centre from 1985 through 1999 to determine the incidence of mould infection. The incidence of proven and probable invasive *Aspergillus* infection increased from just over 4% of patients in 1990 to almost 12% in 1998 in allograft patients, and from just over 0% to about 5% in autograft patients (**Marr 2002**).

Japan

According to a paper by Izumikawa, the estimated incidence of chronic pulmonary aspergillosis was 1 per 100,000 patients in 2016, affecting 1,308 people annually. Of those, 1255 were observed in cancer or transplanted patients and 103 in intensive care units (**Izumikawa 2016**). No data on the incidence of invasive aspergillosis infection were available for the Japanese population.

Prevalence

Prevalence data of IA are limited and the precise estimate of global prevalence for IA remains unknown. However, a number of studies reported a prevalence ranging between 0.2% (in the general population) and 35.8% (in patients with acute or chronic liver failure).

Europe

Arsenijevic *et al*, in a study conducted to estimate the burden of serious fungal infections or disease, estimated that in Serbia within the overall number of fungal infections, there were 619 cases of IA (0.4%) in 2016. Despite the study methodology, based on estimates and assumption, the results obtained from this study is in alignment with the findings of other studies (**Arsenijevic 2018**).

Bongomin *et al* completed a very extensive review on global and multinational prevalence of fungal disease and found that in Greece IA ranged between 1% and 10% according to the underlying condition (1% in patients with kidney problems, 1.3% of patients with chronic obstructive pulmonary disease at admission, 4% in lung or liver transplanted patients, 6% in those that had heart transplant, 8% HSCT and 10% in AML). Closely matching data were estimated for Ireland, Belgium, Denmark, Germany, United Kingdom (UK), Austria, Spain, and Portugal (**Bongomin 2017**).

United States

Zilberberg *et al* in a retrospective cohort study aimed at exploring the epidemiology and outcomes of hospitalizations with IA in the US, found that upon 148,533,858 patients discharged from 2010 and 2013 in the NIS database, 155,888 (0.2%) had a diagnosis of IA. Patients with IA were more likely to be male (50.9% in the IA vs 46.7% in non-IA group; P <.001) and African American (15.3% vs 12.5%; P <.001) (**Zilberberg 2018**).

Japan

Shimoidara *et al* extracted the documented cases of fungal infection from autopsy records kept from 1955 to 2006. A total of 411 cases of IFIs were extracted from 10,297 autopsy records. During the 52-year period covered by the investigation, the overall prevalence of IFIs was 4.0%. The cumulative prevalence of IA increased from 1.1% to 2% during the study period. Overall, 105 cases of IA were recorded, accounting for nearly 26% of overall fungal infections (**Shimoidara 2012**).

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

Europe

In a prospective surveillance programme (2005 – 2007) conducted to assess the incidence of IA in 12 French academic hospitals, including patients of all ages, regardless of underlying diagnosis, 424 case-patients were identified, of which 31 were children (i.e., < 18 years) and 393 adults (62% men and 38% women, mean age was 56 years) (**Lortholary 2011**). Among the 393 adults (62% men, 56 years [16 – 84 years]), 15% had proven IA, 78% haematological conditions, and 92.9% had lung involvement. Acute leukaemia (34.6%) and allogeneic stem cell transplantation (21.4%) were major host factors, together with chronic lymphoproliferative disorders (21.6%). The other risk host factors consisted of solid organ transplantation (8.7%), solid tumours (4.3%), systemic inflammatory diseases (4.6%) and chronic respiratory diseases (2.3%). Serum galactomannan tests were more often positive (> 69%) for acute leukaemia and allogeneic stem cell transplantation than for the others (< 42%). When positive (n = 245), cultures mainly yielded *Aspergillus fumigatus* (79.7%) (**Lortholary 2011**).

United States

Neofytos *et al* conducted a retrospective observational study to evaluate the epidemiology of proven and probable IMI. Mean age of the population sampled was 53 years, 33.3% were females and 90.5% Caucasians. In HSCT recipients, the overall rate of IMI was 0.2% (2 of 874) and 3.8% (42 of 1109) in autologous and allogeneic HSCT recipients, respectively. The overall rate of IA among allogeneic HSCT recipients was 2.5% (n = 28). Underlying diseases were acute leukaemia (23.8%), chronic leukaemia (23.8%), lymphoma (23.8%), multiple myeloma (19%), and myelodysplastic syndrome (4.8%) (**Neofytos 2013**).

In the PATH Alliance registry in North America, IFIs occurred in all age groups and genders. The mean age was 52.3 years (range 0.0 – 97.0 years). The majority of patients were male (~56%), and Caucasian (68%). Of 6,845 patients, the majority were in general medicine (n = 4,170, 60.9%), surgical non-transplant (n = 2,098, 30.7%), haematologic malignancy (n = 1,235, 18.0%), solid tumour (n = 999, 14.6%), solid organ transplant (n = 979, 14.3%), HSCT (n = 509, 7.4%), Human Immunodeficiency Virus (HIV)/Acquired Deficiency Syndrome (AIDS) (n = 324, 4.7%), neonatal ICU (n = 64, 0.9%), and inherited immunodeficiency disorder (n = 30, 0.4%) (**Azie 2012**).

Japan

Due to the limited data on the epidemiology of IA in the Japanese population, no significant data on the age and gender stratification and risk factors for the disease were identified.

The main existing treatment options

Europe

In ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukaemia and haematopoietic stem cell transplant patients; isavuconazole appears to be as effective as voriconazole for the treatment of IA and has a better safety profile (**Tissot 2017**). Therefore, a grade A I for strength of recommendation and quality of evidence respectively, similar to the grading for voriconazole has been given to isavuconazole. Liposomal amphotericin B (AmB) is an alternative carrying a BI grading. Other monotherapy alternatives with lower gradings include other formulations of AmB, caspofungin and itraconazole. Recommendations for salvage therapy are primarily AmB (both liposomal and lipid complex formulations, then caspofungin, posaconazole or voriconazole).

United States

In the Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America, triazoles are named as the preferred agents for treatment and prevention of IA in most patients (*strong recommendation; high-quality evidence*) (**Patterson 2016**). Specific agents recommended for primary treatment are voriconazole (*strong recommendation; high-quality evidence*). Alternative therapies include liposomal AmB (*strong recommendation; moderate-quality evidence*), isavuconazole (*strong recommendation; moderate-quality evidence*), or other lipid formulations of AmB (*weak recommendation; low-quality evidence*).

For salvage therapy, agents include lipid formulations of AmB, micafungin, caspofungin, posaconazole, or itraconazole. The use of a triazole as salvage therapy should take into account prior antifungal therapy, host factors, pharmacokinetic considerations, and possible antifungal resistance (*strong recommendation; moderate-quality evidence).*

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Lin *et al* conducted a systematic review of the literature to assess aspergillosis case-fatality rates (CFR). After excluding the studies with insufficient information, the authors assessed CFR according to age. CFR ranged between 59.2% in patients between 51 and 60 years of age and 68.2% in the younger age group (< 20). The study population included 373 patients and of those, 72% were male and patient age ranged between 3 and 91 years (mean age 44.2 years). The most commonly reported underlying disease was malignancy (44.2%; 858 of 1941), of which lymphoma and leukaemia constituted the large majority (42.6%). Transplants (38.7%) and lung diseases (20%), which included pneumonia due to cytomegalovirus, bacterial pneumonia, and tuberculosis, were also common underlying conditions. The aspergillosis CFR varied significantly according to underlying disease or comorbidity (**Lin 2011**).

Europe (including global data)

Without rapid and appropriate systemic anti-mould therapy, there is almost 100% mortality (**Denning 1996**). A review by Hadrich *et al* reported that mortality rate of patients with IA ranged between 80–95% for those without treatment and was 29% or 42% with treatment (voriconazole or amphotericin B, respectively) (**Hadrich 2012**). Singh and Paterson reviewed the epidemiology of IA in transplant patients and reported the following incidence rate and mortality rate ranges (**Singh 2005**):

- HSCT: incidence rates 0.08–2.6% (autologous) and 3.6–10.3% (allogeneic), with 67–80% mortality rate
- Liver transplant: incidence rate 1–8%, with 83–88% mortality rate
- Lung transplant: incidence rate 3–15%, with overall mortality rate of 52–55%, but the incidence rate ranged from 24–29% in patients with trachea-bronchial infections and from 67–82% in those with invasive pulmonary infections
- Heart transplant: incidence rate 3.3–14%, with mortality rate of 53–78% in those with invasive pulmonary aspergillosis and 90% for disseminated infections
- Kidney transplant: incidence rate 0.7–4%; 75–80% mortality (**Singh 2005**).

United States

The overall one-year mortality rate for all mould infections among patients who underwent HSCT at the US Fred Hutchinson Cancer Research Centre from 1985 through 1999 was approximately 80% (**Marr 2002**).

In a review of PATH Alliance registry study (in North America), Azie *et al* reported the 12-weeks post-diagnosis survival among patients with IA to be 66.3% (equivalent to mortality rate of 34%) (**Azie 2012**).

Brakhage reported that mortality from IA ranges from 30–90% and remains the leading cause of death in patients with acute leukaemia and liver transplantation (**Brakhage 2005**).

Japan

No data on the mortality of IA in the Japanese population were identified.

Important co-morbidities

Important co-morbidities are the same for both indications and are presented in Section SI.3.

SI.2 Indication: Mucormycosis

Mucormycosis is a fungal infection caused by the filamentous fungi of the *Mucorales* order of the class of Zygomycetes. Zygomycosis refers to a fungal infection caused by fungi of the class Zygomycetes (consisting of the orders *Mucorales* and *Entomophthorales*). Since the majority of human cases of zygomycosis are caused by *Mucorales* fungi, the terms "mucormycosis" and "zygomycosis" are used interchangeably in the literature (**Petrikkos 2012**), and hereafter are described as "mucormycosis" in this document.

Incidence

Data on incidence estimates for mucormycosis are very limited. However, a number of studies reported an incidence ranging between 0.43 and 12 per 100,000 in-hospital admissions.

Europe

Guinea *et al* recorded the incidence of mucormycosis and clinical and microbiological data of infected patients in a large Spanish hospital between 2007 and 2015 and observed that incidence increased from 1.2 to 3.3 per 100,000 hospital admissions (**Guinea 2017**).

Estimates of annual incidence rates include: 0.4 cases per million population and 0.62 per 100,000 hospital admissions (based on a population-based study in Spain during 2005) (**Torres-Narbona 2007**), and 1.2 cases per million (based on data from 2006 in France) (**Bitar 2009**).

Analysis of hospital records in France also showed an increasing incidence for mucormycosis from 0.7 per million in 1997 to 1.2 per million in 2006 ($P < 0.001$), which constituted a yearly increase of approximately 7.4% (**Bitar 2009**).

In a retrospective cohort study presented above of 11,802 patients in Italy with haematologic malignancies between 1999 and 2003, Pagano *et al* reported 14 cases of Zygomycetes (incidence of 0.1%) and 15 cases of Fusarium species (incidence of 0.1%) (**Pagano 2006**).

In a prospective observational study described above, out of 186 cases of IMI (representing 2.36 cases per 100,000 inhabitants), incidence of Zygomycetes was 28% (**Perkhofer 2010**).

United States

In the studies of Webb *et al*, also cited above, the mean incidence of *Mucorales* was 0.3 per 100000 patients in the period 2006 – 2015, accounting for 1.1% of cases. Male gender was disproportionately represented (72.2%). Diabetes mellitus was present in 36.1%,

haematological malignancy in 19.4%, and HSCT in 11.1%; 61.1% of patients were on immunosuppressive medications, of which corticosteroids were predominant (41.7%). Lymphopenia or neutropenia directly preceded diagnosis in 38.9% and 27.8% of cases, respectively. Sinus (38.9%) and lung (27.8%) were the most frequent sites of infection. Breakthrough infection despite prophylaxis (most often with an echinocandin) occurred in 33.3% of cases (**Webb 2018**). Annual US incidence rate was estimated as 1.7 cases per million population (based on data collected from 1992–1993) (**Wingard 2006**).

According to the PATH Alliance® (data collected in North America from 2004 to 2008), of the 7,526 IFIs identified in 6,845 patients, the following non-*Aspergillus* mould species were reported: *Mucormycetes* spp. (n = 121, 1.6%), Fusarium spp. (n = 65, 0.9%), and Cryptococcus spp. (n = 340, 4.5%) (**Azie 2012**). Of 5,589 patients who underwent HSCT at the Fred Hutchinson Cancer Research Centre from 1985 through 1999 (study also described above for IA), the incidence of non-*Aspergillus* infections was: 31 (0.6%) patients with proven or probable invasive Fusarium infection, 29 (0.5%) patients with proven or probable invasive Zygomycetes infection, 10 (0.2%) patients with proven or probable invasive *Scedosporium* infection and 6 (0.1%) patients were infected with other moulds (**Marr 2002**). In a retrospective observational study (described above for IA), among the adult HSCT (n=1983) and solid organ transplant recipients (n = 2557) from 2000 to 2009, 106 patients were identified with IMI (representing incidences of 0.2% in autologous HSCT patient, 3.8% in allogeneic HSCT recipients), 9/106 (8.5%) had mucormycosis (**Neofytos 2013**).

Japan

According to Izumikawa *et al*, the estimated incidence of mucormycosis was 0.1 per 100,000 patients in 2016, affecting 254 people annually (**Izumikawa 2016**).

Prevalence

Europe

Mucormycosis is considered to be a rare disease (i.e., affecting ≤ 1 person per 2,000) on the Orphanet orphan drug registry (**Orphanet 2013**). The 2011 AMR data reported the following prevalence based on patients who received systemic antifungal treatment during hospital stay for mucormycosis: 664 cases in UK, 386 cases in France, no cases in Germany, 380 cases in Italy, and 262 cases in Spain (**AMR 2011**).

United States

Kontoyiannis *et al*, reported on prevalence of mucormycosis in a retrospective study using the Premier Perspective™ Comparative Database, with more than 560 participating hospitals covering 104 million patients (January 2005–June 2014). The prevalence of mucormycosis-related hospitalisations was estimated as 0.12 per 10,000 discharges during January 2005–June 2014. It increased to 0.16 per 10,000 discharges if the definition of mucormycosis was relaxed to not require the use of AmB or posaconazole. The median length of stay was 17 days, with 23% dead at discharge; readmission rates were high, with 30 and 37% of patients readmitted within one and three months of discharge, respectively (**Kontoyiannis 2016**).

Mucormycosis is considered to be a rare disease by the US National Institute of Health Office of Rare Diseases Research (National Institute of Health 2014). The 2011 AMR data reported US prevalence for mucormycosis to be 2788 cases, based on patients who received systemic antifungal treatment during hospital stay (**AMR 2011**).

Japan

Shimoidara *et al* (2012) extracted the documented cases of fungal infection from autopsy records kept from 1955 to 2006. A total of 411 cases of IFIs were extracted from 10,297 autopsy records. During the 52-year period covered by the investigation, the overall prevalence of IFIs was 4.0%. The cumulative prevalence of mucormycosis showed no significant fluctuation during the period and overall, where counted 21 cases of mucormycosis, accounting for approximately 5% of the overall fungal infections and 0.2% of the overall autopsies performed (**Shimoidara 2012**).

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

Europe

Ambrosioni *et al* (2010) in a retrospective chart analysis of 55 patients reported the demographic characteristics of patients with invasive mucormycosis in Geneva, Switzerland as follows: median age 52 years (range 10–77 years), 68% female. The most frequently isolated genus was *Rhizopus* (42%), followed by *Rhizomucor* (32%), *Absidia* (16%), *Cunninghamella* (5%), and *Mucor* (5%) (**Ambrosioni 2010**).

United States

In the study contacted by Webb *et al* (2018), the male population infected with mucormycosis accounted for 72.2% of the overall population. Diabetes mellitus was present in 36.1%, haematological malignancy in 19.4%, and HSCT in 11.1%; 61.1% of patients were on immunosuppressive medications, of which corticosteroids were predominant (41.7%). Lymphopenia or neutropenia directly preceded diagnosis in 38.9% and 27.8% of cases, respectively. Sinus (38.9%) and lung (27.8%) were the most frequent sites of infection (**Webb 2018**).

Japan

Due to the limited data on the epidemiology of mucormycosis in the Japanese population, no significant data on the age and gender stratification and risk factors for the disease were identified.

The main existing treatment options

Europe

The European Confederation of Medical Mycology guidelines on the treatment of mucormycosis strongly recommends first-line treatment with high-dose liposomal amphotericin B. If pre-existing renal compromise, isavuconazole IV or posaconazole IV are recommended. Intravenous isavuconazole and intravenous or delayed release tablet posaconazole are recommended with moderate strength. Both triazoles are strongly

recommended salvage treatments. Amphotericin B deoxycholate is recommended against, because of substantial toxicity, but may be the only option in resource-limited settings (**Cornely 2019**).

United States

In the PATH Alliance registry, the majority of patients with mucormycosis were treated with a lipid formulation of amphotericin B, followed by posaconazole as the second most commonly administered drug. Treatment for other yeasts, predominately cryptococcosis, included liposomal amphotericin B, followed by fluconazole, while in approximately one-third of cases, courses of combination therapy were administered (**Azie 2012**).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Europe (including global data)

A review of literature on outcomes in patients with mucormycosis reported an overall mortality of 54%; risk factors for death included disseminated disease, renal failure, and infection with Cunninghamella species; type 1 diabetes and absence of an underlying condition at time of infection appeared to be associated with a reduced risk of death (**Roden 2005**).

Invasive mucormycosis is associated with high morbidity and mortality rates in immunosuppressed patients (**Ambrosioni 2010**). Left untreated, mucormycosis is almost always lethal and is often lethal even with appropriate medical management (**Wingard 2006**). Published mortality rates vary. A retrospective and multicentre study of 25 cases of proven mucormycosis in Spain reported an overall mortality rate of 72% (**Llorente 2011**). Among patients in Italy with haematological malignancy in the SEIFEM-2004 survey (11,802 patients admitted between 1999 and 2003), the mucormycosis-related mortality rate was reported to be 64% (**Pagano 2006**). Other studies have suggested that the mortality rate may be as high as 80% in infected transplant recipients (**Greenberg 2004**).

United States

In the study conducted by Webb *et al* (2018) already cited above, forty-two-day and 1-year crude mortality in the studied population were 27.8% and 41.7%, respectively (**Webb 2018**).

In the review of PATH Alliance registry data (North America), Azie *et al* (2012) reported the following mortality rates: mucormycosis 35%, cryptococcosis 23%, and patients with endemic mycoses 17% (**Azie 2012**).

Japan

No data on the mortality of mucormycosis in the Japanese population were identified.

SI.3 Important co-morbidities

Important co-morbidities are the same for both indications.

The following important co-morbidities were selected based on disease prevalence, severity, and public health impact relative to the target population (IA and mucormycosis), as outlined in the subsequent tables:

- Haematologic malignancy (patients who undergo bone marrow transplant) (Table 1)
- Malignancy treated with chemotherapy (Table 2)
- Bacterial sepsis (Table 3)
- HIV/AIDS (Table 4)
- Solid organ transplants (Table 5)
- Renal impairment (Table 6)
- Hepatic impairment (Table 7)
- Diabetes mellitus (Table 8)

Table 1 Epidemiology of haematologic malignancy in the target population (specifically, patients who undergo bone marrow transplant)

Indication/target population	Haematologic malignancy; specifically, patients who undergo bone marrow transplant
Incidence of co-morbidity	Incidence data of haematologic malignancy or patient that underwent bone marrow transplant in the target population, both for IA and mucormycosis were not identified.
Prevalence of co-morbidity	In a retrospective cohort study in Italy of 11,802 patients with haematologic malignancies (1999–2003), 4.6% of patients had proven or probable IFI: 2.6% with *Aspergillus* infections, 0.3% with other mould infections, and 1.6% with yeast infections including candidemia (**Pagano 2006**). A retrospective study in France conducted from 2001-2010, reported a prevalence of IFI in patients with haematologic malignancies, 4.2% has invasive aspergillosis, 10.3% had mucormycosis (**Bitar 2014**). The prevalence of haematologic malignancy among 6,845 patients treated for IFIs in the PATH Alliance registry in North America was 18.0% (**Azie 2012**). Kurosawa *et al* (2012) evaluated the incidence and treatment outcomes of 2821 patients with haematological malignancies with proven and probable IFI in 22 institutions in Hokkaido, Japan between 2006 and 2008. They reported a 47% prevalence of chemotherapy treatment alone among 38 patients diagnosed with IFIs (**Kurosawa 2012**). The Gruppo Italiano Trapianto Midollo Osseo (GITMO) prospectively registered data on 1858 consecutive patients undergoing allo-HSCT between 2008 and 2010. The cumulative incidence of proven/probable-IFDs was 5.1% at 40 days, 6.7% at 100 days, and 8.8% at 12 months post-transplantation (**Girmenia 2014**)

Indication/target population	Haematologic malignancy; specifically, patients who undergo bone marrow transplant
Mortality of co-morbidity	In the Italian cohort study of patients with haematologic malignancies described above, the overall mortality rate was 2%; IFI-attributable mortality rate was 39%, with the highest for mucormycosis (64%) followed by fusariosis (53%), and aspergillosis (42%) (**Pagano 2006**). In the GITMO study, the mortality rate at 100 days from the diagnosis of proven/probable-IFD was 46.3% (76 of 164 patients). In patients with IA, invasive candidiasis, and non-*Aspergillus*–non-*Candida* infections, it accounted for 48.5%, 39%, and 75%, respectively. Among the 76 patients who died within 100 days from the diagnosis of a proven/probable-IFD, the infection was considered the primary cause of death in 34 (44.7%), with an attributable mortality rate of 20.7% (**Girmenia 2014**). Nivoix *et al* (2008) performed a retrospective analysis of 289 cases of IA occurring in adult patients hospitalised in ICUs in a French hospital from 01 February 1997 through 30 April 2006. They reported that the 12-week disease specific survival among patients with haematologic malignancies was 64.3% (95% CI, 57.2–70.9) (**Nivoix 2008**). The 90-day mortality rate of patients with haematologic malignancies in the PATH Alliance study in North America was 51.6% (**Azie 2012**). Neofytos *et al* (2013) reported that the 12-week mortality among US allogeneic HSCT recipients with invasive mould infections was 52.4%. Predictors of mortality for allogeneic HSCT included male gender (OR: 14.4, p = 0.007) and elevated bilirubin (OR: 5.7, p = 0.04) (**Neofytos 2013**).
Main co-prescribed medicinal products	According to guidelines by the European Society for Medical Oncology, the standard treatment of patients with early CLL disease is a watch and wait strategy; chemotherapy should only be given to patients with active, symptomatic disease (**Eichhorst 2011**). In physically fit CLL patients with advanced disease, improved survival has been demonstrated following FCR as the standard first-line therapy. Combinations based on other purine analogues such as cladribine or pentostatin have shown similar activity, but it is uncertain whether they can replace fludarabine in the FCR regimen (**Eichhorst 2011**). The most recent guidelines from BCSH for the management of early stage classical HL include: 2 × ABVD and 20 Gy RT for patients with favourable early stage HL (BCSH 2014). The standard of care for unfavourable early stage HL is 4 × ABVD and 30 Gy RT. A treatment option for unfavourable early stage HL is escalated BEACOPP + 2 × ABVD and 30 Gy RT (**BCSH 2014**). Filgrastim is often the drug of choice if a G-CSF is chosen, and is typically administered at least 24 hours after chemotherapy completion (**Godwin 2013**). Before undergoing HSCT, patients are required to follow a conditioning regimen to ablate their immune system. These regimens include different combinations of busulfan, fludarabine, melphalan, cyclophosphamide, treosulfan, and total body irradiation. Additionally, patients undergoing HSCT follow an immunosuppressive regimen to prevent GVHD. These regimens include methotrexate combined with a calcineurin inhibitor (cyclosporine or tacrolimus). Other regimens are based on a calcineurin inhibitor in combination with mycophenolate. Additionally, T-cell depletion is achieved using monoclonal antibodies (e.g., alemtuzumab) or polyclonal antisera (e.g., ATG) (**Rezvani 2012**).

Indication/target population	Haematologic malignancy; specifically, patients who undergo bone marrow transplant
	A multinational committee of organ transplant, haematology, infectious disease, and other experts has provided guidelines for the prevention of infectious complications among haematopoietic cell transplantation recipients (**Tomblyn 2009**). The committee recommends the administration of antibacterial prophylaxis with a fluoroquinolone such as levofloxacin, to prevent bacterial infections for adult HSCT patients with anticipated neutropenic periods of 7 days or more (**Tomblyn 2009**). Additionally, fluconazole is recommended as the drug of choice for the prophylaxis of invasive candidiasis before engraftment in allogeneic HSCT recipients, and may be started from the beginning or just after the end of the conditioning regimen (**Tomblyn 2009**).

ABVD = Doxorubicin, Bleomycin, Vinblastine, Dacarbazine; ATG = Antithymocyte Globulin; BEACOPP = Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone; BCSH = British Committee for Standards in Haematology; CI = Confidence Interval; CLL = Chronic Lymphocytic Leukaemia; FCR = Fludarabine, Cyclophosphamide And Rituximab; G-CSF = Granulocyte Colony-Stimulating Factor; GVHD = Graft Versus Host Disease; HL = Hodgkin's Lymphoma; HSCT = Haematopoietic Stem Cell Transplant; IA = Invasive Aspergillosis; ICU = Intensive Care Unit; IFI = Invasive Fungal Infection; OR = Odds Ratio; PATH Alliance = Prospective Antifungal Therapy Alliance; RT = Radiotherapy.

Table 2 Epidemiology of malignancy treated with chemotherapy in the target population

Indication/target population	Malignancy treated with chemotherapy
Incidence of co-morbidity	Incidence data of malignancy treated with chemotherapy in the target population, both for IA and mucormycosis were not identified.
Prevalence of co-morbidity	Epidemiologic data on malignancy treated with chemotherapy in the target population are lacking; however, there are reports of IFI infections among patients with malignant tumours that are treated with chemotherapy. Ohmagari *et al* (2004) reported that of 13 solid tumour patients with a diagnosis of IA that were treated at the University of Texas MD Anderson Cancer Centre between 1994–2003, 30.8% received chemotherapy within 30 days prior to the diagnosis of IA (**Ohmagari 2004**). Kurosawa *et al* evaluated the incidence and treatment outcomes of 2821 patients with haematological malignancies with proven and probable IFI in 22 institutions in Hokkaido, Japan between 2006 and 2008. They reported that of 38 patients diagnosed with IFIs in this study, 47% had received treatment with chemotherapy (alone) prior to IFI diagnosis (**Kurosawa 2012**).
Mortality of co-morbidity	In a Japanese multi-institutional study of patients with haematological malignancy patients who underwent chemotherapy, the IFI-attributable mortality due to chemotherapy alone was 22.2% (**Kurosawa 2012**).
Main co-prescribed medicinal products	The chemotherapy used in the treatment of patients with malignancies depends on malignancy type and patient factors (characteristics/status).

IA = Invasive Aspergillosis; IFI = Invasive Fungal Infection.

Table 3 Epidemiology of bacterial sepsis in the target population

Indication/target population	Bacterial sepsis
Incidence of co-morbidity	Baddley *et al* (2013) conducted a retrospective analysis of multicentre ICU patients using a US administrative database. The study evaluated the clinical and economic outcomes of patients with IA. Of 412 patients with IA, 148 (35.9%) had septicaemia or septic shock (**Baddley 2013**). A multinational observational study of ICU patients in Europe reported sepsis rate of over 35% among hospitalised patients in the ICU (**Vincent 2006**).
Prevalence of co-morbidity	Prevalence data of bacterial sepsis in the target population, both for IA and mucormycosis were not identified.
Mortality of co-morbidity	In a US study by Baddley *et al* (2013), the overall in-hospital mortality was 45.6%, with 33.1% fatalities occurring within 30 days of hospitalisation (**Baddley 2013**). Vincent *et al* (2006) reported high mortality rates, with 27% of patients with sepsis dying in the ICU in a multinational study of ICUs in Europe, with mortality rates rising to over 50% in patients with septic shock (**Vincent 2006**).
Main co-prescribed medicinal products	Appropriate antimicrobial therapy depends on adequate coverage of the resident flora of the organ system presumed to be the source of the septic process (**Cunha 1995**, **Cunha 2004**, **Morrell 2009**). Agents used for monotherapy regimens include the following: imipenem, meropenem, tigecycline, piperacillin-tazobactam, sulbactam-ampicillin, and moxifloxacin. Combination therapeutic regimens include metronidazole plus either levofloxacin, aztreonam, or an aminoglycoside. Alternative agents may be used alone or in combination, with a good adverse-effect profile. Antibiotics are normally continued until the septic process and surgical interventions have controlled the source of infection. Ordinarily, patients are treated for approximately 2 weeks. As soon as patients are able to tolerate medications orally, they may be switched to an equivalent oral antibiotic regimen in an IV-to-oral conversion programme.

IA = Invasive Aspergillosis; ICU = Intensive Care Unit; US = United States.

Table 4 Epidemiology of human immunodeficiency virus / acquired immune deficiency syndrome in the target population

Indication/target population	HIV/AIDS
Incidence of co-morbidity	Incidence data of HIV/AIDS in the target population, both for IA and mucormycosis were not identified.
Prevalence of co-morbidity	In a prospective surveillance study of 6,845 hospitalised patients with IFIs in 25 North American medical centres, Azie *et al* (2012) reported that the prevalence of HIV/AIDS at baseline was 4.7% (**Azie 2012**).
Mortality of co-morbidity	In the PATH Alliance registry (North America), the 90-day survival rate of HIV/AIDS patients treated for IFIs was 76% (95% CI 71.3–80.6) (**Azie 2012**).

Indication/target population	HIV/AIDS
Main co-prescribed medicinal products	The medicinal products used in the treatment of patients with HIV/AIDS depend on a wide variety of patient factors (**Barlett 2013**). **Europe** The EACS Guidelines recommend the following combination regimens for antiretroviral-naïve adult HIV-positive patients (**EACS 2013**): NNRTI (EFV or RPV) + NRTI (ABC/3TC or TDF/FTC); Protease inhibitor pharmacologically boosted with ritonavir (ATV/r or DRV/r) + NRTI (ABC/3TC or TDF/FTC); Integrase strand transfer inhibitor (RAL + NRTI [TDF/FTC or ABC/3TC]). **USA** The US Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents recommends the following as preferred regimens (listed in order of FDA approval) for antiretroviral-naïve patients (**HHS 2018**): EFV/TDF/FTC; Ritonavir-boosted atazanavir + tenofovir /emtricitabine (ATV/r + TDF/FTC); Ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC); RAL + TDF/FTC.

ABC = Abacavir; AIDS = Acquired Immune Deficiency Syndrome; ATV = Atazanavir; CI = Confidence Interval; EACS = European AIDS Clinical Society; EFV = Efavirenz; DRV = Darunavir; FDA = Food and Drug Administration; FTC = Emtricitabine; HHS = Department of Health and Human Services; HIV = Human Immunodeficiency Virus; IFI = Invasive Fungal Infection; NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI = Nucleos(t)ide Reverse Transcriptase Inhibitor; PATH Alliance = Prospective Antifungal Therapy Alliance; r = Ritonavir; RAL = Raltegravir; RPV = Rilpivirine; 3TC = Lamivudine; TDF = Tenofovir; US = United States.

Table 5 Epidemiology of solid organ transplants in the target population

Indication/target population	Solid organ transplants
Incidence of co-morbidity	Incidence data of solid organ transplant in the target population, both for IA and mucormycosis were not identified.
Prevalence of co-morbidity	In a retrospective study of clinical charts and microbiology records of patients with a positive culture for Zygomycetes (N = 19) in Switzerland, Ambrosioni *et al* (2010) reported a prevalence of patients that have undergone solid organ transplant of 15.8% (3/19) (**Ambrosioni 2010**). In North America, the prevalence of SOT among patients with IFIs was 14.3% in the PATH Alliance registry (**Azie 2012**). Using data from the PATH Alliance database, Horn *et al* (2009) reported a prevalence of 8.2% SOT among 2,019 patients with IFI (**Horn 2009**).

Indication/target population	Solid organ transplants
Mortality of co-morbidity	Azie *et al* (2012) reported that the 90-day survival rate of SOT patients in North America treated for IFIs was 77.5% (95% CI 74.9–80.1) (**Azie 2012**). Neofytos *et al* (2013) reported that the 12-week mortality among US allogeneic liver, kidney, heart, and lung recipients with IMI was 47.1%, 27.8%, 16.7%, and 9.5%, respectively. Male gender (OR: 14.4, p = 0.007) and elevated bilirubin (OR: 5.7, p = 0.04) were predictors of mortality for allogeneic HSCT and SOT recipients with IA, respectively (**Neofytos 2013**).
Main co-prescribed medicinal products	Induction therapy shortly after transplantation and an immunosuppressive regimen (**Morgan 2012**)

CI = Confidence interval; HSCT = Haematopoietic Stem Cell Transplant; IA = Invasive Aspergillosis; IFI = Invasive Fungal Infection; IMI = Invasive mould infections; OR = Odds ratio; SOT = Solid organ transplant.

Table 6 Epidemiology of renal impairment in the target population

Indication/target population	Renal impairment
Incidence of co-morbidity	Incidence data of renal impairment in the target population, both for IA and mucormycosis were not identified.
Prevalence of co-morbidity	In a retrospective study of multicentre ICU patients using an administrative database, Baddley *et al* (2013) reported that 41.3% of 412 patients with IA had acute renal failure (**Baddley 2013**).
Mortality of co-morbidity	A study by Baddley *et al* (2010) enrolled transplant patients from 23 centres in the US from March 2001 to October 2005, of 415 haematopoietic stem cell transplant with IA, 118 had renal impairment. The 12-week mortality after IA diagnosis among the renal impaired patients was 73.7% (n = 87) (**Baddley 2010**). In the same study, there were 106 renal impaired patients among 227 SOT recipients with IA. The 12-week mortality after IA diagnosis among renal impaired SOT recipients was 46.2% (n = 49) (**Baddley 2010**).
Main co-prescribed medicinal products	Diuretics (hydrochlorothiazide, loop diuretic), IV fluids, pressors (dopamine, norepinephrine).

IA = Invasive Aspergillosis; IFI = Invasive Fungal Infection; ICU = Intensive Care Unit; IV = Intravenous; US = United States.

Table 7 Epidemiology of hepatic impairment in the target population

Indication/target population	Hepatic impairment
Incidence of co-morbidity	Raghuram *et al* (2012) conducted a retrospective study in US to assess the incidence of and risk factors for IFIs in recipients of liver transplantation, and the associated mortality rates, using records of first-time deceased-donor liver transplant recipients (January 2003 to December 2007). They reported a 12% incidence of IFIs (**Raghuram 2012**). In a nationwide multicentre clinical study in Japan to evaluate the efficacy and safety of IV itraconazole in the management of invasive candidiasis in non-neutropenic patients undergoing surgery and critical care, Takesue *et al* (2012) reported an 8% incidence of hepatic impairment (**Takesue 2012**).
Prevalence of co-morbidity	In a French study of 393 adults with IA, Lortholary *et al* (2011) reported that 2.3% underwent liver transplantation from underlying liver disease (**Lortholary 2011**).
Mortality of co-morbidity	The one-year survival for hepatic impaired patients with IA was 50% in a retrospective study in US to assess the incidence of and risk factors for IFIs in recipients of liver transplantation (**Raghuram 2012**).
Main co-prescribed medicinal products	Anti-emetics, vitamin supplementation, interferon, and corticosteroids.

IA = Invasive Aspergillosis; IFI = Invasive Fungal Infection; US = United States.

Table 8 Epidemiology of type 1 diabetes mellitus in the target population

Indication/target population	Type 1 Diabetes mellitus
Incidence of co-morbidity	Data on the incidence of type 1 diabetes mellitus in patients with mucormycosis infection is unclear. However, in a nationwide retrospective study in France it was shown a 9% annual incidence increase in mucormycosis incidence in diabetics (**Bitar 2009**).
Prevalence of co-morbidity	Type 2 diabetes is more frequently associated with mucormycosis, whereas type 1 has been reported to be less prevalent. Prevalence of type 1 diabetes in patients with mucormycosis ranges between 6% and 43%. While, the prevalence of diabetes mellitus in patients with mucormycosis range between 9% and 72%. Type 1 accounted for 20% of the diabetes cases in the largest retrospective cohort (**Roden 2005**). In contrast, only 6% of the 178 patients in an Indian cohort had type 1 diabetes (**Chakrabarti 2006**), and 43% of the diabetic patients in a French retrospective cohort (**Lanternier 2012**). In the paediatric population, the association between type 1 diabetes and mucormycosis is less frequent, accounting for 13% of 157 mucormycosis cases published (**Zaoutis 2007**). In a large study from Mexico, reviewing 418 cases of mucormycosis and entomophthoromycosis, diabetes was the underlying disease in 72% of patients (**Corzo-Leon 2018**). In the largest registry of the European Confederation of Medical Mycology Working Group, 230 cases occurring between 2005 and 2007 were analysed and found that diabetes was the sole predisposing factor in 21 (9%) patients. In another

Indication/target population	**Type 1 Diabetes mellitus**
	18 (8%) patients, diabetes was combined with other underlying conditions, such as malignancy or trauma (**Petrikkos 2012**, **Skiada 2011**). An exhaustive analysis was performed at country level in France (all hospital) and a total of 101 cases of mucormycosis were found. Of those 23% occurred in patients with diabetes (**Petrikkos 2012**). In a review of 929 patients with mucormycosis assessed between 1940–2003, diabetes was the most frequent underlying condition (36%) (**Roden 2005**).
Mortality of co-morbidity	Mortality data in patients with type 1 diabetes mellitus infected with mucormycosis are scarce. However, one European study analysing 230 cases occurring between 2005 and 2007 it was reported a 55% of mortality rate within 39 patients with diabetes mellitus (**Skiada 2011**). The study cited above concerning the 230 cases occurring between 2005 and 2007 in Europe showed that in 18 (8%) patients, diabetes was combined with other underlying conditions, such as malignancy or trauma (**Petrikkos 2012**, **Skiada 2011**).
Main co-prescribed medicinal products	Guidelines for the treatment of mucormycosis are also applicable to patients with other underlying diseases, such as type 1 diabetes mellitus since most of the existing studies were performed on mixed populations (both haematologic and non-haematologic patients) and the approach to diagnosis and treatment is similar. In that an important aspect of management of mucormycosis is to correct any underlying, uncontrolled diabetes, the local standard of care in type 1 diabetes should be followed to achieve this.

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

The non-clinical safety programme was designed to support the clinical use of oral and IV isavuconazonium sulfate for the proposed indication. Comprehensive safety evaluations of isavuconazonium sulfate, isavuconazole, and the inactive cleavage product (BAL8728) were performed and included safety pharmacology, genotoxicity, single- and repeated-dose toxicity, fertility, embryofoetal and pre- and postnatal development studies.

The toxicities, which were observed at relatively low exposures in animals (0.5 to 1.2-fold the human dose) during the toxicological assessment of isavuconazonium sulfate, are outlined as follows: liver hypertrophy, which is secondary to hepatic liver enzyme induction (mice, rats and monkeys); rodent-specific thyroid hypertrophy, which is secondary to induction of liver metabolic enzymes (rats); increased adrenal weight with associated thickening of the zona fasciculata (monkeys); local infusion site effects, which includes vascular and perivascular irritation and inflammation that were dose- and/or duration-limiting (rats and monkeys). In general, these adverse findings resolved or showed signs of ongoing recovery after withdrawal of treatment.

At higher doses, mortality was observed in mice and monkeys, although the cause of death could not be determined. In mice, either no overt symptoms or an impairment of the clinical condition (characterised by some neurological and respiratory effects) preceded death without any relevant histopathology findings. In monkeys, mortality was preceded by a deterioration of general condition. These observations in animals suggest a steep dose response curve for the lethal effects of isavuconazole.

Further details of the non-clinical safety findings from safety pharmacology and toxicology studies are summarised in Table 9 and the sections below.

Table 9 Key safety findings from non-clinical studies and relevance to human usage

Key safety findings from non-clinical studies	Relevance to human usage
Repeat-dose toxicity (by target organ for toxicity) ***Hepatocellular hypertrophy*** Increased liver weight related to hepatocellular hypertrophy, attributable to induction of cytochrome P450 (CYP) enzymes, was seen in rats and cynomolgus monkeys. These changes, indicative of metabolism, were reversible at the end of 4-week recovery period. Sprague-Dawley 4-day old SPF rats were dosed orally once daily for 13 weeks at dose levels of 0, 10, 30 and 90 mg/kg/day (Study 9766-TX-0066). At 30 mg/kg/day or 90 mg/kg/day, increased liver weight and centrilobular hepatocellular	Not relevant for human usage. The liver changes seen in rats and monkeys are considered adaptive and are common in this class of drug. These changes are considered not to be relevant to clinical settings, since the aetiology, liver metabolising enzyme induction, is not relevant in humans at the therapeutic doses.

Key safety findings from non-clinical studies	Relevance to human usage
hypertrophy were noted in both males and females	
Thyroid: Hypertrophy (rats) Increased thyroid organ weight and enlargement of the thyroid in rats. These changes were reversible, except for persistence of focal hyperplasia in the thyroids of male animals. Sprague-Dawley 4-day old SPF rats were dosed orally once daily for 13 weeks at dose levels of 0, 10, 30, and 90 mg/kg/day (Study 9766-TX-0066). At 90 mg/kg/day, increased thyroid gland weights and thyroid follicular cell hypertrophy were noted in both males and females.	Not relevant for human usage. The increased thyroid weight and cellular hypertrophy (increased small follicles) in rats are considered not relevant for humans. These findings are specific to rodents that lack thyroid hormone-binding globulin (**Klaasen 2013**).
Adrenal: Hypertrophy of adrenocortical cells (cynomolgus monkeys) Repeated administration of isavuconazonium to cynomolgus monkeys resulted in increases in or a trend towards increases in adrenal weights and/or vacuolation/hypertrophy of adrenocortical cells.	Not relevant for human usage. The increased adrenal weight, cortical vacuolation, and thickening of zona fasciculata observed in cynomolgus monkeys, are hypothesised to be the result of increased steroid synthesis secondary to increased glucocorticoid metabolism due to CYP3A and CYP2B induction mediated by isavuconazole in animals (**Harvey 2010**, **You 2004**). The clinical significance of the non-clinical adrenal findings is unclear, however, since it occurred at a human equivalent dose 4-fold higher than the maintenance dose, it is probably of little clinical significance.
Blood and lymphatic system disorders Sprague-Dawley 4-day old SPF rats were dosed orally once daily for 13 weeks at dose levels of 0, 10, 30, and 90 mg/kg/day. At 90 mg/kg/day, there was evidence of anaemia and prolongation of activated partial thromboplastin time in female rats.	Potentially relevant for human usage. Anaemia is a known adverse reaction for isavuconazole.
Genotoxicity	Neither the prodrug, isavuconazonium, nor the active moiety, isavuconazole, showed genotoxic potential.
Developmental and reproductive Isavuconazonium did not affect the fertility of male or female rats treated with oral doses up to 90 mg/kg/day (2.3 times the maintenance dose, based on mg/m^2/day comparisons). Skeletal anomalies were reported in both rats and rabbits at systemic exposures below that observed at the human therapeutic maintenance dose (0.2-fold and 0.1-fold, respectively).	Potentially relevant for human usage. Based on animal data, isavuconazonium is predicted to have the potential for increasing the risk of adverse developmental outcomes above background risk. Isavuconazole must not be used during pregnancy except in patients with severe or potentially life-threatening fungal infections in whom isavuconazole may be used if the anticipated benefits outweigh the possible risks to the foetus.

Key safety findings from non-clinical studies	Relevance to human usage
Administration of isavuconazonium to rats at a dose of 90 mg/kg/day (2.3-times the maintenance dose based on mg/m2/day) during pregnancy through the weaning period showed an increased perinatal mortality of the pups. There was no effect on the fertility of pups exposed to the active moiety, isavuconazole, either in utero or during the perinatal period via the mother's milk.	
Exposure to isavuconazole via breast milk Administration of radio-labelled isavuconazonium sulfate to lactating rats resulted in recovery of radiolabel in the milk. Isavuconazonium (90 mg/kg/day) orally administered to rats during pregnancy through the weaning period resulted in an increased perinatal mortality of the pups.	Potentially relevant for human usage. It is not known whether isavuconazole is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with isavuconazole.
Safety Pharmacology as applicable: Cardiovascular system including potential effect on QT interval A non-clinical ion channel effects study demonstrated that isavuconazole has the potential to cause dose-dependent QT shortening	QT shortening is a known adverse reaction for isavuconazole.
Other toxicity-related information or data Hypertrophy of adrenocortical cells in cynomolgus monkeys;	All have been adequately assessed or are of limited relevance for usage in adult humans:
Infusion-rate-related reactions Single dose bolus injections of isavuconazonium were lethal in rats and monkeys. Changing the intravenous administration regimen by reducing the administration rate from 1.0 to 0.1 mL/min resulted in no mortality in rats and similarly in monkeys. Bolus IV injections of isavuconazonium in rats and monkeys were associated with infusion reactions including mortality at human equivalent doses 0.48-fold the clinical maintenance dose (rats) or 6-fold above the clinical maintenance dose (monkeys).	Potentially relevant for human usage. Infusion-related systemic reactions are likely if isavuconazole is intravenously administered as a bolus injection. Isavuconazole must be infused over a minimum of 1 hour to reduce the risk of infusion-related reactions.

CYP = Cytochrome P450; IV = Intravenous.

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

From the Development International Birth Date (DIBD; 21 October 2002) up to the Data Lock Point (DLP) of this RMP (31 July 2023), 2,142 healthy subjects and 1,627 patients have been enrolled in the isavuconazole clinical development programme, of whom approximately 2,213 received isavuconazole.

At the cut-off date of the initial marketing authorisation application (MAA) (30 September 2013), a total of 1,548 subjects had been exposed to isavuconazole, including 257 in the Phase 3 Controlled Study, 547 in the Phase 2 and Phase 3 programme, and 1,001 in the Phase 1 programme.

In the following sections, isavuconazole exposure (patients and patient exposure years) in adults is summarised for the Phase 3 controlled study and the Phase 2 and 3 programmes. All patients in the Phase 3 controlled study received isavuconazole for the same indication (treatment of IFD caused by *Aspergillus* species or other filamentous fungi). Exposure for the Phase 2 and 3 population is presented for each Summary of Clinical Safety (SCS) treatment group (Total isavuconazole, Phase 2 isavuconazole and Phase 3 isavuconazole) in order to show pooled exposure for the indication of invasive fungal disease.

Isavuconazole exposure in paediatric population is also summarised by duration, dosing formulation and other characteristics, for the cumulative Phase 1 and Phase 2 paediatric clinical trials.

Exposure data in adults

Exposure by duration

Isavuconazole exposure (patients and patient exposure years) for the Phase 3 controlled study and Phase 2 and 3 population are summarised by duration of exposure in Phase 3 controlled study and Phase 2 and 3 population, respectively.

Phase 3 controlled study

Table 10 summarises the clinical trial exposure to isavuconazole by duration of exposure in the Phase 3 controlled study.

Table 10 Isavuconazole exposure by duration in the indication of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi – Phase 3 controlled study

Duration of exposure	Patients	Patient exposure years
≥ 1 day	257	33.005
≥ 7 days	228	32.693
≥ 14 days	191	31.786
≥ 21 days	172	30.886
≥ 28 days	159	30.042
≥ 42 days	138	28.005
≥ 56 days	113	24.805
≥ 84 days	60	14.010
≥ 126 days	0	0
≥ 180 days	0	0

For each subject, the total duration of exposure (days) is calculated as (last dosing date - first dosing date + 1). The total subject exposure years is calculated as the sum over subjects of the total duration of exposure divided by 365.25.
Included: Study 9766-CL-0104

Phase 2 and 3 population

Table 11 summarises the clinical trial exposure to isavuconazole by duration of exposure and SCS treatment group in the Phase 2 and 3 population.

Table 11 Isavuconazole exposure by duration – Phase 2 and 3 population

Duration of exposure	Patients	Patient exposure years
Phase 2 and 3, All indications		
≥ 1 day	547	89.747
≥ 7 days	499	89.248
≥ 14 days	448	87.921
≥ 21 days	309	82.289
≥ 28 days	276	80.222
≥ 42 days	241	77.035
≥ 56 days	206	72.548
≥ 84 days	144	59.929
≥ 126 days	67	41.563
≥ 180 days	52	34.927

Duration of exposure	Patients	Patient exposure years
Phase 2, Indications: Prophylaxis in AML; Treatment of oesophageal candidiasis		
≥ 1 day	144	5.837
≥ 7 days	138	5.799
≥ 14 days	130	5.561
≥ 21 days	21	1.347
≥ 28 days	7	0.537
Phase 3, Indications: Treatment of IFD caused by *Aspergillus* in subjects with renal impairment or caused by rare moulds, yeasts, or dimorphic fungi; Treatment of IFD caused by *Aspergillus* species or other filamentous fungi		
≥ 1 day	403	83.910
≥ 7 days	361	83.450
≥ 14 days	318	82.360
≥ 21 days	288	80.942
≥ 28 days	269	79.685
≥ 42 days	241	77.035
≥ 56 days	206	72.548
≥ 84 days	144	59.929
≥ 126 days	67	41.563
≥ 180 days	52	34.927

AML=acute myeloid leukaemia; IFD=invasive fungal disease.
Includes studies 9766-CL-0101, 9766-CL-0102, 9766-CL-0103, and 9766-CL-0104.
For each subject, the total duration of exposure (days) is calculated as (last dosing date - first dosing date + 1). The total subject exposure years is calculated as the sum over subjects of the total duration of exposure divided by 365.25.

Exposure by dose

Isavuconazole exposure (patients and patient exposure years) for the Phase 3 controlled study and Phase 2 and 3 population is summarised by dose. Dose levels for multiple dose studies were based on the protocol planned dose levels during the maintenance period.

Phase 3 controlled study

Table 12 summarises the clinical trial exposure to isavuconazole by randomised maintenance dose level in the Phase 3 Controlled Study.

Table 12 Isavuconazole exposure by maintenance dose in the indication of IFD caused by *Aspergillus* species or other filamentous fungi – Phase 3 controlled study

Maintenance dose level	Patients	Patient exposure years
200 mg daily	257	33.005

IFD = Invasive Fungal Disease. For each subject, the total duration of exposure (days) is calculated as (last dosing date - first dosing date + 1). The total subject exposure years is calculated as the sum over subjects of the total duration of exposure divided by 365.25.
Included: Study 9766-CL-0104

Phase 2 and 3 population

Table 13 summarises the clinical trial exposure to isavuconazole by randomised maintenance dose level and SCS treatment group in the Phase 2 and 3 population.

Table 13 Isavuconazole exposure by maintenance dose – Phase 2 and 3 population

Maintenance dose level	Patients	Patient exposure years
Phase 2 and 3, All Indications		
50 mg daily	40	1.574
100 mg daily	41	1.637
200 mg daily	414	84.348
400 mg daily	12	0.602
400 mg weekly	40	1.585
Phase 2, Indications: Prophylaxis in AML; Treatment of oesophageal candidiasis		
50 mg daily	40	1.574
100 mg daily	41	1.637
200 mg daily	11	0.438
400 mg daily	12	0.602
400 mg weekly	40	1.585
Phase 3, Indications: Treatment of IFD caused by *Aspergillus* in subjects with renal impairment or caused by rare moulds, yeasts, or dimorphic fungi; Treatment of IFD caused by *Aspergillus* species or other filamentous fungi		
200 mg daily	403	83.910

AML = Acute Myeloid Leukaemia; IFD = Invasive Fungal Disease.
Includes studies 9766-CL-0101, 9766-CL-0102, 9766-CL-0103, and 9766-CL-0104. Dose level is based on the protocol planned dose levels during the maintenance period.
For each subject, the total duration of exposure (days) is calculated as (last dosing date - first dosing date + 1). The total subject exposure years is calculated as the sum over subjects of the total duration of exposure divided by 365.25.

Exposure by age group and gender

Phase 3 controlled study

Table 14 summarises the clinical trial exposure to isavuconazole by age group and gender in the Phase 3 controlled study. One paediatric patient (i.e., < 18 years of age) was exposed to isavuconazole in this study population (study 9766-CL-0104, Subject 3204-29 was dosed with isavuconazole at the age of 17 years).

Table 14 Isavuconazole exposure by age group and gender in the indication of IFD caused by *Aspergillus* species or other filamentous fungi – Phase 3 controlled study

Age group (years)	Patients		Patient exposure years	
	Male	Female	Male	Female
≤ 45	52	42	7.581	5.229
> 45 to ≤ 65	56	51	7.291	5.717
> 65 to ≤ 75	33	13	4.186	1.530
> 75 to ≤ 85	4	6	0.682	0.789
> 85	0	0	0	0

IFD = Invasive Fungal Disease.

For each subject, the total duration of exposure (days) is calculated as (last dosing date - first dosing date + 1). The total subject exposure years is calculated as the sum over subjects of the total duration of exposure divided by 365.25.

Included: Study 9766-CL-0104

Phase 2 and 3 population

Table 15 summarises the clinical trial exposure to isavuconazole by age group/sex and SCS treatment group in the Phase 2 and 3 population. One paediatric patient (i.e., < 18 years of age) was exposed to isavuconazole in study 9766-CL-0104 (Subject 3204-29 was dosed with isavuconazole at the age of 17 years).

Table 15 Isavuconazole exposure by age group and gender – Phase 2 and 3 population

Age group (years)	Patients		Patient exposure years	
	Male	Female	Male	Female
Phase 2 and 3, All indications				
≤45	179	76	25.875	14.355
>45 to ≤65	122	84	21.670	12.893
>65 to ≤75	48	18	9.320	3.107
>75 to ≤85	11	8	1.336	1.136
>85	1	0	0.055	0
Phase 2, Indications: Prophylaxis in AML; Treatment of oesophageal candidiasis				
≤45	90	13	3.559	0.449
>45 to ≤65	25	15	1.172	0.580
>65 to ≤75	1	0	0.077	0
>75 to ≤85	0	0	0	0
>85	0	0	0	0
Phase 3, Indications: Treatment of IFD caused by *Aspergillus* in subjects with renal impairment or caused by rare moulds, yeasts, or dimorphic fungi; Treatment of IFD caused by *Aspergillus* species or other filamentous fungi				
≤45	89	63	22.316	13.906
>45 to ≤65	97	69	20.498	12.312
>65 to ≤75	47	18	9.243	3.107
>75 to ≤85	11	8	1.336	1.136
>85	1	0	0.055	0

AML = acute myeloid leukaemia; IFD = invasive fungal disease.

Includes studies 9766-CL-0101, 9766-CL-0102, 9766-CL-0103, and 9766-CL-0104.

For each subject, the total duration of exposure (days) is calculated as (last dosing date - first dosing date + 1). The total subject exposure years is calculated as the sum over subjects of the total duration of exposure divided by 365.25.

Exposure by race

Isavuconazole exposure (patients and patient exposure years) for the Phase 3 controlled study and Phase 2 and 3 population are summarised by race in (Phase 3 controlled study and Phase 2 and 3 population), respectively.

Phase 3 controlled study

Table 16 summarises the clinical trial exposure to isavuconazole by race in the Phase 3 controlled study.

Table 16 Isavuconazole exposure by race in the indication of IFD caused by *Aspergillus* species or other filamentous fungi – Phase 3 controlled study

Race	Patients	Patient exposure years
White	211	28.153
Black/African American	1	0.156
Asian	44	4.578
Other	1	0.118

IFD = invasive fungal disease.
Includes: Study 9766-CL-0104.
For each subject, the total duration of exposure (days) is calculated as (last dosing date - first dosing date + 1). The total subject exposure years is calculated as the sum over subjects of the total duration of exposure divided by 365.25.

Phase 2 and 3 population

Table 17 summarises the clinical trial exposure to isavuconazole by race and SCS treatment group in the Phase 2 and 3 population.

Table 17 Isavuconazole exposure by race – Phase 2 and 3 population

Race	Patients	Patient exposure years
Phase 2 and 3, All Indications		
White	343	67.250
Black/African American	128	7.573
Asian	68	12.925
Other	8	1.999
Phase 2, Indications: Prophylaxis in AML; Treatment of oesophageal candidiasis		
White	24	1.079
Black / African American	117	4.624
Asian	0	0
Other	3	0.134
Phase 3, Indications: Treatment of IFD caused by *Aspergillus* in subjects with renal impairment or caused by rare moulds, yeasts, or dimorphic fungi; Treatment of IFD caused by *Aspergillus* species or other filamentous fungi		
White	319	66.171
Black/African American	11	2.949
Asian	68	12.925
Other	5	1.864

AML = acute myeloid leukaemia; IFD = invasive fungal disease.

Includes studies 9766-CL-0101, 9766-CL-0102, 9766-CL-0103, and 9766-CL-0104.

For each subject, the total duration of exposure (days) is calculated as (last dosing date - first dosing date + 1). The total subject exposure years is calculated as the sum over subjects of the total duration of exposure divided by 365.25.

Exposure data in the paediatric population

The dosage regimen for paediatric participants in studies 9766-CL-0046 and 9766-CL-0107 was 5.4 mg/kg isavuconazole (equivalent to 10 mg/kg of the prodrug isavuconazonium sulfate) every 8 hours on Days 1 and 2 (total of six doses), followed by 5.4 mg/kg once daily. The milligram dose was capped at a maximum of 200 mg isavuconazole (equivalent to 372 mg isavuconazonium sulfate) per administration. A total of 77 paediatric participants received at least one dose of isavuconazole (Table 18). Mean exposure overall was 31.68 (range: 1 – 181) days, with 46 of 77 participants (59.7%) received isavuconazole for at least 14 days, and 19 participants (24.7%) for at least 21 days.

Table 18 Summary of study drug exposure in the All Paediatric studies (Safety analysis set)

Characteristic	All Paediatric (N = 77)
Total duration (days)	
Mean (SD)	31.68 (36.75)
Median	15
Min - Max	1 – 181
Total duration category (days), n (%)	
1 to 7	18 (23.4)
8 to 14	16 (20.8)
15 to 21	10 (13.0)
22 to 42	14 (18.2)
43 to 56	4 (5.2)
57 to 84	9 (11.7)
> 84	6 (7.8)

Total duration is defined as the number of days between the start and the end date of study drug, where the duration is calculated by: end date − start date + 1.

In the paediatric population, the median age was 10.0 years (Table 19). The paediatric population was evenly split between the 6 to < 12 years and the 12 to < 18 years groups (39.0% vs 41.6%, respectively), with 19.5% aged 1 to < 6 years. A total of 45.5% of paediatric patients were male, and 67.5% were classified as White. The other races represented in the All Paediatric population were Asian (10.4%) and Black or African American (7.8%), with the remainder classified as in the Other category (11.7%).

Table 19 Demographic and baseline characteristics (Safety analysis set)

Parameter Category	**All Paediatric (N = 77)**
Sex, n (%)	
Male	35 (45.5)
Female	42 (54.5)
Race, n (%)	
White	52 (67.5)
Black or African American	6 (7.8)
Asian	8 (10.4)
Other†	9 (11.7)
Missing/not calculated	2 (2.6)
Age (years)‡	
Mean (SD)	10.1 (4.7)
Median	10
Range	1 – 17
Age group (years), n (%)	
1 to < 6 years	15 (19.5)
6 to < 12 years	30 (39.0)
12 to ≤ 18 years	32 (41.6)
> 18 years	0

† This 'Other' category includes all other races besides White, Black or African American, or Asian. It may differ from what was defined in each individual study.

‡ One participant in the All Adult population from study 9766-CL-0104 was aged 17 years at the time of enrolment

Cumulative subject exposure in Basilea and Astellas clinical trials

Basilea and Astellas completed clinical trials

From the DIBD up to the DLP of this RMP, 1,992 healthy subjects and 1,524 patients have been enrolled in the isavuconazole clinical development programme, of whom approximately 2,006 received isavuconazole.

Overall cumulative subject exposure is provided in Table 20, based on exposure data from completed studies.

Table 20 Cumulative exposure in isavuconazole completed clinical trials conducted by Basilea and Astellas

Treatment	Cumulative exposure [a]		
	Healthy subjects	Patients	Total
Isavuconazole	1066	940	2,006
Placebo	103	0	103
Voriconazole	0	259	259
Fluconazole	0	38	38
Caspofungin [b]	0	220	220
Other [c]	823	67	890
Total	**1,992**	**1,524**	**3,516**

[a] Includes patients and healthy subjects from studies with completed enrolment, as of 31 July 2023.

[b] Intravenous caspofungin with optional switch to oral voriconazole regimen.

[c] Includes substrates from drug-drug interaction studies.

Overall cumulative subject exposure by age and sex is provided in Table 21, based on exposure data from completed studies.

Table 21 Cumulative exposure in isavuconazole completed clinical trials by age and sex

Age group (years)	Number of subjects [a]		
	Male	Female	Total
1 to < 6	6	9	15
6 to < 12	13	17	30
12 to < 18	16	16	32
18–65	1,228	508	1,736
66–75	84	43	127
≥ 76	42	24	66
Total	**1,389**	**617**	**2,006**

[a] Data from completed studies as of 31 July 2023. Only one patient who took isavuconazole in study 9766-CL-0103 was excluded from this table because at the time the patient was enrolled, the site did not have local Independent Ethics Committee (IEC) approval, and the IEC requested removal of this patient from the study database.

Overall cumulative subject exposure by racial group is provided in Table 22, based on exposure data from completed studies.

Table 22 Cumulative exposure in isavuconazole completed clinical trials by racial group

Race	Number of subjects [a]
White	1,360
Black or African American	380
Asian	202
American Indian or Alaska native	5
Native Hawaiian or other Pacific Islander	1
Other	56
Missing	2
Total	**2,006**

[a] Data from completed studies as of 31 July 2023. Only one patient who took isavuconazole in study 9766-CL-0103 was excluded from this table, because when the patient was enrolled, the site did not have local IEC approval and the IEC requested removal of the patient from the study database.

Cumulative subject exposure from Asahi Kasei-sponsored clinical trials

From the DIBD to the DLP of this report, Basilea co-development and commercial Partner in Japan, Asahi Kasei, completed one Phase 1 clinical study (study AK1820-101), one biopharmaceutical clinical trial in Japan (Study AK1820-102), and one Phase 3 clinical study (Study AK1820-301) with isavuconazole. Cumulative exposure in clinical trials and cumulative isavuconazole exposure are presented in Table 23.

Table 23 Cumulative subject exposure to isavuconazole by age group and gender in Asahi Kasei clinical studies

Age range (years)	Number of subjects		
	Male	Female	Total
18–65	155	5	160
66–75	23	6	29
≥ 76	15	3	18
Total	**193**	**14**	**207**

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

SIV.1 Important exclusion criteria in pivotal clinical studies within the development programme

Criterion	Reason for exclusion	Considered to be included as missing information?	Rationale
Concomitant use of ketoconazole, St. John's wort, ritonavir or efavirenz. Concomitant use of rifampicin, carbamazepine, long acting barbiturates, rifabutin.	Exclusion due to lack/limitations of data or experience related to the investigational drug and/or comparator. Potential for drug interactions.	No	Isavuconazole is a substrate of CYP3A4 and CYP3A5. Co-administration of medicinal products which are inhibitors of CYP3A4 and/or CYP3A5 may increase the plasma concentrations of isavuconazole. Co-administration of medicinal products that are inducers of CYP3A4 and/or CYP3A5 may decrease the plasma concentrations of isavuconazole.
Patients > 65 years-old.	General protection of subject safety.	No	Results from study 9766-CL-0041 support use of isavuconazole in these patients. PK for isavuconazole in elderly volunteers (≥ 65 years-old) compared to non-elderly adult volunteers (18 to 45 years-old) was not found to be significantly influenced by age. No dose adjustment is necessary for older patients.
Women who are pregnant or of childbearing potential.	Based on non-clinical findings and data for other azoles, isavuconazole has the potential to adversely affect human embryofoetal development.	No	Teratogenicity is included in the RMP as an important potential risk (see Part II.SVII.3.1.2).
Women who are breast-feeding.	Based on non-clinical findings in which isavuconazole appeared in milk in lactating rats Effects of postulated similar maternal isavuconazole secretion on breast-feeding infant, are unknown. As a standard precautionary measure, pregnant and lactating women	No	Not applicable.

Criterion	Reason for exclusion	Considered to be included as missing information?	Rationale
	are excluded from the clinical studies.		
Patients with use of concomitant medications that prolong QT/QTc interval. Patients with baseline prolongation of QTcF ≥500 msec. Patients with risk factors for TdP Family history of long QT syndrome.	General protection of subject safety. Potential for drug interactions Class effects of QT prolongation with azoles.	No	No QT prolongation was observed in the thorough QT study. There were no reported TEAEs of TdP in isavuconazole-treated patients in the Phase 2 and 3 population. A publication of Astellas studies indicated isavuconazole shortens the cardiac QT interval in a dose-related manner, with no evidence of an associated cardiac risk. One of the studies was a thorough QT study designed to rule out QT prolongation; study results confirmed no evidence of QT prolongation associated with use of isavuconazole (**Keims 2017**).
Patients with calculated CLcr < 50 mL/min Patients with calculated CLcr <10 mL/min Patients currently on dialysis or likely to require dialysis during administration of study medication.	General protection of subject safety.	No	Results from study of patients with renal impairment support use of isavuconazole in these patients including those with ESRD undergoing dialysis. No clinically relevant differences for PK in patients with renal impairment (9766-CL-0018, 9766-CL-0103). No dose adjustment is necessary in patients with renal impairment, including patients with ESRD.
Patients with total bilirubin ≥ 3 × upper limit of normal (ULN), ALT, or AST ≥ 5 × ULN Patients with known cirrhosis or chronic hepatic failure.	General protection of subject safety and class effect of hepatotoxicity in azoles.	No	Results from 2 studies in patients with mild and moderate hepatic impairment (9766-CL-0008; 9766-CL-0014) as well as the population PK evaluation of isavuconazole, support use of isavuconazole in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, with no need for dose adjustment. Isavuconazole has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. These patients should be carefully monitored for potential drug toxicity.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CLcr = Creatinine clearance; ESRD = End-Stage Renal Disease; PK= Pharmacokinetic; QTcF = QT interval corrected by Fridericia's Correction Formula; TdP = Torsades de pointes; TEAE = Treatment-emergent adverse event.

SIV.2 Limitations in detection of adverse reactions in clinical trial development programmes

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

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 24 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breast-feeding women	Not included in the clinical development programme.
Patients with renal impairment	Two clinical studies assessed the PK of isavuconazole administered orally or intravenously n subjects with renal impairment: • One Phase 1 study 9766- CL-0018 enrolled 11 subjects with end stage-renal disease, 8 subjects with severe renal impairment, 8 subjects with moderate renal impairment and 8 subjects with mild renal impairment • One Phase 3 study 9766-CL-0103 enrolled 59 subjects with at least mild renal impairment (defined as an estimated glomerular filtration rate of < 60 mL/min/1.73m^2).
Patients with hepatic impairment	Two Phase 1 studies assessed the PK of isavuconazole, administered orally or intravenously, in patients with mild Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment: • Study 9766-CL-0008 (WSA-CP-008) enrolled 16 patients with mild hepatic impairment and 16 patients with moderate hepatic impairment • Study 9766-CL-0014 (WSA-CP-018) enrolled 16 subjects with liver cirrhosis classified as Child-Pugh A; 16 subjects with liver cirrhosis classified as Child-Pugh B.
Patients with other relevant co-morbidities: • Immunocompromised patients • Cardiovascular impairment	 Subset of exposure not available. Subset of exposure not available.
Patients of different racial and/or ethnic origin	In the Phase 2 and 3 Population, the majority of patients exposed to isavuconazole were white (343/547, 62.7%), with 128/547 (23.4%) black/African American, 68/547 (12.4%) Asian, and 8/547 (1.5%) other race. See Table 17 for a summary of the exposure by race in the Phase 2 and 3 Population.

PART II: MODULE SV – POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Cumulative post-marketing exposure does not alter considerations on the risk evaluation for isavuconazole.

The following assumptions were used to estimate the number of patients exposed to the product:

- Loading dose in accordance with the RSI: 372 mg isavuconazonium sulfate (200 mg isavuconazole) every 8 hours for six doses
- Maintenance dose in accordance with the RSI: 372 mg isavuconazonium sulfate (200 mg isavuconazole) once daily
- Mean duration of therapy based on data from clinical trials of 47 days (2 days loading dose, 45 days maintenance dose).

Calculations:	Total milligrams = (number of vials × 372 mg) + (number of capsules × 186 mg) Average course of therapy = (372 mg × 6) + (372 mg × 45) = 18,972 mg/patient Estimated number of patients = total mg / 18,972 mg/patient

Cumulatively, from the post-marketing experience, as of 30 June 2023, an estimated 247,737 patients had been exposed to isavuconazole worldwide.

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

Potential for misuse for illegal purposes

The pharmacologic profile of isavuconazole and the post-marketing and clinical safety data collected do not suggest any potential for misuse for illegal purposes.

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns have been identified since the previous version of this RMP (Version 9.0, dated 30 April 2021) was approved.

SVII.3 Details of important identified, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

SVII.3.1.1 Important Identified Risks

The safety profile of isavuconazole in the paediatric population was found to be similar to that in the adult population, and no new safety signals were detected. Therefore, the below described identified risks are also applicable to the paediatric population.

Infusion-related reactions

Potential mechanisms

Infusion-related reactions are known to occur with intravenously administered medicinal products. The exact mechanism of isavuconazole-induced infusion-related reactions is unknown, they can be immune mediated reactions.

Evidence source and strength of evidence

Infusion-related reactions are considered to be an important identified risk based on non-clinical data, experience with other products of the same class, and clinical data.

During clinical trials, infusion-related reactions (e.g., hypotension, dyspnoea, chills, dizziness, paraesthesia, nausea, and headache) were reported. Infusion-related reactions are therefore considered an identified risk for isavuconazole.

Characterisation of the risk

Frequency:

- *Phase 3 Controlled Study*: The overall frequency of potential infusion-related reaction serious treatment-emergent adverse events (TEAEs) occurring within 2 days after IV dosing among isavuconazole-treated patients in the Phase 3 Controlled Study was 10.1% compared to 6.9% in the voriconazole treatment group. (Note: All patients in this study were included in this analysis as all received at least one IV dose). The overall frequency of potential infusion-related reaction TEAEs that led to study drug discontinuation occurring within 2 days after IV dosing among isavuconazole-treated

patients in the Phase 3 Controlled Study was 3.1% compared to 2.3% in the voriconazole treatment group.

- *Phase 2 and 3 Population*: The overall frequency of potential infusion-related reaction serious TEAEs occurring within 2 days after IV dosing among isavuconazole-treated patients who received at least one IV dose was 8.9% in the Phase 2 and 3 Population, and 9.5% in the Phase 3 Studies. The overall frequency of potential infusion-related reaction TEAEs that led to study drug discontinuation occurring within 2 days after IV dosing among isavuconazole-treated patients who received at least one IV dose was 2.9% in the Phase 2 and 3 Population, and 2.2% in the Phase 3 Studies.
- *Phase 1 Population*: There were no potential infusion-related reaction serious TEAEs or TEAEs that led to study drug discontinuation reported among isavuconazole-treated subjects who received at least one IV dose in the Phase 1 Population.

Severity and nature of risk:

Table 25 summarises the potential infusion-related reaction TEAEs by severity in the Phase 3 controlled study (isavuconazole-treated and voriconazole-treated patients) and Phase 2 and 3 population (isavuconazole-treated patients).

Table 25 Potential infusion-related reaction TEAEs by severity: Phase 3 controlled study and Phase 2 and 3 population

Population/Treatment Group	Grade (Severity)		
	Mild n (%)	**Moderate n (%)**	**Severe n (%)**
Phase 3 controlled study [a]			
Voriconazole (N = 259)	20 (7.7%)	35 (13.5%)	21 (8.1%)
Isavuconazole (N = 257)	22 (8.6%)	19 (7.4%)	29 (11.3%)
Phase 2 and 3 population [b]			
Total Isavuconazole (N = 380) [b]	40 (10.5%)	32 (8.4%)	44 (11.6%)
Phase 3 Isavuconazole (N = 357) [c]	34 (9.5%)	30 (8.4%)	38 (10.6%)

Infusion-related reaction TEAEs identified using selected PTs, occurring within 2 days after IV dose. N = Subjects who received at least one IV dose. Note: All patients in study 9766-CL-0104 were included in this analysis as all received at least one IV dose

[a] Study 9766-CL-0104.
[b] Includes studies 9766-CL-0101, 9766-CL-0102, 9766-CL-0103, and 9766-CL-0104.
[c] Includes studies 9766-CL-0103 and 9766-CL-0104.

Risk factors and risk groups

A history of allergic conditions appears to be associated with higher risk of infusion-related reactions (**O'Neil 2007**). Risk factors for allergic drug reaction include the following: female gender, being an adult, HIV infection, concomitant viral infection, asthma, use of beta blockers, systemic lupus erythematosus, specific genetic polymorphisms, and previous hypersensitivity to a chemically-related drug (**Riedl 2003**).

Preventability

Generally, in any treatment, patients who have experienced a severe infusion reaction may require close observation for the following 24 hours because of the risk for a biphasic episode. People with reactive airway disease may also need longer observation periods. Biphasic (recurrent) reactions occur in 1%–20% of anaphylactic cases. Symptoms may recur within the first eight hours to up to 72 hours after resolution of the initial phase (**Vogel 2010**).

Intravenous isavuconazole is not for bolus injection. As stated in the Summary of Product Characteristics (SmPC; section 4.2 Posology and method of administration), CRESEMBA must not be given as a bolus injection, and should be administered over a minimum of 1 hour.

As stated in the SmPC (section 4.4 Special warnings and precautions for use), caution should be used in prescribing CRESEMBA to patients with hypersensitivity to other azole antifungal agents; infusion-related reactions including hypotension, dyspnoea, dizziness, paraesthesia, nausea, and headache were reported during IV administration of CRESEMBA. The infusion should be stopped if these reactions occur.

Impact on the risk-benefit balance of the product

Infusion-related reactions are characterised by systemic symptoms occurring in association with IV administration of isavuconazole. Prompt recognition of infusion-related reactions coupled with discontinuing the infusion and proper management of the event may ameliorate clinical sequelae.

An isavuconazole-treated individual with an infusion-related reaction may require discontinuation of IV isavuconazole, which may limit its potential for therapeutic benefit.

In rare cases, an infusion-related reaction might lead to serious medical complications with a major impact on the individual patient. Overall, the benefit of isavuconazole as verified in clinical studies is considered to clearly outweigh the risk of infusion-related reactions.

Public health impact

Considering the expected low incidence of severe infusion-related reactions, and the predictability of the event in some cases based on patient risk factors, the impact of the event on the benefit-risk balance is considered low, based on the reversibility of the reactions given close monitoring and prompt recognition of the event, and appropriate treatment.

SVII.3.1.2 Important potential risks

Teratogenicity

Potential mechanisms

Teratogenicity is a posited azole class effect. The exact mechanism of teratogenicity observed in non-clinical studies with isavuconazole and other triazole antifungals has not been elucidated.

In isavuconazole embryofoetal development studies in rats' skeletal abnormalities were observed; in rabbits, visceral variations and skeletal abnormalities were observed.

Evidence source and strength of evidence

There is no clinical data on the use of isavuconazole in pregnancy as the use of isavuconazole during pregnancy was strictly avoided.

Teratogenicity is an important potential risk based on non-clinical findings (skeletal anomalies in rats and rabbits), which are consistent with findings previously reported for other azole antifungal agents. Early embryonic and foetal developmental toxicity have been observed in non-clinical studies with isavuconazole; the teratogenic potential of isavuconazole at higher doses was similar to other azoles. Administration of isavuconazole to rats at a dose of 90 mg/kg/day (2.3-times the maintenance dose based on mg/m^2/day) during pregnancy through the weaning period showed an increased perinatal mortality of the pups.

Characterisation of the risk

No clinical data. No pregnant women have been exposed to isavuconazole. (Clinical experience with isavuconazole in pregnant women was strictly avoided per protocol and has not occurred).

A follow-up questionnaire has been designed aiming at gaining further information on this risk in case of accidental pregnancy.

Risk factors and risk groups

No specific risk factors or risk groups, other than exposure in pregnant women have yet been identified.

Preventability

Although no information is available about the effects of isavuconazole on the foetus during pregnancy or its ability to cross the placenta in humans, based on animal data, isavuconazole is predicted to have the potential for increasing the risk of adverse developmental outcomes above background risk. CRESEMBA is not recommended during pregnancy and in women of childbearing potential not using contraception.

Impact on the risk-benefit balance of the product

Even though the nature and severity of teratogenicity events cannot be fully predicted based on the currently available data, occurrence of such events would have a significant impact on individual patients and has, therefore, impact on the overall benefit-risk profile of isavuconazole.

Public health impact

Not yet established. Pregnant females would potentially be at risk. These patients represent a small proportion of the target population for isavuconazole.

SVII.3.2 Presentation of the missing information

There is no missing information.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 26 lists the important identified risks, important potential risks, and missing information for isavuconazole.

Table 26 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Infusion-related reactions
Important potential risks	• Teratogenicity
Missing information	• None

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse drug reactions reporting and signal detection are presented below.

Specific adverse reaction follow-up questionnaires

The following guided questionnaires (which can be found in Annex 4) are used for CRESEMBA:

- Infusion-related reactions: Adverse drug reaction questionnaire
- Teratogenicity: Pregnancy data collection form

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned or ongoing.

III.3 Summary table of additional pharmacovigilance activities

No additional pharmacovigilance activities are planned or ongoing.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable - there are no post-authorisation efficacy studies.

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

V.1 Routine risk minimisation measures

The proposed minimisation measures are summarized in for each safety concern.

Table 27 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Infusion-related reactions	Routine risk communication: SmPC sections 4.2, 4.4, and 4.8. PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to administer by intravenous infusion over a minimum of 1-hour to reduce the risk of infusion-related reactions is warranted in Section 4.2 of the SmPC. Recommendation to stop the infusion, when infusion-related reactions suggestive of systemic hypersensitivity occur (such as anaphylactic reaction, hypotension, dyspnoea, dizziness, paraesthesia, nausea, and headache) is presented in Section 4.4 and PL Section 2. The side effects assimilated with infusion-related reactions are described in section 4.8 of SmPC and section 4 of PL. Other routine risk minimisation measures beyond the Product Information: None.
Important Potential risks	
Teratogenicity	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Isavuconazole is not recommended for women of childbearing potential who are not using contraception, as specified in Section 4.6 of the SmPC and preclinical teratogenicity is described in section 5.3 In pregnant women, isavuconazole should be used only if the anticipated benefits outweigh the possible risks to the foetus as specified in Section 4.6 of the SmPC and PL section 2. Other routine risk minimisation measures beyond the Product Information: None.
Missing Information	
None.	

PL = Package leaflet; SmPC = Summary of Product Characteristics.

V.2 Additional risk minimisation measures

Not applicable.

V.3 Summary of risk minimisation measures

Table 28 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Infusion-related reactions	Routine risk communication: SmPC section 4.2, 4.4, 4.8. PL section 2 and 4.	Pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire. Additional pharmacovigilance activities: None
Important Potential Risks		
Teratogenicity	Routine risk communication: SmPC section 4.6 and 5.3. PL section 2	Pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pregnancy Follow-up Questionnaire. Additional pharmacovigilance activities: None

PL = Package leaflet; SmPC = Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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

CRESEMBA's SmPC and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how CRESEMBA should be used.

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

VI.I The medicine and what it is used for

CRESEMBA is indicated in adults and paediatric patients 1 year of age and older for the treatment of:

- Invasive aspergillosis
- Mucormycosis in patients for whom amphotericin B is inappropriate

It contains isavuconazonium sulfate, which is the prodrug for the active substance isavuconazole, and it is given either orally or intravenously.

Further information about the evaluation of CRESEMBA's benefits can be found in CRESEMBA's EPAR, including in its plain-language summary.

VI.II Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise the risks identified for medicinal products:

- 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 public (e.g., with or without prescription) can help to minimise its risks.

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

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 CRESEMBA is not yet available, it is listed under 'missing information' below.

VI.II.A List of important risks and missing information

Important risks of CRESEMBA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 CRESEMBA. 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).

List of important risks and missing information	
Important identified risks	• Infusion-related reactions
Important potential risks	• Teratogenicity
Missing information	None

VI.II.B Summary of important risks

Important identified risk: Infusion-related reactions	
Evidence for linking the risk to the medicine	During clinical trials, infusion-related reactions e.g., hypotension, dyspnoea, dizziness, paraesthesia, nausea, and headache were reported. Infusion-related reactions are therefore considered an identified risk for isavuconazole. Clinical study data from the development programme provide the evidence for this risk.
Risk factors and risk groups	A history of allergic conditions appears to be associated with higher risk of infusion-related reactions. Risk factors for allergic drug reaction include the following: female gender, being an adult, HIV infection, concomitant viral infection, asthma, use of beta blockers, systemic lupus erythematosus, specific genetic polymorphisms, and previous hypersensitivity to a chemically-related drug.

Important identified risk: Infusion-related reactions	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4 Section 2 of the PL Recommendation to administer by intravenous infusion over a minimum of 1 hour to reduce the risk of infusion-related reactions is warranted in Section 4.2 of the SmPC. Recommendation to stop the infusion, when infusion-related reactions suggestive of systemic hypersensitivity occur (such as anaphylactic reaction, hypotension, dyspnoea, dizziness, paraesthesia, nausea, and headache) is presented in Section 4.4 and PL Section 2. Additional risk minimisation measures: None.

Important Potential Risk: Teratogenicity	
Evidence for linking the risk to the medicine	Teratogenicity is considered to be an important potential risk based on non-clinical findings (skeletal anomalies in rats and rabbits). There is no clinical data on the use of isavuconazole in pregnancy.
Risk factors and risk groups	No specific risk factors or risk groups, other than exposure in pregnant women have yet been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 PL Section 2 Isavuconazole is not recommended for women of childbearing potential who are not using contraception, as specified in Section 4.6 of the SmPC. In pregnant women, isavuconazole should be used only if he anticipated benefits outweigh the possible risks to the foetus as specified in Section 4.6 of the SmPC and PL section 2. Additional risk minimisation measures: None.

VI.II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

None.

II.C.2 Other studies in post-authorisation development plan

None.

PART VII: ANNEXES

Annex 1 EudraVigilance interface

Not applicable.

Annex 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

There are no planned or ongoing pharmacovigilance studies.

Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report
WSA-REG-001 Mucormycosis registry study Category 3	To evaluate the epidemiology and clinical course of invasive mould disease (IMD) caused by *Mucorales* and treated with systemic antifungal therapy (AFT).	Clinical efficacy and safety of isavuconazole treatment in patients infected with *Mucorales* species	16 Sep 2020

Annex 3 Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

A3: 1 Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable.

A3: 2 Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable.

A3: 3 Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority

Not applicable.

Annex 4 Specific adverse drug reaction follow-up forms

Adverse event follows up forms will be distributed for the safety concerns of Infusion-related reaction and Teratogenicity (see Part III [*Pharmacovigilance Plan*] of the RMP for details).

The follow-up forms for distribution are provided in this Annex below:

- Infusion-related reactions
- Teratogenicity

Adverse Drug Reaction Questionnaire – Infusion-related reactions

Cresemba® (isavuconazonium sulfate) **Adverse Drug Reaction Questionnaire** **Infusion-related reaction / hypersensitivity** Case number:	

Please complete this form and send it back to:

Name:

Fax:

Email:

Patient and background information
Date of birth (for adults, please provide only month and year):
Gender:
Weight:
Does the patient have any medical history of allergy? if yes please specify:
Indication of Cresemba treatment:
Dose:
Date of first administration of Cresemba:
Concomitant medication:

Therapy details
Infusion start date and time:
Infusion solution:
☐ Sodium chloride 9 mg/mL (0.9%) solution for injection OR
☐ 50 mg/mL (5%) dextrose solution OR
☐ Other, please specify
Total volume of the infusion solution after Cresemba dilution:
Type of infusion in-line filter:
Infusion rate:
Was this the first Cresemba infusion for this patient?

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Version 2.0, 08 Apr 2021

Cresemba® (isavuconazonium sulfate) **Adverse Drug Reaction Questionnaire** **Infusion-related reaction / hypersensitivity** Case number:	

Infusion related reactions (IRR) description
IRR start date and time: What was the first symptom of IRR: IRR stop date and time: Overall severity of the IRR:
Please mark the signs and symptoms of the IRR (select all those that apply): ☐ Abdominal pain ☐ Back pain ☐ Chest discomfort ☐ Chills ☐ Pyrexia ☐ Dizziness ☐ Cough ☐ Stridor ☐ Wheeze-bronchospasm ☐ Hypoxia ☐ Dyspnoea ☐ Facial oedema ☐ Fatigue ☐ Flushing ☐ Headache ☐ Hypertension ☐ Hypotension ☐ Syncope ☐ Incontinence ☐ Nausea ☐ Vomiting ☐ Palpitations ☐ Paraesthesia ☐ Rash ☐ Tachycardia ☐ OTHER. Please specify:
Narrative description

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Version 2.0, 08 Apr 2021

Cresemba® (isavuconazonium sulfate) **Adverse Drug Reaction Questionnaire** **Infusion-related reaction / hypersensitivity** Case number:	

Please provide a detailed narrative description of the IRR:
Action taken
Was the infusion interrupted as a result of the IRR?
Did the IRR abate as a result of the interruption of the infusion?
Was the infusion reintroduced?
Was the infusion rate decreased as a result of the IRR?
Did the IRR recur after reducing the rate of infusion?
Was any treatment given for the IRR?
Were any laboratory tests done and/or was any monitoring undertaken due to the IRR? Please specify:
Reporter details
Form completed by: **Name:** _____ **Function:** _____ **Signature:** _____

Thank you for reporting adverse events to (name of your company) . All the information and personal data you share with us will be protected and kept confidential in line with company policies and local regulations. The information you provide will be used for the purpose of drug safety surveillance, and may be shared with Health Authorities or involved third parties. You have the right of access to your personal data which we hold about you. If you wish to contact us regarding our use of your personal data, to object to the processing of your personal data, or to ask for the deletion or rectification of your personal data, please email us at (please add).

Data Collection Form – Teratogenicity

Pregnancy Report from postmarketing

Please complete this form and send it back to:
Name: PrimeVigilance
Fax: EU +44-8000-669-192 / US +1-866-902-7489
Email: basilea@primevigilance.com

Thank you for reporting the pregnancy to Basilea Pharmaceutica International Ltd. Allschwil. All the information and personal data you share with us will be protected and kept confidential in line with company policies and local regulations. The information you provide will be used for the purpose of drug safety surveillance, and it may be shared anonymized with Health Authorities or involved third parties. You have the right of access to your personal data which we hold about you. If you wish to contact us regarding our use of your personal data, object to the processing of your personal data, or ask for the deletion or rectification of your personal data, please email us at dataprotection@basilea.com.

Initial report ☐ Follow-up ☐

PART A - To be completed when pregnancy is confirmed

1. Parents' demographics

Mother	Year of birth	Age	Height (cm)	Weight (kg)
Father	Year of birth	Age	Height (cm)	Weight (kg)

2. Suspected drug(s) information in order of suspicion - Continue overleaf if necessary

Parent treated with Basilea drug: Mother ☐ Father ☐

Trade Name (generic name if trade name not known)	Lot number	Dose / Frequency / Dosage form / Route of administration	Condition for which drug was prescribed	Therapy dates		
				Start date	On-going	End date
					☐	
					☐	
					☐	

3. Relevant concomitant treatments of mother / father - Specify prescribed medications, OTC products, pregnancy supplements such as Folic Acid, multivitamins - Add extra lines if necessary

☐ None

Trade Name (generic name if trade name not known)	Lot number	Dose / Frequency/ Dosage form / Route of administration	Condition for which drug was prescribed	Therapy dates			Mother / Father
				Start date	On-going	End date	
					☐		M ☐ F ☐

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Pregnancy Report from postmarketing

					☐		M ☐ F ☐
					☐		M ☐ F ☐
					☐		M ☐ F ☐
					☐		M ☐ F ☐
					☐		M ☐ F ☐

4. Relevant medical history and current conditions of mother and father - Continue overleaf if necessary

Medical History, Current Conditions Including hypertension, seizure disorder, diabetes, psychiatric disorder, malignancy, infection							
Mother				**Father** (in case of exposure via semen)			
Medical history present: ☐ No ☐ Unknown ☐ Yes, If Yes specify below:				**Medical history present:** ☐ No ☐ Unknown ☐ Yes, If Yes specify below:			
Medical history (Multiple history details + start dates)				**Medical history** (Multiple history details + start dates)			
Current condition present: ☐ No ☐ Unknown ☐ Yes, If Yes specify (Multiple details + start dates)				**Current condition present:** ☐ No ☐ Unknown ☐ Yes, If Yes specify (Multiple details + start dates):			
Family history:	☐ No	☐ Unknown		**Family history:**	☐ No	☐ Unknown	
Congenital Anomaly:	☐ No	☐ Unknown	☐ Yes*	Congenital Anomaly:	☐ No	☐ Unknown	☐ Yes*
Mental Illness:	☐ No	☐ Unknown	☐ Yes*	Mental Illness:	☐ No	☐ Unknown	☐ Yes*
Other family history:	☐ No	☐ Unknown	☐ Yes*	Other family history:	☐ No	☐ Unknown	☐ Yes*
*Please specify:				*Please specify:			

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Pregnancy Report from postmarketing

5. Relevant obstetrical / pregnancy history - Continue overleaf if necessary

☐ **None** ☐ **Unknown**

Contraception
List primary (highly effective) and secondary (e.g., barrier) methods
1: ☐ None
2: ☐ Unknown

Number of previous pregnancies: ☐ Unknown
Gravida (i.e. number of confirmed pregnancies):
Para (i.e. number of pregnancies > 20 weeks):
Multiple:

Outcome of Pregnancies and details:
☐ Live Birth:
☐ Spontaneous/Abortion/Miscarriage:
☐ Elective Abortion:
☐ Breech Pregnancy:
☐ Ectopic Pregnancy:
☐ Stillbirth:
☐ Other:

Treatment for Infertility: ☐ No ☐ Yes, specify: ☐ In Vitro Fertilization ☐ Other:

Previous complications: ☐ No ☐ Unknown ☐ Yes, specify:

Previous Neonatal Abnormalities: ☐ No ☐ Yes, specify:

Risk Factors: ☐ None ☐ Unknown

Smoking: ☐ Yes ☐ No ☐ Unknown
☐ Cigarettes ☐ Other, specify: Packs per day:
Stopped before / during Pregnancy: ☐ No ☐ Yes - Stop Date

Alcohol: ☐ Yes ☐ No ☐ Unknown
☐ Beer ☐ Wine ☐ Spirits ☐ Other, specify: Amount per Day:
Stopped before / during Pregnancy: ☐ No ☐ Yes - Stop Date

Other consumption/recreational drug use items:
☐ Yes ☐ No ☐ Unknown Specify: Amount per Day:
Stopped before / during Pregnancy: ☐ No ☐ Yes - Stop Date

Other Risk Factors / Additional Information / Laboratory results (including e.g. serology tests, rubella, toxoplasmosis)

Pregnancy Report from postmarketing

6. Pregnancy information / Status - Continue overleaf if necessary

Please provide any information about adverse event/s occurred during the pregnancy ☐ None
Date of last menstrual period: ☐Estimated Estimated date of conception: Date of first obstetrical ultrasonography examination: Estimated duration of pregnancy: weeks Number of foetus: Estimated date of delivery: Based on: ☐ Ultrasound or ☐ Last Menstrual Period Other relevant findings:
Date of status: ☐ Ongoing ☐ Lost to follow-up - Reason:

If the delivery has already occurred, please populate the PART B and C.

If the delivery has not yet occurred, please populate the PART C.

Pregnancy Report from postmarketing

PART B - To be completed when the delivery has occurred

☐ Lost to follow-up	☐ Unknown

1. **Delivery** - Continue overleaf if necessary

End of Pregnancy: Date: Duration of Gestation: |__|__| Weeks |__| Days

Outcome of Pregnancy: ☐ Live Birth → ☐ Vaginal Birth
→ ☐ Suction
→ ☐ Induced
→ ☐ Clamp
→ ☐ C-section Reason:
☐ Spontaneous Abortion/miscarriage Reason:
☐ Induced Abortion Reason:
☐ Elective Abortion Reason:
☐ Stillbirth Reason:

Normal Placenta: ☐ Yes ☐ No, specify:
Post-delivery care needed: ☐ No ☐ Yes, specify:
Breastfeeding: ☐ Yes ☐ No, specify:

2. **Additional details of the adverse event during pregnancy / delivery details**

☐ None

3. **Fetal outcome / Infant information** - Continue overleaf if necessary especially in case of multiple birth

If multiple births, number of neonates: ☐ NA

Sex: ☐ Male ☐ Female ☐ Unknown	**Apgar** scores at birth / at 5 minutes / at 10 minutes	**Length** cm / **Weight** kg / **Head circumference** cm

Pregnancy Report from postmarketing

☐ Normal Neonate
☐ Birth defect - Specify:
☐ Death - Date: Reason:
Autopsy results available: ☐ No ☐ Yes, specify:
Need for Resuscitation: ☐ Yes ☐ No
Admission to Intensive Care Unit: ☐ Yes ☐ No (if yes, please complete Adverse event below)

4. Adverse events of the neonate

To be completed in case of late fetal death, stillbirth, spontaneous abortion, elective termination

Any adverse event/ complications occurred: ☐ No ☐ Yes Complete the table below

Adverse Event	Seriousness criteria[1]	Outcome[2]	Severity[3]	Relationship with Basilea drug[4]	Onset date	On-going	End date

[1]Seriousness Criteria:	[2] Outcome:	[3] Severity:	[4] Relationship:
1 Death 2 Life-Threatening 3 Permanent Disability/Incapacity 4 Hospitalization/Prolonged hospitalization 5 Congenital Anomaly 6 Important Medical Event 7 Non-serious	1 Recovered 2 Recovering 3 Not Recovered 4 Recovered w/ Sequelae 5 Death 6 Unknown	1 Mild 2 Moderate 3 Severe	1 Not Related 2 Unlikely 3 Possible 4 Probable

5. Additional details of the adverse event of the neonate

☐ None

Please populate the PART C.

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Pregnancy Report from postmarketing

PART C - To be completed for each report sent

Reporter's details - At least one detail is required

Can the Company contact you regarding this case?
☐ Yes ☐ No, I cannot obtain/ exchange any further information

Name		☐ **Health Care Professional**	
Job title		☐ **Pharmacist** ☐ **Physician** ☐ **Consumer / Patient / Familiar** ☐ **Other:**	
Address		**Contact phone number**	
Date		**Signature**	

If reported by a patient, do you allow the Company to contact the treating physician?
☐ No
☐ Yes; please provide details of treating physician:

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Annex 5 Protocols for proposed and ongoing studies in RMP part IV

Not applicable.

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 Other supporting data (including referenced material)

All literature references are provided in Module 4 or Module 5 of the isavuconazonium sulfate dossier.

Annex 8 Summary of changes to the Risk Management Plan over time

Version number(s)	Procedure number Approval date	Major changes
1.0	EMEA/H/C/002734	Not applicable – Initial version.
2.0	EMEA/H/C/002734	Update of RMP according to the responses to D120 questions related to the RMP: • 'Elevated hepatic enzymes' has been replaced with 'hepatic function abnormal or hepatitis'. • Missing information 'embryofoetal toxicity' was renamed 'teratogenicity'. • Revised information on the use of isavuconazole during pregnancy. • Amendment to the proposed risk minimisation measures related to missing clinical experience in patients with severe hepatic impairment (Child-Pugh C). • Revision to treat patients with Candida spp. Infections. • Corresponding section has been revised to reflect the fact that isavuconazole capsules will be marketed in a single strength (100 mg), and that each 100-mg capsule will be packaged in individual blisters (aluminium monolayer) which will reduce the risk of medication errors that could lead to overdose. • Inclusion of a warning not to swallow or use the desiccant. • Clinical relevance of the safety margins observed in the repeated-dose toxicity studies is discussed.
3.0	EMEA/H/C/002734	Update of RMP according to the responses to D180 questions related to the RMP: • Revision of indications. • Adding of 'arrhythmia due to QT shortening' as an important identified risk.
4.0	EMEA/H/C/002734	Response to PRAC Rapporteur's RMP Assessment Report as endorsed by PRAC on 9 July 2015 (response to D181 Joint Assessment Report): • Clinical trial exposure and conclusions on the populations not studied and other limitations of the clinical trial development program: Addition that clinical data for isavuconazole in the treatment of mucormycosis are limited.

Version number(s)	Procedure number Approval date	Major changes
5.0	EMEA/H/C/002734 15 October 2015	Response to final outstanding issues – final version submitted with closing sequence: • Part IV: Deletion of the PAES registry study (Mucormycosis Registry Study) from efficacy studies which are specific obligations and/or conditions of the MA to other efficacy studies.
6.0	EMEA/H/C/PSUSA/00010426/201809	**General updates:** Updates were made to all Parts and Modules of the RMP in order to implement the updated GVP Module V (Rev. 2) EU RMP template. **Major changes to Part II:** Module SII (Non-Clinical part of the Safety Specification) was updated with the results of a juvenile rat toxicology study. Module SVII (Identified and potential risks) and Module SVIII (Summary of safety concerns) were updated to downgrade the previous important identified risk of 'Severe cutaneous adverse reactions' to a potential risk. Furthermore, to align with the SmPC/CCSI, the identified risk term 'Arrhythmia due to QT shortening' has been corrected to Electrocardiogram QT shortened. Module III (Clinical trial exposure) and Module V (Post-marketing exposure) were updated to reflect the latest exposure data. **Major changes to Part III:** A follow-up questionnaire for infusion-related reactions / hypersensitivity reactions was added as a routine pharmacovigilance activity. **Major changes to Part V:** Updated to align with the changes in safety concerns, as described above. **Major changes to Part VI:** Updated to reflect overall EU RMP changes.
7.0	EMEA/H/C/PSUSA/00010426/201809 11 April 2019 (date of PRAC recommendation)	The Rapporteur requested to supply the routine PhV activities description with information regarding a follow-up questionnaire for infusion-related reaction/hypersensitivity reactions on the page 92 of the RMP version 6.0.

Version number(s)	Procedure number Approval date	Major changes
8.0 (previous 7.1)	EMEA/H/C/002734/R/0027 CHMP opinion: 28 May 2020	**Major changes to Part II:** Following the re-evaluation of all available data, the following safety concerns were removed from the RMP (changed reflected in Module VII [*Identified and potential risks*] and Module SVIII [*Summary of safety concerns*]): • *Important identified risks*: Hepatic function abnormal or hepatitis; and Electrocardiogram QT shortened • *Important potential risk*: Severe cutaneous adverse reactions (SCARs); Effect on children exposed to isavuconazole via breast milk; Off label use; and Development of resistant strains • *Missing information*: Use in patients with severe hepatic impairment; and Use in patients under 18-years-old. In addition, Module III (Clinical trial exposure) and Module V (Post-marketing exposure) were updated to reflect the latest exposure data. **Major changes to Part III:** Completed Study 9766-CL-0046 was removed. **Major changes to Part V:** Safety concerns were removed, in line with the changes made to Part II, Module SVIII. **Major changes to Part VI:** Updated to reflect overall EU RMP changes.

Version number(s)	Procedure number Approval date	Major changes
Version 9.0	EMEA/H/C/002734/II/0035/G EC decision: 21 June 2022	**Major changes to Part II:** Following the completion of the Basilea Mucormycosis Registry Study (within the FungiScope™ Registry), WSA-REG-001 study, the area of missing information of *'Clinical efficacy and safety of Isavuconazole treatment in patients with Mucorales species'* was removed from the RMP. The area of missing information of '*Efficacy in invasive aspergillosis in Asian patients'* was also removed from the RMP. In addition, Module III (Clinical trial exposure) and Module V (Post-marketing exposure) were updated to reflect the latest exposure data. **Major changes to Part III:** Completed Study WSA-REG-001was removed. Study AK1820-301 was removed. **Major changes to Part V:** Areas of missing information of *'Clinical efficacy and safety of Isavuconazole treatment in patients with Mucorales species'* and *'Efficacy in invasive aspergillosis in Asian patients'* were removed, in line with the changes made to Part II, Module SVIII. **Major changes to Part VI:** Updated to reflect overall EU RMP changes.

Version number(s)	Procedure number Approval date	Major changes
Version 9.1	EMEA/H/C/002734/X/0042/G	**Major changes to Part I:** Extension of the currently approved indications to paediatric patients and addition of a new strength of the oral hard capsule formulation. Consequential update of the dosage to reflect the treatment of paediatric patients. **Minor changes to PART II: Module SIII: Clinical trial exposure:** Updated to reflect latest exposure data. **Minor changes to PART II: Module SV: Post-authorisation experience**: Updated to reflect latest exposure data. **Minor changes to PART II: Module SVII: Identified and Potential Risks:** Deletion of information related to mucormycosis registry study WSA-REG-001. Statement regarding paediatric population added: *The safety profile of isavuconazole in the paediatric population was found to be similar to that in the adult population, and no new safety signals were detected. Therefore, the below described identified risks are also applicable for the paediatric population.* **Minor change to PART V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) and PART VI: Summary of RMP:** Editorial change to routine risk minimisation measures activities for infusion-related reactions to reflect latest current SmPC and PL wording according to procedure EMEA/H/C/PSUSA/00010426/202109 with EC Decision dated 21 June 2022. **Minor change to PART VII: Annex 4 - Data Collection Form – Teratogenicity**: The pregnancy report form was updated with the current Basilea logo, and minor editorial changes were made.

Version number(s)	Procedure number Approval date	Major changes
Version 10.0	EMEA/H/C/002734/X/0042/G	**PART I Product Overview:** Intravenous administration: Revised dosing recommendation for paediatric patients aged from 1 year to less than 3 years of age and a bodyweight of less than 18 kg. **PART VI: Summary of RMP:** Updated indication to include paediatric patients as requested by the PRAC Rapporteur.
Version 11.0	EMEA/H/C/002734/X/0042/G	**PART I Product Overview:** Intravenous administration: Reduced dosing recommendation for paediatric patients aged from 1 year to less than 3 years of age. Oral administration: To provide a better-tailored dosage advice for paediatric patients aged 6 years and older with a bodyweight of 32 to less than 37 kg treated with oral isavuconazole.