ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CRESEMBA 200 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg isavuconazole (as 372.6 mg isavuconazonium sulfate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion
White to yellow powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CRESEMBA is indicated in patients from 1 year of age and older for the treatment of
- invasive aspergillosis
- mucormycosis in patients for whom amphotericin B is inappropriate (see sections 4.4 and 5.1)

Consideration should be given to official guidance on the appropriate use of antifungal agents.

4.2 Posology and method of administration

Posology

Early targeted therapy (pre-emptive or diagnostic-driven therapy) may be instituted pending confirmation of the disease from specific diagnostic tests. However, once these results become available, antifungal therapy should be adjusted accordingly.

Detailed information on dosage recommendations is provided in the following table:

Table 1 Dosage recommendation

	Loading dose (every 8 hours for the first 48 hours) [1]	**Maintenance dose (once daily) [2]**
Adults	200 mg isavuconazole (one vial) [3]	200 mg isavuconazole (one vial) [3]
Paediatric patients aged from 1 year to less than 18 years		
Bodyweight ≥ 37 kg	200 mg isavuconazole (one vial) [3]	200 mg isavuconazole (one vial) [3]
Bodyweight < 37 kg	5.4 mg/kg isavuconazole	5.4 mg/kg isavuconazole

[1] Six administrations in total.
[2] Maintenance dose: Starting 12 to 24 hours after the last loading dose.
[3] After reconstitution and dilution.

The maximum of any individual loading or daily maintenance dose to be administered to any paediatric patient is 200 mg isavuconazole.

Duration of therapy should be determined by the clinical response (see section 5.1).

For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered (see sections 5.1 and 5.3).

Switch to oral isavuconazole
CRESEMBA is available as 100 mg and 40 mg hard capsules. On the basis of the high oral bioavailability (98%, see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated. For detailed dosing recommendations, please see section 4.2 of the Summary of Product Characteristics for CRESEMBA 40 mg and 100 mg hard capsules.

Elderly
No dose adjustment is necessary for elderly patients; however, the clinical experience in elderly patients is limited.

Renal impairment
No dose adjustment is necessary in adult patients with renal impairment, including patients with end-stage renal disease (see section 5.2).

No dose recommendation can be made for paediatric patients with renal impairment, as no relevant data are available.

Hepatic impairment
No dose adjustment is necessary in adult patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B) (see sections 4.4 and 5.2).

Isavuconazole has not been studied in adult 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 (see sections 4.4, 4.8 and 5.2).

No dose recommendation can be made for paediatric patients with hepatic impairment, as no relevant data are available.

Paediatric population
The safety and efficacy of isavuconazole in paediatric patients aged less than 1 year has not been established.

Method of administration

Intravenous use.

Precautions to be taken before handling or administering the medicinal product
CRESEMBA must be reconstituted and then further diluted to a concentration corresponding to a range of 0.4 to 0.8 mg/mL isavuconazole prior to administration by intravenous infusion over a minimum of 1 hour to reduce the risk of infusion-related reactions. Higher concentrations should be avoided as these may cause local irritation at the site of infusion. The infusion must be administered via an infusion set with an in-line filter with a microporous membrane made of polyethersulfone (PES) and with a pore size of 0.2 µm to 1.2 µm. CRESEMBA must only be given as an intravenous infusion.

For detailed instructions on the reconstitution and dilution of CRESEMBA before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ketoconazole (see section 4.5).

Co-administration with high-dose ritonavir (>200 mg every 12 hours) (see section 4.5).

Co-administration with strong CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g. phenobarbital), phenytoin and St. John's wort or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine (see section 4.5).

Patients with familial short QT syndrome (see section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity

Hypersensitivity to isavuconazole may result in adverse reactions that include: anaphylactic reaction, hypotension, respiratory failure, dyspnoea, drug eruption, pruritus, and rash (see section 4.8). In case of anaphylactic reaction, isavuconazole should be discontinued immediately and appropriate medical treatment should be initiated.

Caution should be used in prescribing isavuconazole to patients with hypersensitivity to other azole antifungal agents.

Infusion-related reactions

During intravenous administration of isavuconazole, infusion-related reactions including hypotension, dyspnoea, dizziness, paraesthesia, nausea, and headache were reported (see section 4.8). The infusion should be stopped if these reactions occur.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported during treatment with azole antifungal agents. If a patient develops a severe cutaneous adverse reaction, CRESEMBA should be discontinued.

Cardiovascular

QT shortening
Isavuconazole is contraindicated in patients with familial short QT syndrome (see section 4.3).
In a QT study in healthy human subjects, isavuconazole shortened the QTc interval in a concentration-related manner. For the 200 mg dosing regimen, the least squares mean (LSM) difference from placebo was 13.1 ms at 2 hours post dose [90% CI: 17.1, 9.1 ms]. Increasing the dose to 600 mg resulted in an LSM difference from placebo of 24.6 ms at 2 hours post dose [90% CI: 28.7, 20.4 ms].

Caution is warranted when prescribing isavuconazole to patients taking other medicinal products known to decrease the QT interval, such as rufinamide.

Elevated liver transaminases or hepatitis

Elevated liver transaminases have been reported in clinical studies (see section 4.8). The elevations in liver transaminases rarely required discontinuation of isavuconazole. Monitoring of hepatic enzymes should be considered, as clinically indicated. Hepatitis has been reported with azole antifungal agents including isavuconazole.

Severe hepatic impairment

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 (see sections 4.2, 4.8 and 5.2).

Concomitant use with other medicinal products

CYP3A4/5 inhibitors
Ketoconazole is contraindicated (see section 4.3). For the strong CYP3A4 inhibitor lopinavir/ritonavir, a two-fold increase in isavuconazole exposure was observed. For other strong CYP3A4/5 inhibitors, a less pronounced effect can be expected. No dose adjustment of isavuconazole is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see section 4.5).

CYP3A4/5 inducers
Co-administration with mild CYP3A4/5 inducers such as aprepitant, prednisone, and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels; co-administration with mild CYP3A4*/5* inducers should be avoided unless the potential benefit is considered to outweigh the risk (see section 4.5).

CYP3A4/5 substrates including immunosuppressants
Isavuconazole can be considered a moderate inhibitor of CYP3A4/5, and systemic exposure to medicinal products metabolised by CYP3A4 may be increased when co-administered with isavuconazole. Concomitant use of isavuconazole with CYP3A4 substrates such as the immunosuppressants tacrolimus, sirolimus or ciclosporin may increase the systemic exposure to these medicinal products. Appropriate therapeutic drug monitoring and dose adjustment may be necessary during co-administration (see section 4.5).

CYP2B6 substrates
Isavuconazole is an inducer of CYP2B6. Systemic exposure to medicinal products metabolised by CYP2B6 may be decreased when co-administered with isavuconazole. Therefore, caution is advised when CYP2B6 substrates, especially medicinal products with a narrow therapeutic index such as cyclophosphamide, are co-administered with isavuconazole. The use of the CYP2B6 substrate efavirenz with isavuconazole is contraindicated because efavirenz is a moderate inducer of CYP3A4/5 (see section 4.3).

P-gp substrates
Isavuconazole may increase the exposure of medicinal products that are P-gp substrates. Dose adjustment of medicinal products that are P-gp substrates, especially medicinal products with a narrow therapeutic index such as digoxin, colchicine and dabigatran etexilate, may be needed when concomitantly administered with isavuconazole (see section 4.5).

Limitations of the clinical data

The clinical data for isavuconazole in the treatment of mucormycosis are limited to one prospective non-controlled clinical study in 37 adult patients with proven or probable mucormycosis who received isavuconazole for primary treatment, or because other antifungal treatments (predominantly amphotericin B) were inappropriate.
For individual *Mucorales* species, the clinical efficacy data are very limited, often to one or two patients (see section 5.1). Susceptibility data were available in only a small subset of cases. These data indicate that concentrations of isavuconazole required for inhibition *in vitro* are very variable between genera/species within the order of *Mucorales*, and generally higher than concentrations required to inhibit *Aspergillus* species. It should be noted that there was no dose-finding study in mucormycosis, and patients were administered the same dose of isavuconazole as was used for the treatment of invasive aspergillosis.

4.5 Interaction with other medicinal products and other forms of interaction

Potential of medicinal products to affect the pharmacokinetics of isavuconazole

Isavuconazole is a substrate of CYP3A4 and CYP3A5 (see section 5.2). 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 which are inducers of CYP3A4 and/or CYP3A5 may decrease the plasma concentrations of isavuconazole.

Medicinal products that inhibit CYP3A4/5

Co-administration of isavuconazole with the strong CYP3A4/5 inhibitor ketoconazole is contraindicated, since this medicinal product can significantly increase plasma concentrations of isavuconazole (see sections 4.3 and 4.5).

For the strong CYP3A4 inhibitor lopinavir/ritonavir, a two-fold increase in isavuconazole exposure was observed. For other strong CYP3A4 inhibitors, such as clarithromycin, indinavir and saquinavir, a less pronounced effect can be expected, based on their relative potency. No dose adjustment of isavuconazole is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see section 4.4).

No dose adjustment is warranted for moderate to mild CYP3A4/5 inhibitors.

Medicinal products that induce CYP3A4/5

Co-administration of isavuconazole with potent CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g., phenobarbital), phenytoin and St. John's wort, or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine, is contraindicated, since these medicinal products can significantly decrease plasma concentrations of isavuconazole (see section 4.3).

Co-administration with mild CYP3A4/5 inducers such as aprepitant, prednisone and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels; co-administration with mild CYP3A4/5 inducers should be avoided unless the potential benefit is considered to outweigh the risk (see section 4.4).

Co-administration with high-dose ritonavir (>200 mg twice daily) is contraindicated, as at high doses ritonavir may induce CYP3A4/5 and decrease isavuconazole plasma concentrations (see section 4.3).

Potential for isavuconazole to affect exposures of other medicines

Medicinal products metabolised by CYP3A4/5

Isavuconazole is a moderate inhibitor of CYP3A4/5; co-administration of isavuconazole with medicinal products which are substrates of CYP3A4/5 may result in increased plasma concentrations of these medicinal products.

Medicinal products metabolised by CYP2B6

Isavuconazole is a mild CYP2B6 inducer; co-administration of isavuconazole may result in decreased plasma concentrations of CYP2B6 substrates.

Medicinal products transported by P-gp in the intestine

Isavuconazole is a mild inhibitor of P-glycoprotein (P-gp); co-administration with isavuconazole may result in increased plasma concentrations of P-gp substrates.

Medicinal products transported by BCRP

Isavuconazole is an inhibitor *in vitro* of BCRP, and plasma concentrations of substrates of BCRP may therefore be increased. Caution is advised when isavuconazole is given concomitantly with substrates of BCRP.

Medicinal products renally excreted via transport proteins

Isavuconazole is a mild inhibitor of the organic cation transporter 2 (OCT2). Co-administration of isavuconazole with medicinal products which are substrates of OCT2 may result in increased plasma concentrations of these medicinal products.

Uridine diphosphate-glucuronosyltransferases (UGT) substrates

Isavuconazole is a mild inhibitor of UGT. Co-administration of isavuconazole with medicinal products which are substrates of UGT may result in mildly increased plasma concentrations of these medicinal products.

Interaction table

Interactions between isavuconazole and co-administered medicinal products are listed in Table 2 (increase is indicated as "↑", decrease as "↓"), ordered by therapeutic class. Unless otherwise stated, studies detailed in Table 2 have been performed in adults with the recommended dose of isavuconazole.

Table 2 Interactions

Co-administered medicinal product by therapeutic area	**Effects on drug concentrations / Geometric Mean Change (%) in AUC, C_{max} (Mode of action)**	**Recommendation concerning co-administration**
Anticonvulsants		
Carbamazepine, phenobarbital and phenytoin (strong CYP3A4/5 inducers)	Isavuconazole concentrations may decrease (CYP3A induction by carbamazepine, phenytoin and long-acting barbiturates such as phenobarbital).	The concomitant administration of isavuconazole and carbamazepine, phenytoin and long-acting barbiturates such as phenobarbital is contraindicated.
Antibacterials		
Rifampicin (strong CYP3A4/5 inducer)	Isavuconazole : AUC_{tau} : ↓ 90% C_{max} : ↓ 75% (CYP3A4/5 induction)	The concomitant administration of isavuconazole and rifampicin is contraindicated.
Rifabutin (strong CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and rifabutin is contraindicated.
Nafcillin (moderate CY3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and nafcillin is contraindicated.
Clarithromycin (strong CYP3A4/5 inhibitor)	Not studied.	No isavuconazole dose adjustment necessary; caution is

	Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	advised as adverse drug reactions may increase.
Antifungals		
Ketoconazole (strong CYP3A4/5 inhibitor)	Isavuconazole: AUC_{tau}: ↑ 422% C_{max}: ↑ 9% (CYP3A4/5 inhibition)	The concomitant administration of isavuconazole and ketoconazole is contraindicated.
Herbal medicines		
St John's wort (strong CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4 induction).	The concomitant administration of isavuconazole and St John's wort is contraindicated.
Immunosuppresants		
Ciclosporin, sirolimus, tacrolimus (CYP3A4/5 substrates)	Ciclosporin: AUC_{inf}: ↑ 29% C_{max}: ↑ 6% Sirolimus: AUC_{inf}: ↑ 84% C_{max}: ↑ 65% Tacrolimus: AUC_{inf}: ↑ 125% C_{max}: ↑ 42% (CYP3A4 inhibition)	No isavuconazole dose adjustment necessary. Ciclosporin, sirolimus, tacrolimus: monitoring of plasma levels and appropriate dose adjustment if required.
Mycophenolate mofetil (MMF) (UGT substrate)	Mycophenolic acid (MPA, active metabolite): AUC_{inf}: ↑ 35% C_{max}: ↓ 11% (UGT inhibition)	No isavuconazole dose adjustment necessary. MMF: monitoring for MPA-related toxicities is advised.
Prednisone (CYP3A4 substrate)	Prednisolone (active metabolite): AUC_{inf}: ↑ 8% C_{max}: ↓ 4% (CYP3A4 inhibition) Isavuconazole concentrations may decrease. (CYP3A4/5 induction)	Co-administration should be avoided unless the potential benefit is considered to outweigh the risk.
Opioids		
Short-acting opiates (alfentanyl, fentanyl) (CYP3A4/5 substrate)	Not studied. Short-acting opiate concentrations may increase. (CYP3A4/5 inhibition).	No isavuconazole dose adjustment necessary. Short-acting opiates (alfentanyl, fentanyl): careful monitoring for any occurrence of drug toxicity, and dose reduction if required.
Methadone (CYP3A4/5, 2B6 and 2C9 substrate)	S-methadone (inactive opiate isomer) AUC_{inf}: ↓ 35%	No isavuconazole dose adjustment necessary.

	C_{max}: ↑ 1% 40% reduction in terminal half-life R-methadone (active opiate isomer). AUC_{inf}: ↓ 10% C_{max}: ↑ 4% (CYP2B6 induction)	Methadone: no dose adjustment required.
Anti-cancer		
Vinca alkaloids (vincristine, vinblastine) (P-gp substrates)	Not studied. Vinca alkaloid concentrations may increase. (P-gp inhibition)	No isavuconazole dose adjustment necessary. Vinca alkaloids: careful monitoring for any occurrence of drug toxicity, and dose reduction if required.
Cyclophosphamide (CYP2B6, CYP3A4 substrate)	Not studied. Active metabolites of cyclophosphamide concentrations may increase or decrease. (CYP2B6 induction, CYP3A4 inhibition)	No isavuconazole dose adjustment necessary. Cyclophosphamide: careful monitoring for any occurrence of lack of efficacy or increased toxicity, and dose adjustment if required.
Methotrexate (BCRP, OAT1, OAT3 substrate)	Methotrexate: AUC_{inf}: ↓ 3% C_{max}: ↓ 11% 7-hydroxymetabolite: AUC_{inf}: ↑ 29% C_{max}: ↑ 15% (Mechanism unknown)	No isavuconazole dose adjustment necessary. Methotrexate: no dose adjustment required.
Other anticancer agents (daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan) (BCRP substrates)	Not studied. Daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan concentrations may increase. (BCRP inhibition)	No isavuconazole dose adjustment necessary. Daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone or topotecan: careful monitoring for any occurrence of drug toxicity, and dose reduction if required.
Antiemetics		
Aprepitant (mild CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may decrease. (CYP3A4/5 induction)	Co-administration should be avoided unless the potential benefit is considered to outweigh the risk.
Antidiabetics		
Metformin (OCT1, OCT2 and MATE1 substrate)	Metformin: AUC_{inf}: ↑ 52% C_{max}: ↑ 23% (OCT2 inhibition)	No isavuconazole dose adjustment necessary. Metformin: dose reduction may be required.
Repaglinide (CYP2C8 and OATP1B1 substrate)	Repaglinide: AUC_{inf}: ↓ 8% C_{max}: ↓ 14%	No isavuconazole dose adjustment necessary. Repaglinide: no dose adjustment required.
Pioglitazone (mild CYP3A4/5 inducer)	Not studied.	Co-administration should be avoided unless the potential

	Isavuconazole concentrations may decrease. (CYP3A4/5 induction)	benefit is considered to outweigh the risk.
Anticoagulants		
Dabigatran etexilate (P-gp substrate)	Not studied. Dabigatran etexilate concentrations may increase. (P-gp inhibition).	No isavuconazole dose adjustment necessary. Dabigatran etexilate has a narrow therapeutic index and should be monitored, and dose reduction if required.
Warfarin (CYP2C9 substrate)	S-warfarin AUC_{inf}: ↑ 11% C_{max}: ↓ 12% R-warfarin AUC_{inf}: ↑ 20% C_{max}: ↓ 7%	No isavuconazole dose adjustment necessary. Warfarin: no dose adjustment required.
Antiretroviral agents		
Lopinavir 400 mg / Ritonavir 100 mg (CYP3A4/5 strong inhibitors and substrates)	Lopinavir: AUC_{tau}: ↓ 27% C_{max}: ↓ 23% C_{min}, ss: ↓ 16%[a)] Ritonavir: AUC_{tau}: ↓ 31% C_{max}: ↓ 33% (Mechanism unknown) Isavuconazole: AUC_{tau}: ↑ 96% C_{max}: ↑ 74% (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary; caution is advised as adverse drug reactions may increase. Lopinavir/ritonavir: no dose adjustment for lopinavir 400 mg / ritonavir 100 mg every 12 hours required, but careful monitoring for any occurrence of lack of anti-viral efficacy.
Ritonavir (at doses >200 mg every 12 hours) (strong CYP3A4/5 inducer)	Not studied. Ritonavir at high doses may significantly decrease isavuconazole concentrations. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and high doses of ritonavir (>200 mg every 12 hours) is contraindicated.
Efavirenz (CYP3A4/5 moderate inducer and CYP2B6 substrate)	Not studied. Efavirenz concentrations may decrease. (CYP2B6 induction) Isavuconazole drug concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and efavirenz is contraindicated.
Etravirine (moderate CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and etravirine is contraindicated.
Indinavir (CYP3A4/5 strong inhibitor and substrate)	Indinavir:[b)] AUC_{inf}: ↓ 36% C_{max}: ↓ 52%	No isavuconazole dose adjustment necessary; caution is

	(Mechanism unknown) Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	advised as adverse drug reactions may increase. Indinavir: careful monitoring for any occurrence of lack of anti-viral efficacy, and dose increase if required.
Saquinavir (strong CYP3A4 inhibitor)	Not studied. Saquinavir concentrations may decrease (as observed with lopinavir/ritonavir) or increase. (CYP3A4 inhibition) Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary; caution is advised as adverse drug reactions may increase. Saquinavir: careful monitoring for any occurrence of drug toxicity and /or lack of anti-viral efficacy, and dose adjustment if required
Other protease inhibitors (e.g. fosamprenavir) (CYP3A4/5 strong or moderate inhibitors and substrates)	Not studied. Protease inhibitor concentrations may decrease (as observed with lopinavir/ritonavir) or increase. (CYP3A4 inhibition) Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary. Protease inhibitors: careful monitoring for any occurrence of drug toxicity and /or lack of anti-viral efficacy, and dose adjustment if required.
Other NNRTI (e.g. nevirapine) (CYP3A4/5 and 2B6 inducers and substrates)	Not studied. NNRTI concentrations may decrease (CYP2B6 induction by isavuconazole) or increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary. NNRTIs: careful monitoring for any occurrence of drug toxicity and/or lack of anti-viral efficacy, and dose adjustment if required.
Antiacids		
Esomeprazole (CYP2C19 substrate and gastric pH ↑)	Isavuconazole: AUC_{tau}: ↑ 8% C_{max}: ↑ 5%	No isavuconazole dose adjustment necessary. Esomeprazole: no dose adjustment required.
Omeprazole (CYP2C19 substrate and gastric pH ↑)	Omeprazole: AUC_{inf}: ↓ 11% C_{max}: ↓ 23%	No isavuconazole dose adjustment necessary. Omeprazole: no dose adjustment required.
Lipid-lowering agents		
Atorvastatin and other statins (CYP3A4 substrates e.g., simvastatin, lovastatin, rosuvastatin) (CYP3A4/5 and/or BCRP substrates))	Atorvastatin : AUC_{inf}: ↑ 37% C_{max}: ↑ 3% Other statins were not studied. Statins concentrations may increase. (CYP3A4/5 or BCRP inhibition)	No isavuconazole dose adjustment necessary. Based on results with atorvastatin, no statin dose adjustment required. Monitoring of adverse reactions typical of statins is advised.
Antiarrhythmics		

Digoxin (P-gp substrate)	Digoxin: AUC_{inf}: ↑ 25% C_{max}: ↑ 33% (P-gp inhibition)	No isavuconazole dose adjustment necessary. Digoxin: serum digoxin concentrations should be monitored and used for titration of the digoxin dose.
Oral contraceptives		
Ethinyl oestradiol and norethindrone (CYP3A4/5 substrates)	Ethinyl oestradiol AUC_{inf}: ↑ 8% C_{max}: ↑ 14% Norethindrone AUC_{inf}: ↑ 16% C_{max}: ↑ 6%	No isavuconazole dose adjustment necessary. Ethinyl oestradiol and norethindrone: no dose adjustment required.
Antitussives		
Dextromethorphan (CYP2D6 substrate)	Dextromethorphan: AUC_{inf}: ↑ 18% C_{max}: ↑ 17% Dextrorphan (active metabolite): AUC_{inf}: ↑ 4% C_{max}: ↓ 2%	No isavuconazole dose adjustment necessary. Dextromethorphan: no dose adjustment required.
Benzodiazepines		
Midazolam (CYP3A4/5 substrate)	Oral midazolam: AUC_{inf}: ↑ 103% C_{max}: ↑ 72% (CYP3A4 inhibition)	No isavuconazole dose adjustment necessary. Midazolam: careful monitoring of clinical signs and symptoms recommended, and dose reduction if required.
Antigout agent		
Colchicine (P-gp substrate)	Not studied. Colchicine concentrations may increase. (P-gp inhibition)	No isavuconazole dose adjustment necessary. Colchicine has a narrow therapeutic index and should be monitored, dose reduction if required.
Natural products		
Caffeine (CYP1A2 substrate)	Caffeine: AUC_{inf}: ↑ 4% C_{max}: ↓ 1%	No isavuconazole dose adjustment necessary. Caffeine: no dose adjustment required.
Smoking cessation aids		
Bupropion (CYP2B6 substrate)	Bupropion: AUC_{inf}: ↓ 42% C_{max}: ↓ 31% (CYP2B6 induction)	No isavuconazole dose adjustment necessary. Bupropion: dose increase if required.

NNRTI, non-nucleoside reverse-transcriptase inhibitor; P-gp, P-glycoprotein.

[a)] % decrease of the mean trough level values

[b)] Indinavir was only studied after a single dose of 400 mg isavuconazole.

AUC_{inf} = area under the plasma concentration-time profiles extrapolated to infinity; AUC_{tau} = area under the plasma concentration-time profiles during the 24 h interval at steady state; C_{max} = peak plasma concentration; C_{min},ss = trough levels at steady state.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of CRESEMBA in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

CRESEMBA 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.

Women of child-bearing potential

CRESEMBA is not recommended for women of childbearing potential who are not using contraception.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of isavuconazole/metabolites in milk (see section 5.3).

A risk to newborns and infants cannot be excluded.

Breast-feeding should be discontinued during treatment with CRESEMBA.

Fertility

There are no data on the effect of isavuconazole on human fertility. Studies in animals did not show impairment of fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Isavuconazole has a moderate potential to influence the ability to drive and use machines. Patients should avoid driving or operating machinery if symptoms of confusional state, somnolence, syncope, and/or dizziness are experienced.

4.8 Undesirable effects

Summary of the safety profile

The most common treatment-related adverse reactions in adults were elevated liver chemistry tests (7.9%), nausea (7.4%), vomiting (5.5%), dyspnoea (3.2%), abdominal pain (2.7%), diarrhoea (2.7%), injection site reaction (2.2%), headache (2.0%), hypokalaemia (1.7%) and rash (1.7%).

The adverse reactions which most often led to permanent discontinuation of isavuconazole treatment in adults were confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnoea (0.5%), epilepsy (0.5%), respiratory failure (0.5%) and vomiting (0.5%).

Tabulated list of adverse reactions

Table 3 presents adverse reactions with isavuconazole in the treatment of invasive fungal infections in adults, by System Organ Class and frequency.

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100); not known (frequency cannot be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Summary of adverse reactions by MedDRA System Organ Class and frequency

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	
Uncommon	Neutropenia; Thrombocytopenia^; Pancytopenia; Leukopenia^; Anaemia^
Immune system disorders	
Uncommon	Hypersensitivity^
Not known	Anaphylactic reaction*
Metabolism and nutrition disorders	
Common	Hypokalaemia; Decreased appetite
Uncommon	Hypomagnesaemia; Hypoglycaemia; Hypoalbuminaemia; Malnutrition^; Hyponatraemia
Psychiatric disorders	
Common	Delirium^#
Uncommon	Depression; Insomnia^
Nervous system disorders	
Common	Headache; Somnolence
Uncommon	Convulsion^; Syncope; Dizziness; Paraesthesia^; Encephalopathy; Presyncope; Neuropathy peripheral; Dysgeusia
Ear and labyrinth disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Atrial fibrillation; Tachycardia; Bradycardia^; Palpitations; Atrial flutter; Electrocardiogram QT shortened; Supraventricular tachycardia; Ventricular extrasystoles; Supraventricular extrasystoles
Vascular disorders	
Common	Thrombophlebitis^
Uncommon	Circulatory collapse; Hypotension
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea^; Acute respiratory failure^
Uncommon	Bronchospasm; Tachypnoea; Haemoptysis; Epistaxis
Gastrointestinal disorders	
Common	Vomiting; Diarrhoea; Nausea; Abdominal pain^
Uncommon	Dyspepsia; Constipation; Abdominal distension
Hepatobiliary disorders	
Common	Elevated liver chemistry tests^#
Uncommon	Hepatomegaly; Hepatitis
Skin and subcutaneous tissue disorders	
Common	Rash^; Pruritus
Uncommon	Petechiae; Alopecia; Drug eruption; Dermatitis^
Musculoskeletal and connective tissue disorders	
Uncommon	Back pain
Renal and urinary disorders	
Common	Renal failure
General disorders and administration site conditions	
Common	Chest pain^; Fatigue; Injection site reaction^
Uncommon	Oedema peripheral^; Malaise; Asthenia

^ Indicates that grouping of appropriate preferred terms into a single medical concept occurred.

* ADR identified post-marketing.

See section Description of selected adverse reactions below.

Description of selected adverse reactions

Delirium includes reactions of confusional state.
Elevated liver chemistry tests includes events of alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, liver function test abnormal, and transaminases increased.

Laboratory effects

In a double-blind, randomized, active-controlled clinical study of 516 patients with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi, elevated liver transaminases (alanine aminotransferase or aspartate aminotransferase) > 3 × Upper Limit of Normal (ULN) were reported at the end of study treatment in 4.4% of patients who received isavuconazole. Marked elevations of liver transaminases > 10 × ULN developed in 1.2% of patients on isavuconazole.

Paediatric population

The clinical safety of isavuconazole was assessed in 77 paediatric patients who received at least one dose of intravenous or oral isavuconazole. This included 46 paediatric patients who received isavuconazole as a single dose and who also received other antifungals for prophylaxis, and 31 patients with suspected or confirmed invasive aspergillosis or mucormycosis who received isavuconazole as primary therapy for up to 181 days. Overall, the safety profile of isavuconazole in the paediatric population was similar to that in adults.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

Symptoms reported more frequently at supratherapeutic doses of isavuconazole (equivalent to isavuconazole 600 mg/day) evaluated in a QT study than in the therapeutic dose group (equivalent to isavuconazole 200 mg/day dose) included: headache, dizziness, paraesthesia, somnolence, disturbance in attention, dysgeusia, dry mouth, diarrhoea, oral hypoaesthesia, vomiting, hot flush, anxiety, restlessness, palpitations, tachycardia, photophobia and arthralgia.

Management of overdose

Isavuconazole is not removed by haemodialysis. There is no specific antidote for isavuconazole. In the event of an overdose, supportive treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole- and tetrazole derivative, ATC code: J02AC05.

Mechanism of action

Isavuconazole is the active moiety formed after oral or intravenous administration of isavuconazonium sulfate (see section 5.2).

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.

Microbiology

In animal models of disseminated and pulmonary aspergillosis, the pharmacodynamic (PD) index important in efficacy is exposure divided by minimum inhibitory concentration (MIC) (AUC/MIC). No clear correlation between *in vitro* MIC and clinical response for the different species (*Aspergillus* and *Mucorales*) could be established.

Concentrations of isavuconazole required to inhibit *Aspergillus* species and genera/species of the order *Mucorales in vitro* have been very variable. Generally, concentrations of isavuconazole required to inhibit *Mucorales* are higher than those required to inhibit the majority of *Aspergillus* species.

Clinical efficacy has been demonstrated for the following *Aspergillus* species: *Aspergillus fumigatus*, *A. flavus*, *A. niger*, and *A. terreus (see further below).*

Mechanism(s) of resistance

Reduced susceptibility to triazole antifungal agents has been associated with mutations in the fungal *cyp51A* and *cyp51B* genes coding for the target protein lanosterol 14-alpha-demethylase involved in ergosterol biosynthesis. Fungal strains with reduced *in vitro* susceptibility to isavuconazole have been reported, and cross-resistance with voriconazole and other triazole antifungal agents cannot be excluded.

Table 4 EUCAST Breakpoints

Aspergillus species	**Minimal Inhibitory Concentration (MIC) breakpoint (mg/L)**	
	≤S (Susceptible)	**>R (Resistant)**
Aspergillus flavus	1	2
Aspergillus fumigatus	1	2
Aspergillus nidulans	0.25	0.25
Aspergillus terreus	1	1

There are currently insufficient data to set clinical breakpoints for other Aspergillus species.

Clinical efficacy and safety

Treatment of invasive aspergillosis
The safety and efficacy of isavuconazole for the treatment of adult patients with invasive aspergillosis was evaluated in a double-blind, active-controlled clinical study in 516 patients with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi. In the intent-to-treat (ITT) population, 258 patients received isavuconazole and 258 patients received voriconazole.

Isavuconazole was administered intravenously (equivalent to 200 mg isavuconazole) every 8 hours for the first 48 hours, followed by once-daily intravenous or oral treatment (equivalent to 200 mg isavuconazole). The protocol-defined maximum treatment duration was 84 days. Median treatment duration was 45 days.

The overall response at end-of-treatment (EOT) in the myITT population (patients with proven and probable invasive aspergillosis based on cytology, histology, culture or galactomannan testing) was assessed by an independent blinded Data Review Committee. The myITT population comprised 123 patients receiving isavuconazole and 108 patients receiving voriconazole. The overall response in this population was n = 43 (35%) for isavuconazole and n = 42 (38.9%) for voriconazole. The adjusted treatment difference (voriconazole−isavuconazole) was 4.0% (95% confidence interval: −7.9; 15.9).

The all-cause mortality at Day 42 in this population was 18.7% for isavuconazole and 22.2% for voriconazole. The adjusted treatment difference (isavuconazole−voriconazole) was −2.7% (95 % confidence interval: −12.9; 7.5).

Treatment of mucormycosis
In an open-label non-controlled study, 37 adult patients with proven or probable mucormycosis received isavuconazole at the same dose regimen as that used to treat invasive aspergillosis. Median treatment duration was 84 days for the overall mucormycosis patient population, and 102 days for the 21 patients not previously treated for mucormycosis. For patients with probable or proven mucormycosis as defined by the independent Data Review Committee (DRC), all-cause mortality at Day 84 was 43.2% (16/37) for the overall patient population, 42.9% (9/21) for mucormycosis patients receiving isavuconazole as primary treatment, and 43.8% (7/16) for mucormycosis patients receiving isavuconazole who were refractory to, or intolerant of, prior antifungal therapy (mainly amphotericin B-based treatments). The DRC-assessed overall success rate at EOT was 11/35 (31.4%), with 5 patients considered completely cured and 6 patients partially cured. A stable response was observed in an additional 10/35 patients (28.6%). In 9 patients with mucormycosis due to *Rhizopus* spp., 4 patients showed a favourable response to isavuconazole. In 5 patients with mucormycosis due to *Rhizomucor* spp., no favourable responses were observed. The clinical experience in other species is very limited (*Lichtheimia* spp. n=2, *Cunninghamella* spp. n=1, *Actinomucor* elegans n=1).

Paediatric population

The clinical safety of isavuconazole was assessed in 77 paediatric patients who received at least one dose of intravenous or oral isavuconazole, including 31 paediatric patients who received isavuconazole in a clinical study for treating invasive aspergillosis or mucormycosis. Isavuconazole was safe and well tolerated in the treatment of invasive aspergillosis and mucormycosis at the intended treatment durations.

5.2 Pharmacokinetic properties

Isavuconazonium sulfate is a water-soluble prodrug that can be administered as an intravenous infusion or orally as hard capsules. Following administration, isavuconazonium sulfate is rapidly hydrolysed by plasma esterases to the active moiety isavuconazole; plasma concentrations of the prodrug are very low, and detectable only for a short time after intravenous dosing.

Absorption

Following oral administration of CRESEMBA in healthy adult subjects, the active moiety isavuconazole is absorbed and reaches maximum plasma concentrations (C_{max}) approximately 2–3 hours after single and multiple dosing (see Table 5).

Table 5 Steady state pharmacokinetic parameters of isavuconazole following oral administration of CRESEMBA in healthy adults

Parameter Statistic	**Isavuconazole 200 mg (n = 37)**	**Isavuconazole 600 mg (n = 32)**
C_{max} (mg/L)		
Mean	7.5	20.0
SD	1.9	3.6
CV %	25.2	17.9
t_{max} (h)		
Median	3.0	4.0
Range	2.0 – 4.0	2.0 – 4.0
AUC (h•mg/L)		
Mean	121.4	352.8
SD	35.8	72.0
CV %	29.5	20.4

As shown in Table 6 below, the absolute bioavailability of isavuconazole following oral administration of a single dose of CRESEMBA is 98%. Based on these findings, intravenous and oral dosing can be used interchangeably.

Table 6 Pharmacokinetic comparison for oral and intravenous dose (Mean) in adults

	Isavuconazole 400 mg oral	**Isavuconazole 400 mg i.v.**
AUC (h•mg/L)	189.5	194.0
CV %	36.5	37.2
Half-life (h)	110	115

Effect of food on absorption
Oral administration of CRESEMBA equivalent to 400 mg isavuconazole with a high-fat meal reduced isavuconazole C_{max} by 9% and increased AUC by 9%. CRESEMBA can be taken with or without food.

Distribution

Isavuconazole is extensively distributed, with a mean steady state volume of distribution (V_{ss}) of approximately 450 L. Isavuconazole is highly bound (> 99%) to human plasma proteins, predominantly to albumin.

Biotransformation

In vitro / in vivo studies indicate that CYP3A4, CYP3A5, and subsequently uridine diphosphate-glucuronosyltransferases (UGT), are involved in the metabolism of isavuconazole.

Following single doses of [cyano-^{14}C] isavuconazonium and [pyridinylmethyl-^{14}C] isavuconazonium sulfate in humans, in addition to the active moiety (isavuconazole) and the inactive cleavage product, a number of minor metabolites were identified. Except for the active moiety isavuconazole, no individual metabolite was observed with an AUC > 10% of total radio-labelled material.

Elimination

Following oral administration of radio-labelled isavuconazonium sulfate to healthy subjects, a mean of 46.1% of the radioactive dose was recovered in faeces, and 45.5% was recovered in urine.

Renal excretion of intact isavuconazole was less than 1% of the dose administered.

The inactive cleavage product is primarily eliminated by metabolism and subsequent renal excretion of the metabolites.

Linearity/non-linearity

Studies in healthy subjects have demonstrated that the pharmacokinetics of isavuconazole are proportional up to 600 mg per day.

Pharmacokinetics in special populations

Paediatric patients
The paediatric dosage regimens were confirmed using a population pharmacokinetic (popPK) model developed using data from three clinical studies (N = 97); this included two clinical studies (N = 73) conducted in paediatric patients aged 1 to < 18 years, of whom 31 received isavuconazole for treating invasive aspergillosis or mucormycosis.
The predicted exposures to isavuconazole for paediatric patients at steady state based on different age groups, weight, route of administration, and dose are shown in Table 7.

Table 7 Isavuconazole AUC (h•mg/L) values at steady state by age group, weight, route of administration, and dose

Age group (years)	Route	Weight (kg)	Dose	AUCss (h•mg/L)
1 – < 3	Intravenous	< 37	5.4 mg/kg	108 (29 – 469)
3 – < 6	Intravenous	< 37	5.4 mg/kg	123 (27 – 513)
6 – < 18	Intravenous	< 37	5.4 mg/kg	138 (31 – 602)
6 – < 18	Oral	16 – 17	80 mg	116 (31 – 539)
6 – < 18	Oral	18 – 24	120 mg	129 (33 – 474)
6 – < 18	Oral	25 – 31	160 mg	140 (36 – 442)
6 – < 18	Oral	32 – 36	180 mg	137 (27 – 677)
6 – < 18	Intravenous and oral	≥ 37	200 mg	113 (27 – 488)
≥ 18	Intravenous and oral	≥ 37	200 mg	101 (10 – 343)

The predicted exposures for paediatric patients, regardless of route of administration and age group, were comparable to exposures at steady state (AUCss) from a clinical study conducted in adult patients with infections caused by *Aspergillus* species and other filamentous fungi (mean AUCss = 101.2 h•mg/L with standard deviation (SD) = 55.9, see Table 7).

The predicted exposures under the paediatric dosing regimen were lower than the exposures of adults who received multiple daily supratherapeutic doses of 600 mg isavuconazole (Table 5), where there was a greater occurrence of adverse events (see section 4.9).

Renal impairment
No clinically relevant changes were observed in the total C_{max} and AUC of isavuconazole in adult subjects with mild, moderate or severe renal impairment compared to subjects with normal renal function. Of the 403 patients who received isavuconazole in the Phase 3 studies, 79 (20%) of patients had an estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2. No dose adjustment is required in patients with renal impairment, including those patients with end-stage renal disease. Isavuconazole is not readily dialysable (see section 4.2).

No data are available in paediatric patients with renal impairment (see section 4.2).

Hepatic impairment
After a single 100 mg dose of isavuconazole was administered to 32 adult patients with mild (Child-Pugh Class A) hepatic insufficiency and 32 patients with moderate (Child-Pugh Class B) hepatic insufficiency (16 intravenous and 16 oral patients per Child-Pugh class), the least square mean

systemic exposure (AUC) increased 64% in the Child-Pugh Class A group, and 84% in the Child-Pugh Class B group, relative to 32 age- and weight-matched healthy subjects with normal hepatic function. Mean plasma concentrations (C_{max}) were 2% lower in the Child-Pugh Class A group and 30% lower in the Child-Pugh Class B group. The population pharmacokinetic evaluation of isavuconazole in healthy subjects and patients with mild or moderate hepatic dysfunction demonstrated that the mild and moderate hepatic impairment populations had 40% and 48% lower isavuconazole clearance (CL) values, respectively, than the healthy population.

No dose adjustment is required in adult patients with mild to moderate hepatic impairment.

Isavuconazole has not been studied in adult 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 (see sections 4.2 and 4.4).

No data are available in paediatric patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

In rats and rabbits, isavuconazole at systemic exposures below the therapeutic level were associated with dose-related increases in the incidence of skeletal anomalies (rudimentary supernumerary ribs) in offspring. In rats, a dose-related increase in the incidence of zygomatic arch fusion was also noted in offspring (see section 4.6).

Administration of isavuconazonium sulfate to rats at a dose of 90 mg/kg/day (approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole) during pregnancy through the weaning period showed an increased perinatal mortality of the pups. *In utero* exposure to the active moiety isavuconazole had no effect on the fertility or the normal development of the surviving pups.

Intravenous administration of ^{14}C-labelled isavuconazonium sulfate to lactating rats resulted in the recovery of radiolabel in the milk.

Isavuconazole did not affect the fertility of male or female rats treated with oral doses up to 90 mg/kg/day (approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole).

Isavuconazole has no discernible mutagenic or genotoxic potential. Isavuconazole was negative in a bacterial reverse mutation assay, was weakly clastogenic at cytotoxic concentrations in the L5178Y tk+/- mouse lymphoma chromosome aberration assay, and showed no biologically relevant or statistically significant increase in the frequency of micronuclei in an *in vivo* rat micronucleus test.

Isavuconazole has demonstrated carcinogenic potential in 2-year rodent carcinogenicity studies. Liver and thyroid tumours are likely caused by a rodent-specific mechanism that is not relevant for humans. Skin fibromas and fibrosarcomas were seen in male rats. The mechanism underlying this effect is unknown. Endometrial adenomas and carcinomas of the uterus were seen in female rats, which is likely due to a hormonal disturbance. There is no safety margin for these effects. The relevance for humans of the skin and uterine tumours cannot be excluded.

Isavuconazole inhibited the hERG potassium channel and the L-type calcium channel with an IC_{50} of 5.82 µM and 6.57 µM respectively (34- and 38-fold the human non-protein bound C_{max} at maximum recommended human dose [MRHD], respectively). The *in vivo* 39-week repeated-dose toxicology studies in monkeys did not show QTcF prolongation at doses up to 40 mg/kg/day (approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole).

Juvenile animal studies

Isavuconazonium sulfate, when administered to juvenile rats, demonstrated a similar toxicological profile to that observed in adult animals. In juvenile rats, treatment-related toxicity considered rodent specific was observed in the liver and thyroid. These changes are not considered clinically relevant. Based on the no-observed-adverse-effect level in juvenile rats, the safety margins for isavuconazonium sulfate were approximately 0.2- to 0.5-fold the systemic exposure at the clinical maintenance dose for paediatric patients, similar to those observed in adult rats.

Environmental risk assessment (ERA)

Environmental risk assessment has shown that isavuconazole may pose a risk for the aquatic environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sulfuric acid (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years

Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 2 °C to 8 °C, or 6 hours at room temperature.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

One 10 mL Type I glass vial with rubber stopper and an aluminum cap with plastic seal.

6.6 Special precautions for disposal and other handling

Reconstitution

One vial of the powder for concentrate for solution for infusion should be reconstituted by addition of 5 mL water for injections to the vial. The reconstituted concentrate contains 40 mg isavuconazole per mL. The vial should be shaken to dissolve the powder completely. The reconstituted solution should

be inspected visually for particulate matter and discoloration. Reconstituted concentrate should be clear and free of visible particulate. It must be further diluted prior to administration.

Dilution

Adults and paediatric patients with bodyweight from 37 kg:

After reconstitution, the entire content of the reconstituted concentrate should be removed from the vial and added to an infusion bag containing 250 mL of either sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) dextrose solution. The infusion solution contains approximately 0.8 mg isavuconazole per mL.

Paediatric patients with bodyweight below 37 kg:

The final concentration of the infusion solution should be in the range of 0.4 to 0.8 mg isavuconazole per mL. Higher concentrations should be avoided as these may cause local irritation at the site of infusion.
To obtain the final concentration, the appropriate volume of the reconstituted concentrate based on paediatric dosing recommendations (see section 4.2) should be removed from the vial and added to an infusion bag containing the appropriate amount of diluent.
The appropriate volume of the infusion bag is calculated as follows:

[Required dose (mg)/final concentration (mg/mL)] – Volume of the concentrate (mL)

The concentrate can be diluted with either 9 mg/mL (0.9%) sodium chloride solution for injection or 50 mg/mL (5%) dextrose solution.

Administration

After the reconstituted concentrate is further diluted, the diluted solution may show fine white-to-translucent particulates of isavuconazole that do not sediment (but will be removed by in-line filtration). The diluted solution should be mixed gently, or the bag should be rolled to minimise the formation of particulates. Unnecessary vibration or vigorous shaking of the solution should be avoided. The solution for infusion must be administered via an infusion set with an in-line filter (pore size 0.2 µm to 1.2 µm) made of polyether sulfone (PES). Infusion pumps can be used and must be placed before the infusion set. Regardless of the infusion solution container size used, the entire volume of the container should be administered to ensure the complete dose is administered.

Isavuconazole should not be infused into the same line or cannula concomitantly with other intravenous products.

Storage conditions after reconstitution and dilution are provided in section 6.3.

If possible, the intravenous administration of isavuconazole should be completed within 6 hours after reconstitution and dilution at room temperature. If this is not possible, the infusion solution should be immediately refrigerated after dilution, and infusion should be completed within 24 hours. Further information regarding the storage conditions after reconstitution and dilution of the medicinal product is provided in section 6.3.

An existing intravenous line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) dextrose solution.

This medicinal product is for single use only. Discard partially-used vials.

This medicinal product may pose a risk to the environment (see section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Basilea Pharmaceutica Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1036/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 October 2015.
Date of latest renewal: 13 August 2020.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

CRESEMBA 40 mg hard capsules

CRESEMBA 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CRESEMBA 40 mg hard capsule contains 40 mg isavuconazole (as 74.5 mg isavuconazonium sulfate).

Each CRESEMBA 100 mg hard capsule contains 100 mg isavuconazole (as 186.3 mg isavuconazonium sulfate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CRESEMBA 40 mg hard capsule: Swedish Orange (reddish-brown) capsules marked with ”CR40” on the capsule cap in black ink. Capsules length: 15.9 mm.

CRESEMBA 100 mg hard capsule: Swedish Orange (reddish-brown) capsule body marked with ”100” in black ink and a white cap marked with "C" in black ink. Capsules length: 24.2 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CRESEMBA hard capsules are indicated in adults and in paediatric patients from 6 years of age for the treatment of

- invasive aspergillosis
- mucormycosis in patients for whom amphotericin B is inappropriate (see sections 4.4 and 5.1)

Consideration should be given to official guidance on the appropriate use of antifungal agents.

CRESEMBA 40 mg hard capsules are intended to be used for paediatric patients.

4.2 Posology and method of administration

Posology

Early targeted therapy (pre-emptive or diagnostic-driven therapy) may be instituted pending confirmation of the disease from specific diagnostic tests. However, once these results become available, antifungal therapy should be adjusted accordingly.

Treatment
Detailed information on dosage recommendations is provided in the following tables:

Table 1 Recommended dosage for CRESEMBA in adult patients

Loading dose (three times daily)[1]		Maintenance dose (once daily)[2]
every 8 hours during Days 1 and 2	**total daily dose during Days 1 and 2**	
Two 100 mg capsules	Six 100 mg capsules	Two 100 mg capsules
[1] Six administrations in total. [2] Starting 12 to 24 hours after the last loading dose.		

Table 2 Recommended Dosage for CRESEMBA in paediatric patients aged from 6 years to less than 18 years

Bodyweight (kg)	Loading dose (three times daily)[1]		Maintenance dose (once daily)[2]
	every 8 hours during Days 1 and 2	**total daily dose during Days 1 and 2**	
16 kg to < 18 kg	Two 40 mg capsules	Six 40 mg capsules	Two 40 mg capsules
18 kg to < 25 kg	Three 40 mg capsules	Nine 40 mg capsules	Three 40 mg capsules
25 kg to < 32 kg	Four 40 mg capsules	Twelve 40 mg capsules	Four 40 mg capsules
32 kg to < 37 kg	One 100 mg capsule **and** two 40 mg capsules	Three 100 mg capsules **and** six 40 mg capsules	One 100 mg capsule **and** two 40 mg capsules
≥ 37 kg	Five 40 mg capsules **or** two 100 mg capsules	Fifteen 40 mg capsules **or** six 100 mg capsules	Five 40 mg capsules **or** two 100 mg capsules
[1] Six administrations in total. [2] Starting 12 to 24 hours after the last loading dose.			

The maximum of any individual loading or daily maintenance dose to be administered to any patient is 200 mg isavuconazole.

All capsules per dose must be taken at the same time.
Duration of therapy should be determined by the clinical response (see section 5.1).

For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered (see sections 5.1 and 5.3).

Elderly
No dose adjustment is necessary for elderly patients; however, the clinical experience in elderly patients is limited.

Renal impairment
No dose adjustment is necessary in adult patients with renal impairment, including patients with end-stage renal disease (see section 5.2).

No dose recommendation can be made for paediatric patients with renal impairment, as no relevant data are available.

Hepatic impairment
No dose adjustment is necessary in adult patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B) (see sections 4.4 and 5.2).

Isavuconazole has not been studied in adult 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 (see sections 4.4, 4.8 and 5.2).

No dose recommendation can be made for paediatric patients with hepatic impairment, as no relevant data are available.

Paediatric population
Paediatric patients from one year to below 6 years of age, or with a bodyweight less than 16 kg, or are not able to swallow CRESEMBA hard capsules may receive CRESEMBA as intravenous infusion.

The use of CRESEMBA 100 mg capsules has not been studied in paediatric patients (see section 4.4). The safety and efficacy of CRESEMBA in paediatric patients aged less than 1 year has not been established.

Switch to intravenous infusion
CRESEMBA is also available as powder for concentrate for solution for infusion containing 200 mg isavuconazole.

On the basis of the high oral bioavailability (98%, see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

Method of administration

CRESEMBA capsules can be taken with or without food.
CRESEMBA capsules should be swallowed whole. Do not chew, crush, dissolve or open the capsules.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ketoconazole (see section 4.5).

Co-administration with high-dose ritonavir (>200 mg every 12 hours) (see section 4.5).

Co-administration with strong CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g. phenobarbital), phenytoin and St. John's wort or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine (see section 4.5).

Patients with familial short QT syndrome (see section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity

Hypersensitivity to isavuconazole may result in adverse reactions that include: anaphylactic reaction, hypotension, respiratory failure, dyspnoea, drug eruption, pruritus, and rash (see section 4.8). In case of anaphylactic reaction, isavuconazole should be discontinued immediately and appropriate medical treatment should be initiated.

Caution should be used in prescribing isavuconazole to patients with hypersensitivity to other azole antifungal agents.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported during treatment with azole antifungal agents. If a patient develops a severe cutaneous adverse reaction, CRESEMBA should be discontinued.

Cardiovascular

QT shortening
Isavuconazole is contraindicated in patients with familial short QT syndrome (see section 4.3).
In a QT study in healthy human subjects, isavuconazole shortened the QTc interval in a concentration-related manner. For the 200 mg dosing regimen, the least squares mean (LSM) difference from placebo was 13.1 ms at 2 hours post dose [90% CI: 17.1, 9.1 ms]. Increasing the dose to 600 mg resulted in an LSM difference from placebo of 24.6 ms at 2 hours post dose [90% CI: 28.7, 20.4 ms].

Caution is warranted when prescribing isavuconazole to patients taking other medicinal products known to decrease the QT interval, such as rufinamide.

Elevated liver transaminases or hepatitis

Elevated liver transaminases have been reported in clinical studies (see section 4.8). The elevations in liver transaminases rarely required discontinuation of isavuconazole. Monitoring of hepatic enzymes should be considered, as clinically indicated. Hepatitis has been reported with azole antifungal agents including isavuconazole.

Severe hepatic impairment

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 (see sections 4.2, 4.8 and 5.2).

Paediatric patients

Isavuconazole has not been studied in paediatric patients with renal or hepatic impairment.

Paediatric patients from 6 years to less than 18 years of age and with a bodyweight at least 32 kg may receive CRESEMBA 100 mg capsules. However, the use of CRESEMBA 100 mg capsules has not been studied in paediatric patients.

Concomitant use with other medicinal products

CYP3A4/5 inhibitors
Ketoconazole is contraindicated (see section 4.3). For the strong CYP3A4 inhibitor lopinavir/ritonavir, a two-fold increase in isavuconazole exposure was observed. For other strong CYP3A4/5 inhibitors, a less pronounced effect can be expected. No dose adjustment of isavuconazole is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see section 4.5).

CYP3A4/5 inducers
Co-administration with mild CYP3A4/5 inducers such as aprepitant, prednisone, and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels; co-administration with mild CYP3A4/5 inducers should be avoided unless the potential benefit is considered to outweigh the risk (see section 4.5).

CYP3A4/5 substrates including immunosuppressants
Isavuconazole can be considered a moderate inhibitor of CYP3A4/5, and systemic exposure to medicinal products metabolised by CYP3A4 may be increased when co-administered with isavuconazole. Concomitant use of isavuconazole with CYP3A4 substrates such as the immunosuppressants tacrolimus, sirolimus or ciclosporin may increase the systemic exposure to these

medicinal products. Appropriate therapeutic drug monitoring and dose adjustment may be necessary during co-administration (see section 4.5).

CYP2B6 substrates
Isavuconazole is an inducer of CYP2B6. Systemic exposure to medicinal products metabolised by CYP2B6 may be decreased when co-administered with isavuconazole. Therefore, caution is advised when CYP2B6 substrates, especially medicinal products with a narrow therapeutic index such as cyclophosphamide, are co-administered with isavuconazole. The use of the CYP2B6 substrate efavirenz with isavuconazole is contraindicated because efavirenz is a moderate inducer of CYP3A4/5 (see section 4.3).

P-gp substrates
Isavuconazole may increase the exposure of medicinal products that are P-gp substrates. Dose adjustment of medicinal products that are P-gp substrates, especially medicinal products with a narrow therapeutic index such as digoxin, colchicine and dabigatran etexilate, may be needed when concomitantly administered with isavuconazole (see section 4.5).

Limitations of the clinical data

The clinical data for isavuconazole in the treatment of mucormycosis are limited to one prospective non-controlled clinical study in 37 adult patients with proven or probable mucormycosis who received isavuconazole for primary treatment, or because other antifungal treatments (predominantly amphotericin B) were inappropriate.
For individual *Mucorales* species, the clinical efficacy data are very limited, often to one or two patients (see section 5.1). Susceptibility data were available in only a small subset of cases. These data indicate that concentrations of isavuconazole required for inhibition *in vitro* are very variable between genera/species within the order of *Mucorales*, and generally higher than concentrations required to inhibit *Aspergillus* species. It should be noted that there was no dose-finding study in mucormycosis, and patients were administered the same dose of isavuconazole as was used for the treatment of invasive aspergillosis.

4.5 Interaction with other medicinal products and other forms of interaction

Potential of medicinal products to affect the pharmacokinetics of isavuconazole

Isavuconazole is a substrate of CYP3A4 and CYP3A5 (see section 5.2). 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 which are inducers of CYP3A4 and/or CYP3A5 may decrease the plasma concentrations of isavuconazole.

Medicinal products that inhibit CYP3A4/5

Co-administration of isavuconazole with the strong CYP3A4/5 inhibitor ketoconazole is contraindicated, since this medicinal product can significantly increase plasma concentrations of isavuconazole (see sections 4.3 and 4.5).

For the strong CYP3A4 inhibitor lopinavir/ritonavir, a two-fold increase in isavuconazole exposure was observed. For other strong CYP3A4 inhibitors, such as clarithromycin, indinavir and saquinavir, a less pronounced effect can be expected, based on their relative potency. No dose adjustment of isavuconazole is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see section 4.4).

No dose adjustment is warranted for moderate to mild CYP3A4/5 inhibitors.

Medicinal products that induce CYP3A4/5

Co-administration of isavuconazole with potent CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g., phenobarbital), phenytoin and St. John's wort, or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine, is contraindicated, since these medicinal products can significantly decrease plasma concentrations of isavuconazole (see section 4.3).

Co-administration with mild CYP3A4/5 inducers such as aprepitant, prednisone and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels; co-administration with mild CYP3A4/5 inducers should be avoided unless the potential benefit is considered to outweigh the risk (see section 4.4).

Co-administration with high-dose ritonavir (>200 mg twice daily) is contraindicated, as at high doses ritonavir may induce CYP3A4/5 and decrease isavuconazole plasma concentrations (see section 4.3).

Potential for isavuconazole to affect exposures of other medicines

Medicinal products metabolised by CYP3A4/5

Isavuconazole is a moderate inhibitor of CYP3A4/5; co-administration of isavuconazole with medicinal products which are substrates of CYP3A4/5 may result in increased plasma concentrations of these medicinal products.

Medicinal products metabolised by CYP2B6

Isavuconazole is a mild CYP2B6 inducer; co-administration of isavuconazole may result in decreased plasma concentrations of CYP2B6 substrates.

Medicinal products transported by P-gp in the intestine

Isavuconazole is a mild inhibitor of P-glycoprotein (P-gp); co-administration with isavuconazole may result in increased plasma concentrations of P-gp substrates.

Medicinal products transported by BCRP

Isavuconazole is an inhibitor *in vitro* of BCRP, and plasma concentrations of substrates of BCRP may therefore be increased. Caution is advised when isavuconazole is given concomitantly with substrates of BCRP.

Medicinal products renally excreted via transport proteins

Isavuconazole is a mild inhibitor of the organic cation transporter 2 (OCT2). Co-administration of isavuconazole with medicinal products which are substrates of OCT2 may result in increased plasma concentrations of these medicinal products.

Uridine diphosphate-glucuronosyltransferases (UGT) substrates

Isavuconazole is a mild inhibitor of UGT. Co-administration of isavuconazole with medicinal products which are substrates of UGT may result in mildly increased plasma concentrations of these medicinal products.

Interaction table

Interactions between isavuconazole and co-administered medicinal products are listed in Table 3 (increase is indicated as "↑", decrease as "↓"), ordered by therapeutic class. Unless otherwise stated, studies detailed in Table 3 have been performed with the recommended dose of isavuconazole.

Table 3 Interactions

Co-administered medicinal product by therapeutic area	**Effects on drug concentrations / Geometric Mean Change (%) in AUC, C_{max} (Mode of action)**	**Recommendation concerning co-administration**
Anticonvulsants		
Carbamazepine, phenobarbital and phenytoin (strong CYP3A4/5 inducers)	Isavuconazole concentrations may decrease (CYP3A induction by carbamazepine, phenytoin and long-acting barbiturates such as phenobarbital).	The concomitant administration of isavuconazole and carbamazepine, phenytoin and long-acting barbiturates such as phenobarbital is contraindicated.
Antibacterials		
Rifampicin (strong CYP3A4/5 inducer)	Isavuconazole: AUC_{tau}: ↓ 90% C_{max}: ↓ 75% (CYP3A4/5 induction)	The concomitant administration of isavuconazole and rifampicin is contraindicated.
Rifabutin (strong CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and rifabutin is contraindicated.
Nafcillin (moderate CY3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and nafcillin is contraindicated.
Clarithromycin (strong CYP3A4/5 inhibitor)	Not studied. Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary; caution is advised as adverse drug reactions may increase.
Antifungals		
Ketoconazole (strong CYP3A4/5 inhibitor)	Isavuconazole: AUC_{tau}: ↑ 422% C_{max}: ↑ 9% (CYP3A4/5 inhibition)	The concomitant administration of isavuconazole and ketoconazole is contraindicated.
Herbal medicines		
St John's wort (strong CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4 induction).	The concomitant administration of isavuconazole and St John's wort is contraindicated.
Immunosuppresants		
Ciclosporin, sirolimus, tacrolimus (CYP3A4/5 substrates)	Ciclosporin: AUC_{inf}: ↑ 29% C_{max}: ↑ 6% Sirolimus: AUC_{inf}: ↑ 84% C_{max}: ↑ 65%	No isavuconazole dose adjustment necessary. Ciclosporin, sirolimus, tacrolimus: monitoring of plasma levels and appropriate dose adjustment if required.

	Tacrolimus: AUC_{inf}: ↑ 125% C_{max}: ↑ 42% (CYP3A4 inhibition)	
Mycophenolate mofetil (MMF) (UGT substrate)	Mycophenolic acid (MPA, active metabolite): AUC_{inf}: ↑ 35% C_{max}: ↓ 11% (UGT inhibition)	No isavuconazole dose adjustment necessary. MMF: monitoring for MPA-related toxicities is advised.
Prednisone (CYP3A4 substrate)	Prednisolone (active metabolite): AUC_{inf}: ↑ 8% C_{max}: ↓ 4% (CYP3A4 inhibition) Isavuconazole concentrations may decrease. (CYP3A4/5 induction)	Co-administration should be avoided unless the potential benefit is considered to outweigh the risk.
Opioids		
Short-acting opiates (alfentanyl, fentanyl) (CYP3A4/5 substrate)	Not studied. Short-acting opiate concentrations may increase. (CYP3A4/5 inhibition).	No isavuconazole dose adjustment necessary. Short-acting opiates (alfentanyl, fentanyl): careful monitoring for any occurrence of drug toxicity, and dose reduction if required.
Methadone (CYP3A4/5, 2B6 and 2C9 substrate)	S-methadone (inactive opiate isomer) AUC_{inf}: ↓ 35% C_{max}: ↑ 1% 40% reduction in terminal half-life R-methadone (active opiate isomer). AUC_{inf}: ↓ 10% C_{max}: ↑ 4% (CYP2B6 induction)	No isavuconazole dose adjustment necessary. Methadone: no dose adjustment required.
Anti-cancer		
Vinca alkaloids (vincristine, vinblastine) (P-gp substrates)	Not studied. Vinca alkaloid concentrations may increase. (P-gp inhibition)	No isavuconazole dose adjustment necessary. Vinca alkaloids: careful monitoring for any occurrence of drug toxicity, and dose reduction if required.
Cyclophosphamide (CYP2B6, CYP3A4 substrate)	Not studied. Active metabolites of cyclophosphamide concentrations may increase or decrease. (CYP2B6 induction, CYP3A4 inhibition)	No isavuconazole dose adjustment necessary. Cyclophosphamide: careful monitoring for any occurrence of lack of efficacy or increased toxicity, and dose adjustment if required.
Methotrexate (BCRP, OAT1, OAT3 substrate)	Methotrexate: AUC_{inf}: ↓ 3% C_{max}: ↓ 11%	No isavuconazole dose adjustment necessary.

	7-hydroxymetabolite: AUC_{inf}: ↑ 29% C_{max}: ↑ 15% (Mechanism unknown)	Methotrexate: no dose adjustment required.
Other anticancer agents (daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan) (BCRP substrates)	Not studied. Daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan concentrations may increase. (BCRP inhibition)	No isavuconazole dose adjustment necessary. Daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone or topotecan: careful monitoring for any occurrence of drug toxicity, and dose reduction if required.
Antiemetics		
Aprepitant (mild CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may decrease. (CYP3A4/5 induction)	Co-administration should be avoided unless the potential benefit is considered to outweigh the risk.
Antidiabetics		
Metformin (OCT1, OCT2 and MATE1 substrate)	Metformin: AUC_{inf}: ↑ 52% C_{max}: ↑ 23% (OCT2 inhibition)	No isavuconazole dose adjustment necessary. Metformin: dose reduction may be required.
Repaglinide (CYP2C8 and OATP1B1 substrate)	Repaglinide: AUC_{inf}: ↓ 8% C_{max}: ↓ 14%	No isavuconazole dose adjustment necessary. Repaglinide: no dose adjustment required.
Pioglitazone (mild CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may decrease. (CYP3A4/5 induction)	Co-administration should be avoided unless the potential benefit is considered to outweigh the risk.
Anticoagulants		
Dabigatran etexilate (P-gp substrate)	Not studied. Dabigatran etexilate concentrations may increase. (P-gp inhibition).	No isavuconazole dose adjustment necessary. Dabigatran etexilate has a narrow therapeutic index and should be monitored, and dose reduction if required.
Warfarin (CYP2C9 substrate)	S-warfarin AUC_{inf}: ↑ 11% C_{max}: ↓ 12% R-warfarin AUC_{inf}: ↑ 20% C_{max}: ↓ 7%	No isavuconazole dose adjustment necessary. Warfarin: no dose adjustment required.
Antiretroviral agents		
Lopinavir 400 mg / Ritonavir 100 mg (CYP3A4/5 strong inhibitors and substrates)	Lopinavir: AUC_{tau}: ↓ 27% C_{max}: ↓ 23% C_{min}, ss: ↓ 16%[a)] Ritonavir: AUC_{tau}: ↓ 31% C_{max}: ↓ 33%	No isavuconazole dose adjustment necessary; caution is advised as adverse drug reactions may increase. Lopinavir/ritonavir: no dose adjustment for lopinavir 400 mg /

	(Mechanism unknown) Isavuconazole: AUC_{tau}: ↑ 96% C_{max}: ↑ 74% (CYP3A4/5 inhibition)	ritonavir 100 mg every 12 hours required, but careful monitoring for any occurrence of lack of anti-viral efficacy.
Ritonavir (at doses >200 mg every 12 hours) (strong CYP3A4/5 inducer)	Not studied. Ritonavir at high doses may significantly decrease isavuconazole concentrations. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and high doses of ritonavir (>200 mg every 12 hours) is contraindicated.
Efavirenz (CYP3A4/5 moderate inducer and CYP2B6 substrate)	Not studied. Efavirenz concentrations may decrease. (CYP2B6 induction) Isavuconazole drug concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and efavirenz is contraindicated.
Etravirine (moderate CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and etravirine is contraindicated.
Indinavir (CYP3A4/5 strong inhibitor and substrate)	Indinavir:[b)] AUC_{inf}: ↓ 36% C_{max}: ↓ 52% (Mechanism unknown) Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary; caution is advised as adverse drug reactions may increase. Indinavir: careful monitoring for any occurrence of lack of anti-viral efficacy, and dose increase if required.
Saquinavir (strong CYP3A4 inhibitor)	Not studied. Saquinavir concentrations may decrease (as observed with lopinavir/ritonavir) or increase. (CYP3A4 inhibition) Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary; caution is advised as adverse drug reactions may increase. Saquinavir: careful monitoring for any occurrence of drug toxicity and /or lack of anti-viral efficacy, and dose adjustment if required
Other protease inhibitors (e.g. fosamprenavir) (CYP3A4/5 strong or moderate inhibitors and substrates)	Not studied. Protease inhibitor concentrations may decrease (as observed with lopinavir/ritonavir) or increase. (CYP3A4 inhibition)	No isavuconazole dose adjustment necessary. Protease inhibitors: careful monitoring for any occurrence of drug toxicity and /or lack of anti-viral efficacy, and dose adjustment if required.

	Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	
Other NNRTI (e.g. nevirapine) (CYP3A4/5 and 2B6 inducers and substrates)	Not studied. NNRTI concentrations may decrease (CYP2B6 induction by isavuconazole) or increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary. NNRTIs: careful monitoring for any occurrence of drug toxicity and/or lack of anti-viral efficacy, and dose adjustment if required.
Antiacids		
Esomeprazole (CYP2C19 substrate and gastric pH ↑)	Isavuconazole: AUC_{tau}: ↑ 8% C_{max}: ↑ 5%	No isavuconazole dose adjustment necessary. Esomeprazole: no dose adjustment required.
Omeprazole (CYP2C19 substrate and gastric pH ↑)	Omeprazole: AUC_{inf}: ↓ 11% C_{max}: ↓ 23%	No isavuconazole dose adjustment necessary. Omeprazole: no dose adjustment required.
Lipid-lowering agents		
Atorvastatin and other statins (CYP3A4 substrates e.g., simvastatin, lovastatin, rosuvastatin) (CYP3A4/5 and/or BCRP substrates))	Atorvastatin : AUC_{inf}: ↑ 37% C_{max}: ↑ 3% Other statins were not studied. Statins concentrations may increase. (CYP3A4/5 or BCRP inhibition)	No isavuconazole dose adjustment necessary. Based on results with atorvastatin, no statin dose adjustment required. Monitoring of adverse reactions typical of statins is advised.
Antiarrhythmics		
Digoxin (P-gp substrate)	Digoxin: AUC_{inf}: ↑ 25% C_{max}: ↑ 33% (P-gp inhibition)	No isavuconazole dose adjustment necessary. Digoxin: serum digoxin concentrations should be monitored and used for titration of the digoxin dose.
Oral contraceptives		
Ethinyl oestradiol and norethindrone (CYP3A4/5 substrates)	Ethinyl oestradiol AUC_{inf}: ↑ 8% C_{max}: ↑ 14% Norethindrone AUC_{inf}: ↑ 16% C_{max}: ↑ 6%	No isavuconazole dose adjustment necessary. Ethinyl oestradiol and norethindrone: no dose adjustment required.
Antitussives		
Dextromethorphan (CYP2D6 substrate)	Dextromethorphan: AUC_{inf}: ↑ 18% C_{max}: ↑ 17% Dextrorphan (active metabolite): AUC_{inf}: ↑ 4% C_{max}: ↓ 2%	No isavuconazole dose adjustment necessary. Dextromethorphan: no dose adjustment required.
Benzodiazepines		
Midazolam (CYP3A4/5 substrate)	Oral midazolam: AUC_{inf}: ↑ 103% C_{max}: ↑ 72% (CYP3A4 inhibition)	No isavuconazole dose adjustment necessary. Midazolam: careful monitoring of clinical signs and symptoms recommended, and dose reduction if required.

Antigout agent		
Colchicine (P-gp substrate)	Not studied. Colchicine concentrations may increase. (P-gp inhibition)	No isavuconazole dose adjustment necessary. Colchicine has a narrow therapeutic index and should be monitored, dose reduction if required.
Natural products		
Caffeine (CYP1A2 substrate)	Caffeine: AUC_{inf}: ↑ 4% C_{max}: ↓ 1%	No isavuconazole dose adjustment necessary. Caffeine: no dose adjustment required.
Smoking cessation aids		
Bupropion (CYP2B6 substrate)	Bupropion: AUC_{inf}: ↓ 42% C_{max}: ↓ 31% (CYP2B6 induction)	No isavuconazole dose adjustment necessary. Bupropion: dose increase if required.

NNRTI, non-nucleoside reverse-transcriptase inhibitor; P-gp, P-glycoprotein.
[a)] % decrease of the mean trough level values
[b)] Indinavir was only studied after a single dose of 400 mg isavuconazole.
AUC_{inf} = area under the plasma concentration-time profiles extrapolated to infinity; AUC_{tau} = area under the plasma concentration-time profiles during the 24 h interval at steady state; C_{max} = peak plasma concentration; C_{min},ss = trough levels at steady state.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of CRESEMBA in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

CRESEMBA 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.

Women of child-bearing potential

CRESEMBA is not recommended for women of childbearing potential who are not using contraception.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of isavuconazole/metabolites in milk (see section 5.3).

A risk to newborns and infants cannot be excluded.

Breast-feeding should be discontinued during treatment with CRESEMBA.

Fertility

There are no data on the effect of isavuconazole on human fertility. Studies in animals did not show impairment of fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Isavuconazole has a moderate potential to influence the ability to drive and use machines. Patients should avoid driving or operating machinery if symptoms of confusional state, somnolence, syncope, and/or dizziness are experienced.

4.8 Undesirable effects

Summary of the safety profile

The most common treatment-related adverse reactions in adults were elevated liver chemistry tests (7.9%), nausea (7.4%), vomiting (5.5%), dyspnoea (3.2%), abdominal pain (2.7%), diarrhoea (2.7%), injection site reaction (2.2%), headache (2.0%), hypokalaemia (1.7%) and rash (1.7%).

The adverse reactions which most often led to permanent discontinuation of isavuconazole treatment in adults were confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnoea (0.5%), epilepsy (0.5%), respiratory failure (0.5%) and vomiting (0.5%).

Tabulated list of adverse reactions

Table 4 presents adverse reactions with isavuconazole in the treatment of invasive fungal infections in adults, by System Organ Class and frequency.

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100); not known (frequency cannot be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4 Summary of adverse reactions by MedDRA System Organ Class and frequency

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	
Uncommon	Neutropenia; Thrombocytopenia^; Pancytopenia; Leukopenia^; Anaemia^
Immune system disorders	
Uncommon	Hypersensitivity^
Not known	Anaphylactic reaction*
Metabolism and nutrition disorders	
Common	Hypokalaemia; Decreased appetite
Uncommon	Hypomagnesaemia; Hypoglycaemia; Hypoalbuminaemia; Malnutrition^; Hyponatraemia
Psychiatric disorders	
Common	Delirium^#
Uncommon	Depression; Insomnia^
Nervous system disorders	
Common	Headache; Somnolence
Uncommon	Convulsion^; Syncope; Dizziness; Paraesthesia^; Encephalopathy; Presyncope; Neuropathy peripheral; Dysgeusia
Ear and labyrinth disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Atrial fibrillation; Tachycardia; Bradycardia^; Palpitations; Atrial flutter; Electrocardiogram QT shortened; Supraventricular tachycardia; Ventricular extrasystoles; Supraventricular extrasystoles

Vascular disorders	
Common	Thrombophlebitis^
Uncommon	Circulatory collapse; Hypotension
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea^; Acute respiratory failure^
Uncommon	Bronchospasm; Tachypnoea; Haemoptysis; Epistaxis
Gastrointestinal disorders	
Common	Vomiting; Diarrhoea; Nausea; Abdominal pain^
Uncommon	Dyspepsia; Constipation; Abdominal distension
Hepatobiliary disorders	
Common	Elevated liver chemistry tests^#
Uncommon	Hepatomegaly; Hepatitis
Skin and subcutaneous tissue disorders	
Common	Rash^; Pruritus
Uncommon	Petechiae; Alopecia; Drug eruption; Dermatitis^
Musculoskeletal and connective tissue disorders	
Uncommon	Back pain
Renal and urinary disorders	
Common	Renal failure
General disorders and administration site conditions	
Common	Chest pain^; Fatigue
Uncommon	Oedema peripheral^; Malaise; Asthenia

^ Indicates that grouping of appropriate preferred terms into a single medical concept occurred.

* ADR identified post-marketing.

See section Description of selected adverse reactions below.

Description of selected adverse reactions

Delirium includes reactions of confusional state.
Elevated liver chemistry tests includes events of alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, liver function test abnormal, and transaminases increased.

Laboratory effects

In a double-blind, randomized, active-controlled clinical study of 516 patients with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi, elevated liver transaminases (alanine aminotransferase or aspartate aminotransferase) > 3 × Upper Limit of Normal (ULN) were reported at the end of study treatment in 4.4% of patients who received isavuconazole. Marked elevations of liver transaminases > 10 × ULN developed in 1.2% of patients on isavuconazole.

Paediatric population

The clinical safety of isavuconazole was assessed in 77 paediatric patients who received at least one dose of intravenous or oral isavuconazole. This included 46 paediatric patients who received isavuconazole as a single dose and who also received other antifungals for prophylaxis, and 31 patients with suspected or confirmed invasive aspergillosis or mucormycosis who received isavuconazole as primary therapy for up to 181 days. Overall, the safety profile of isavuconazole in the paediatric population was similar to that in adults.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

Symptoms reported more frequently at supratherapeutic doses of isavuconazole (equivalent to isavuconazole 600 mg/day) evaluated in a QT study than in the therapeutic dose group (equivalent to isavuconazole 200 mg/day dose) included: headache, dizziness, paraesthesia, somnolence, disturbance in attention, dysgeusia, dry mouth, diarrhoea, oral hypoaesthesia, vomiting, hot flush, anxiety, restlessness, palpitations, tachycardia, photophobia and arthralgia.

Management of overdose

Isavuconazole is not removed by haemodialysis. There is no specific antidote for isavuconazole. In the event of an overdose, supportive treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole- and tetrazole derivative, ATC code: J02AC05.

Mechanism of action

Isavuconazole is the active moiety formed after oral or intravenous administration of isavuconazonium sulfate (see section 5.2).

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.

Microbiology

In animal models of disseminated and pulmonary aspergillosis, the pharmacodynamic (PD) index important in efficacy is exposure divided by minimum inhibitory concentration (MIC) (AUC/MIC). No clear correlation between *in vitro* MIC and clinical response for the different species (*Aspergillus* and *Mucorales*) could be established.

Concentrations of isavuconazole required to inhibit *Aspergillus* species and genera/species of the order *Mucorales in vitro* have been very variable. Generally, concentrations of isavuconazole required to inhibit *Mucorales* are higher than those required to inhibit the majority of *Aspergillus* species.

Clinical efficacy has been demonstrated for the following *Aspergillus* species: *Aspergillus fumigatus*, *A. flavus*, *A. niger*, and *A. terreus (see further below).*

Mechanism(s) of resistance

Reduced susceptibility to triazole antifungal agents has been associated with mutations in the fungal *cyp51A* and *cyp51B* genes coding for the target protein lanosterol 14-alpha-demethylase involved in ergosterol biosynthesis. Fungal strains with reduced *in vitro* susceptibility to isavuconazole have been reported, and cross-resistance with voriconazole and other triazole antifungal agents cannot be excluded.

Table 5 EUCAST Breakpoints

Aspergillus species	**Minimal Inhibitory Concentration (MIC) breakpoint (mg/L)**	
	≤S (Susceptible)	**>R (Resistant)**
Aspergillus flavus	1	2
Aspergillus fumigatus	1	2
Aspergillus nidulans	0.25	0.25
Aspergillus terreus	1	1

There are currently insufficient data to set clinical breakpoints for other Aspergillus species.

Clinical efficacy and safety

Treatment of invasive aspergillosis
The safety and efficacy of isavuconazole for the treatment of adult patients with invasive aspergillosis was evaluated in a double-blind, active-controlled clinical study in 516 patients with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi. In the intent-to-treat (ITT) population, 258 patients received isavuconazole and 258 patients received voriconazole. Isavuconazole was administered intravenously (equivalent to 200 mg isavuconazole) every 8 hours for the first 48 hours, followed by once-daily intravenous or oral treatment (equivalent to 200 mg isavuconazole). The protocol-defined maximum treatment duration was 84 days. Median treatment duration was 45 days.

The overall response at end-of-treatment (EOT) in the myITT population (patients with proven and probable invasive aspergillosis based on cytology, histology, culture or galactomannan testing) was assessed by an independent blinded Data Review Committee. The myITT population comprised 123 patients receiving isavuconazole and 108 patients receiving voriconazole. The overall response in this population was n = 43 (35%) for isavuconazole and n = 42 (38.9%) for voriconazole. The adjusted treatment difference (voriconazole−isavuconazole) was 4.0% (95% confidence interval: −7.9; 15.9).

The all-cause mortality at Day 42 in this population was 18.7% for isavuconazole and 22.2% for voriconazole. The adjusted treatment difference (isavuconazole−voriconazole) was −2.7% (95 % confidence interval: −12.9; 7.5).

Treatment of mucormycosis
In an open-label non-controlled study, 37 adult patients with proven or probable mucormycosis received isavuconazole at the same dose regimen as that used to treat invasive aspergillosis. Median treatment duration was 84 days for the overall mucormycosis patient population, and 102 days for the 21 patients not previously treated for mucormycosis. For patients with probable or proven mucormycosis as defined by the independent Data Review Committee (DRC), all-cause mortality at Day 84 was 43.2% (16/37) for the overall patient population, 42.9% (9/21) for mucormycosis patients receiving isavuconazole as primary treatment, and 43.8% (7/16) for mucormycosis patients receiving isavuconazole who were refractory to, or intolerant of, prior antifungal therapy (mainly amphotericin B-based treatments). The DRC-assessed overall success rate at EOT was 11/35 (31.4%), with 5 patients considered completely cured and 6 patients partially cured. A stable response was observed in an additional 10/35 patients (28.6%). In 9 patients with mucormycosis due to *Rhizopus* spp., 4 patients showed a favourable response to isavuconazole. In 5 patients with mucormycosis due to *Rhizomucor* spp., no favourable responses were observed. The clinical experience in other species is very limited (*Lichtheimia* spp. n=2, *Cunninghamella* spp. n=1, *Actinomucor* elegans n=1).

Paediatric population

The clinical safety of isavuconazole was assessed in 77 paediatric patients who received at least one dose of intravenous or oral isavuconazole, including 31 paediatric patients who received isavuconazole in a clinical study for treating invasive aspergillosis or mucormycosis. Isavuconazole was safe and well tolerated in the treatment of invasive aspergillosis and mucormycosis at the intended treatment durations.

5.2 Pharmacokinetic properties

Isavuconazonium sulfate is a water-soluble prodrug that can be administered as an intravenous infusion or orally as hard capsules. Following administration, isavuconazonium sulfate is rapidly hydrolysed by plasma esterases to the active moiety isavuconazole; plasma concentrations of the prodrug are very low, and detectable only for a short time after intravenous dosing.

Absorption

Following oral administration of CRESEMBA in healthy adult subjects, the active moiety isavuconazole is absorbed and reaches maximum plasma concentrations (C_{max}) approximately 2–3 hours after single and multiple dosing (see Table 6).

Table 6 Steady state pharmacokinetic parameters of isavuconazole following oral administration of CRESEMBA in healthy adults

Parameter Statistic	**Isavuconazole 200 mg (n = 37)**	**Isavuconazole 600 mg (n = 32)**
C_{max} (mg/L)		
Mean	7.5	20.0
SD	1.9	3.6
CV %	25.2	17.9
t_{max} (h)		
Median	3.0	4.0
Range	2.0 – 4.0	2.0 – 4.0
AUC (h•mg/L)		
Mean	121.4	352.8
SD	35.8	72.0
CV %	29.5	20.4

As shown in table 7 below, the absolute bioavailability of isavuconazole following oral administration of a single dose of CRESEMBA is 98%. Based on these findings, intravenous and oral dosing can be used interchangeably.

Table 7 Pharmacokinetic comparison for oral and intravenous dose (Mean) in adults

	Isavuconazole 400 mg oral	**Isavuconazole 400 mg i.v.**
AUC (h•mg/L)	189.5	194.0
CV %	36.5	37.2
Half-life (h)	110	115

Effect of food on absorption
Oral administration of CRESEMBA equivalent to 400 mg isavuconazole with a high-fat meal reduced isavuconazole C_{max} by 9% and increased AUC by 9%. CRESEMBA can be taken with or without food.

Distribution

Isavuconazole is extensively distributed, with a mean steady state volume of distribution (V_{ss}) of approximately 450 L. Isavuconazole is highly bound (> 99%) to human plasma proteins, predominantly to albumin.

Biotransformation

In vitro / in vivo studies indicate that CYP3A4, CYP3A5, and subsequently uridine diphosphate-glucuronosyltransferases (UGT), are involved in the metabolism of isavuconazole.

Following single doses of [cyano-^{14}C] isavuconazonium and [pyridinylmethyl-^{14}C] isavuconazonium sulfate in humans, in addition to the active moiety (isavuconazole) and the inactive cleavage product, a number of minor metabolites were identified. Except for the active moiety isavuconazole, no individual metabolite was observed with an AUC > 10% of total radio-labelled material.

Elimination

Following oral administration of radio-labelled isavuconazonium sulfate to healthy subjects, a mean of 46.1% of the radioactive dose was recovered in faeces, and 45.5% was recovered in urine.

Renal excretion of intact isavuconazole was less than 1% of the dose administered.

The inactive cleavage product is primarily eliminated by metabolism and subsequent renal excretion of the metabolites.

Linearity/non-linearity

Studies in healthy subjects have demonstrated that the pharmacokinetics of isavuconazole are proportional up to 600 mg per day.

Pharmacokinetics in special populations

Paediatric patients
The paediatric dosage regimens were confirmed using a population pharmacokinetic (popPK) model developed using data from three clinical studies (N = 97); this included two clinical studies (N = 73) conducted in paediatric patients aged 1 to < 18 years, of whom 31 received isavuconazole for treating invasive aspergillosis or mucormycosis.
The predicted exposures to isavuconazole for paediatric patients at steady state based on different age groups, weight, route of administration, and dose are shown in Table 8.

Table 8 Isavuconazole AUC (h•mg/L) values at steady state by age group, weight, route of administration, and dose

Age group (years)	Route	Weight (kg)	Dose	AUCss (h•mg/L)
1 – < 3	Intravenous	< 37	5.4 mg/kg	108 (29 – 469)
3 – < 6	Intravenous	< 37	5.4 mg/kg	123 (27 – 513)
6 – < 18	Intravenous	< 37	5.4 mg/kg	138 (31 – 602)
6 – < 18	Oral	16 – 17	80 mg	116 (31 – 539)
6 – < 18	Oral	18 – 24	120 mg	129 (33 – 474)
6 – < 18	Oral	25 – 31	160 mg	140 (36 – 442)
6 – < 18	Oral	32 – 36	180 mg	137 (27 – 677)
6 – < 18	Intravenous and oral	≥ 37	200 mg	113 (27 – 488)
≥ 18	Intravenous and oral	≥ 37	200 mg	101 (10 – 343)

The predicted exposures for paediatric patients, regardless of route of administration and age group, were comparable to exposures at steady state (AUCss) from a clinical study conducted in adult patients with infections caused by *Aspergillus* species and other filamentous fungi (mean AUCss = 101.2 h•mg/L with standard deviation (SD) = 55.9, see Table 8).

The predicted exposures under the paediatric dosing regimen were lower than the exposures of adults who received multiple daily supratherapeutic doses of 600 mg isavuconazole (Table 6), where there was a greater occurrence of adverse events (see section 4.9).

Renal impairment
No clinically relevant changes were observed in the total C_{max} and AUC of isavuconazole in adult subjects with mild, moderate or severe renal impairment compared to subjects with normal renal function. Of the 403 patients who received isavuconazole in the Phase 3 studies, 79 (20%) of patients had an estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2. No dose adjustment is required in patients with renal impairment, including those patients with end-stage renal disease. Isavuconazole is not readily dialysable (see section 4.2).

No data are available in paediatric patients with renal impairment (see section 4.2).

Hepatic impairment
After a single 100 mg dose of isavuconazole was administered to 32 adult patients with mild (Child-Pugh Class A) hepatic insufficiency and 32 patients with moderate (Child-Pugh Class B) hepatic insufficiency (16 intravenous and 16 oral patients per Child-Pugh class), the least square mean systemic exposure (AUC) increased 64% in the Child-Pugh Class A group, and 84% in the Child-Pugh Class B group, relative to 32 age- and weight-matched healthy subjects with normal hepatic function. Mean plasma concentrations (C_{max}) were 2% lower in the Child-Pugh Class A group and 30% lower in the Child-Pugh Class B group. The population pharmacokinetic evaluation of isavuconazole in healthy subjects and patients with mild or moderate hepatic dysfunction demonstrated that the mild and moderate hepatic impairment populations had 40% and 48% lower isavuconazole clearance (CL) values, respectively, than the healthy population.

No dose adjustment is required in adult patients with mild to moderate hepatic impairment.

Isavuconazole has not been studied in adult 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 (see sections 4.2 and 4.4).

No data are available in paediatric patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

In rats and rabbits, isavuconazole at systemic exposures below the therapeutic level were associated with dose-related increases in the incidence of skeletal anomalies (rudimentary supernumerary ribs) in offspring. In rats, a dose-related increase in the incidence of zygomatic arch fusion was also noted in offspring (see section 4.6).

Administration of isavuconazonium sulfate to rats at a dose of 90 mg/kg/day (approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole) during pregnancy through the weaning period showed an increased perinatal mortality of the pups. *In utero* exposure to the active moiety isavuconazole had no effect on the fertility or the normal development of the surviving pups.

Intravenous administration of ^{14}C-labelled isavuconazonium sulfate to lactating rats resulted in the recovery of radiolabel in the milk.

Isavuconazole did not affect the fertility of male or female rats treated with oral doses up to 90 mg/kg/day (approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole).

Isavuconazole has no discernible mutagenic or genotoxic potential. Isavuconazole was negative in a bacterial reverse mutation assay, was weakly clastogenic at cytotoxic concentrations in the L5178Y tk+/- mouse lymphoma chromosome aberration assay, and showed no biologically relevant or statistically significant increase in the frequency of micronuclei in an *in vivo* rat micronucleus test.

Isavuconazole has demonstrated carcinogenic potential in 2-year rodent carcinogenicity studies. Liver and thyroid tumours are likely caused by a rodent-specific mechanism that is not relevant for humans. Skin fibromas and fibrosarcomas were seen in male rats. The mechanism underlying this effect is unknown. Endometrial adenomas and carcinomas of the uterus were seen in female rats, which is likely due to a hormonal disturbance. There is no safety margin for these effects. The relevance for humans of the skin and uterine tumours cannot be excluded.

Isavuconazole inhibited the hERG potassium channel and the L-type calcium channel with an IC_{50} of 5.82 µM and 6.57 µM respectively (34- and 38-fold the human non-protein bound C_{max} at maximum recommended human dose [MRHD], respectively). The *in vivo* 39-week repeated-dose toxicology studies in monkeys did not show QTcF prolongation at doses up to 40 mg/kg/day (approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole).

Juvenile animal studies

Isavuconazonium sulfate, when administered to juvenile rats, demonstrated a similar toxicological profile to that observed in adult animals. In juvenile rats, treatment-related toxicity considered rodent specific was observed in the liver and thyroid. These changes are not considered clinically relevant. Based on the no-observed-adverse-effect level in juvenile rats, the safety margins for isavuconazonium sulfate were approximately 0.2- to 0.5-fold the systemic exposure at the clinical maintenance dose for paediatric patients, similar to those observed in adult rats.

Environmental risk assessment (ERA)

Environmental risk assessment has shown that isavuconazole may pose a risk for the aquatic environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CRESEMBA 40 mg hard capsules:

Capsule contents
magnesium citrate (anhydrous)
microcrystalline cellulose (E460)
talc (E553b)
silica, colloidal anhydrous
stearic acid

Capsule shell
hypromellose
red iron oxide (E172)
titanium dioxide (E171)

Printing ink
Shellac (E904)
propylene glycol (E1520)
potassium hydroxide
black iron oxide (E172)

CRESEMBA 100 mg hard capsules:

Capsule contents
magnesium citrate (anhydrous)
microcrystalline cellulose (E460)
talc (E553b)
silica, colloidal anhydrous
stearic acid

Capsule shell
hypromellose
red iron oxide (E172) (capsule body only)
titanium dioxide (E171)
gellan gum
potassium acetate
disodium edetate
sodium laurilsulfate

Printing ink
Shellac (E904)
propylene glycol (E1520)
potassium hydroxide
black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original packaging in order to protect from moisture.

6.5 Nature and contents of container

CRESEMBA 40 mg hard capsules:

35 hard capsules (in seven aluminum blisters), with each capsule pocket connected to a pocket with desiccant.

CRESEMBA 100 mg hard capsules:

14 hard capsules (in two aluminum blisters), with each capsule pocket connected to a pocket with desiccant.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Basilea Pharmaceutica Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

8. MARKETING AUTHORISATION NUMBER(S)

CRESEMBA 40 mg hard capsules: EU/1/15/1036/003
CRESEMBA 100 mg hard capsules: EU/1/15/1036/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

CRESEMBA 40 mg hard capsules:

Date of first authorisation: 22 August 2024.
Date of latest renewal:

CRESEMBA 100 mg hard capsules:

Date of first authorisation: 15 October 2015.
Date of latest renewal: 13 August 2020.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
Co. Armagh
BT63 5UA
United Kingdom (Northern Ireland)

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for vial for 200 mg powder for concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

CRESEMBA 200 mg powder for concentrate for solution for infusion
isavuconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 200 mg isavuconazole (as 372.6 mg isavuconazonium sulfate)

3. LIST OF EXCIPIENTS

Excipients: mannitol (E421) and sulfuric acid

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.
Use an in-line filter for infusion.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Basilea Pharmaceutica Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1036/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label on vial for 200 mg powder for concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CRESEMBA 200 mg powder for concentrate for solution for infusion
isavuconazole

IV use after reconsitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for 100 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

CRESEMBA 100 mg hard capsules
isavuconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 100 mg isavuconazole (as 186.3 mg isavuconazonium sulfate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.
The blister card also contains desiccant. Do not swallow the desiccant.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Basilea Pharmaceutica Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1036/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRESEMBA 100 mg hard capsules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister for 100 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

CRESEMBA 100 mg hard capsules
isavuconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Basilea Pharmaceutica Deutschland GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not swallow the desiccant

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for 40 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

CRESEMBA 40 mg hard capsules
isavuconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 40 mg isavuconazole (as 74.5 mg isavuconazonium sulfate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

35 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.
The blister card also contains desiccant. Do not swallow the desiccant.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Basilea Pharmaceutica Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1036/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CRESEMBA 40 mg hard capsules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister for 40 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

CRESEMBA 40 mg hard capsules
isavuconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Basilea

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not swallow the desiccant

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Cresemba 200 mg powder for concentrate for solution for infusion
isavuconazole

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cresemba is and what it is used for

What Cresemba is
Cresemba is an anti-fungal medicine that contains the active substance isavuconazole.

How Cresemba works
Isavuconazole works by killing or stopping the growth of the fungus, which causes the infection.

What Cresemba is used for
Cresemba is used in patients from 1 year of age and older to treat the following fungal infections:
- invasive aspergillosis, caused by a fungus in the 'Aspergillus' group;
- mucormycosis, caused by a fungus belonging to the 'Mucorales' group in patients for whom a treatment with amphotericin B is not appropriate.

2. What you need to know before you use Cresemba

Do not use Cresemba:
- if you are allergic to isavuconazole or any of the other ingredients of this medicine (listed in section 6),
- if you have a heart beat problem called 'familial short QT syndrome',
- **if you are using any of the following medicines:**
  - ketoconazole, used for fungal infections,
  - high doses of ritonavir (more than 200 mg every 12 hours), used for HIV,
  - rifampicin, rifabutin, used for tuberculosis,
  - carbamazepine, used for epilepsy,
  - barbiturate medicines like phenobarbital, used for epilepsy and sleep disorders,
  - phenytoin, used for epilepsy,
  - St John's wort, a herbal medicine used for depression,
  - efavirenz, etravirine, used for HIV,
  - nafcillin, used for bacterial infections.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Cresemba:
- if you have had an allergic reaction to other 'azole' anti-fungal treatments in the past, such as ketoconazole, fluconazole, itraconazole, voriconazole or posaconazole,
- if you are suffering from severe liver disease. Your doctor should monitor you for possible side effects.

Look out for side effects

Stop using Cresemba and tell your doctor straight away if you notice any of the following side effects:
- sudden wheezing, difficulty breathing, swelling of the face, lips, mouth or tongue, severe itching, sweating, dizziness or fainting, fast heartbeat or pounding in the chest – these may be signs of a severe allergic reaction (anaphylaxis).

Problems while having Cresemba as drip into a vein
Tell your doctor straight away if you notice any of the following side effects:
- low blood pressure, feel short of breath, nausea, dizziness, headache, tingling – your doctor may decide to stop the infusion.

Changes in your liver function
Cresemba can sometimes affect your liver function. Your doctor may carry out blood tests while you are taking this medicine.

Skin problems
Tell your doctor straight away if you get severe blistering of the skin, mouth, eyes or genitals.

Children and adolescents
Do not give Cresemba to children younger than 1 year, because there is no information on use in this age group.

Other medicines and Cresemba
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. Some medicines may affect the way Cresemba works or Cresemba may affect the way they work, if they are taken at the same time.

In particular, do not take this medicine and tell your doctor or pharmacist if you are taking any of the following medicines:
- ketoconazole, used for fungal infections,
- high doses of ritonavir (more than 200 mg every 12 hours), used for HIV,
- rifampicin, rifabutin, used for tuberculosis,
- carbamazepine, used for epilepsy,
- barbiturate medicines like phenobarbital, used for epilepsy and sleep disorders,
- phenytoin, used for epilepsy,
- St John's wort, a herbal medicine used for depression,
- efavirenz, etravirine, used for HIV,
- nafcillin, used for bacterial infections.

Unless your doctor tells you otherwise, do not take this medicine and tell your doctor or pharmacist if you are taking any of the following medicines:
- rufinamide or other medicines which decrease the QT interval on the heart tracing (ECG),
- aprepitant, used to prevent nausea and vomiting by cancer treatment,
- prednisone, used for rheumatoid arthritis,
- pioglitazone, used for diabetes.

Tell your doctor or pharmacist if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines are still having the desired effect:
- ciclosporin, tacrolimus and sirolimus, used to prevent rejection of a transplant,

- cyclophosphamide, used for cancer,
- digoxin, used to treat heart failure or an uneven heart beat,
- colchicine, used for gout attack,
- dabigatran etexilate, used to stop blood clots after hip or knee replacement surgery,
- clarithromycin, used for bacterial infections,
- saquinavir, fosamprenavir, indinavir, nevirapine, lopinavir/ritonavir combination, used for HIV,
- alfentanil, fentanyl, used against strong pain,
- vincristine, vinblastine, used for cancer,
- mycophenolate mofetil (MMF), used in transplant patients,
- midazolam, used for severe insomnia and stress,
- bupropion, used for depression,
- metformin, used for diabetes,
- daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan, used for different sorts of cancer.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Do not take Cresemba if you are pregnant, unless your doctor tells you otherwise. This is because it is not known if it may affect or harm your unborn baby.

Do not breast-feed if you are taking Cresemba.

Driving and using machines
Cresemba may make you feel confused, tired or sleepy. It can also make you pass out. Therefore, be very careful when driving or operating machinery.

3. How to use Cresemba

Cresemba will be given to you by a doctor or nurse.

The recommended dose is as follows:

	Starting dose for the first two days (every 8 hours for the first 48 hours) [1]	**Maintenance dose after the first two days (once a day) [2]**
Adults	200 mg isavuconazole (one vial)	200 mg isavuconazole (one vial)
Adolescents and children with an age from 1 year to less than 18 years		
Bodyweight < 37 kg	5.4 mg/kg isavuconazole	5.4 mg/kg isavuconazole
Bodyweight ≥ 37 kg	200 mg isavuconazole (one vial)	200 mg isavuconazole (one vial)
[1] Six administrations in total. [2] This is started 12 to 24 hours after your last starting dose.		

You will be given this dose until your doctor tells you otherwise. The duration of treatment with Cresemba may be longer than 6 months if your doctor considers this necessary.

The vial will be given as a drip into a vein by your doctor or nurse.

If you use more Cresemba than you should
If you think you have been given too much Cresemba, talk to your doctor or nurse straight away. You may have more side effects such as:
- headache, feeling dizzy, restless or sleepy,
- tingling, reduced sense of touch or sensation in the mouth,
- problems being aware of things, hot flushes, anxiety, joint pain,

- changes in the way things taste, dry mouth, diarrhoea, vomiting,
- feeling your heart beat, faster heart rate, being more sensitive to light.

If you forget to use Cresemba
As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However, tell your doctor or nurse if you think that a dose has been forgotten.

If you stop using Cresemba
Cresemba treatment will continue for as long as your doctor tells you. This is to make sure that the fungal infection has gone.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Cresemba and tell your doctor straight away if you notice any of the following side effects:
- a severe allergic reaction (anaphylaxis) such as sudden wheezing, breathing problems, swelling of the face, lips, mouth or tongue, severe itching, sweating, dizziness or fainting, fast heartbeat or pounding in the chest.

Tell your doctor straight away if you notice any of the following side effects:
- severe blistering of the skin, mouth, eyes or genitals.

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common: may affect up to 1 in 10 people
- low potassium in your blood,
- decreased appetite,
- confusion (delirium),
- headache,
- sleepiness,
- inflamed veins that could lead to blood clots,
- shortness of breath or sudden and severe difficulty breathing,
- feeling sick (nausea), being sick (vomiting), diarrhoea, stomach pain,
- changes in blood tests of liver function,
- rash, itching,
- kidney failure (symptoms could include swelling of legs),
- chest pain, feeling tired or sleepy,
- problems where the injection was given.

Uncommon: may affect up to 1 in 100 people
- reduced white blood cells - can increase your risk of infection and fever,
- reduced blood cells called ‘platelets’ - can increase your risk for bleeding or bruising,
- reduced red blood cells - can make you feel weak or short of breath or make your skin pale,
- severe reduction in blood cells - can make you feel weak, cause bruising or make infections more likely,
- rash, swelling of your lips, mouth, tongue or throat with difficulty breathing (hypersensitivity),
- low blood sugar levels,
- low blood levels of magnesium,
- low levels in the blood of a protein called ‘albumin’,
- not getting the right goodness from your diet (malnutrition),

- low blood levels of sodium (hyponatraemia),
- depression, difficulty sleeping,
- seizure, fainting or feeling faint, dizziness,
- sensation of tingling, tickling, or pricking of the skin (paraesthesia),
- altered mental state (encephalopathy),
- changes in taste (dysgeusia),
- feeling of 'spinning' or being dizzy (vertigo),
- heart beat problems - may be too fast or uneven, or extra heart beats – this may show in your heart tracing (electrocardiogram or ECG),
- problems with the blood circulation,
- low blood pressure,
- wheezing, very fast breathing, coughing up blood or blood-stained sputum, nose bleeding,
- indigestion,
- constipation,
- feeling bloated (abdominal distension),
- enlarged liver,
- inflammation of the liver,
- problems with the skin, red or purple spots on the skin (petechiae), inflamed skin (dermatitis), hair loss,
- back pain,
- swelling of the extremities,
- feeling weak, very tired, or sleepy or generally out of sorts (malaise).

Side effects with frequency not known:
- anaphylaxis (a severe allergic reaction).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cresemba

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cresemba contains
- The active substance is isavuconazole. Each vial contains 372.6 mg isavuconazonium sulfate, corresponding to 200 mg isavuconazole.
- The other ingredients (excipients) are mannitol (E421) and sulfuric acid.

What Cresemba looks like and contents of the pack
Cresemba 200 mg is presented in a single use glass vial as a powder for concentrate for solution for infusion.

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Manufacturer:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Cresemba 200 mg powder for concentrate for solution for infusion must be reconstituted and diluted prior to infusion.

Reconstitution

One vial of the powder for concentrate for solution for infusion should be reconstituted by addition of 5 mL water for injection to the vial. The reconstituted concentrate contains 40 mg isavuconazole per mL. The vial should be shaken to dissolve the powder completely. The reconstituted solution should be inspected visually for particulate matter and discoloration. Reconstituted concentrate should be clear and free of visible particulate. It must be further diluted prior to administration.

Dilution

Adults and paediatric patients with bodyweight from 37 kg:

After reconstitution, the entire content of the reconstituted concentrate should be removed from the vial and added to an infusion bag containing 250 mL of either sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) dextrose solution. The infusion solution contains approximately 0.8 mg isavuconazole per mL.

Paediatric patients with bodyweight below 37 kg:

The final concentration of the infusion solution should be in the range of 0.4 to 0.8 mg isavuconazole per mL. Higher concentrations should be avoided as these may cause local irritation at the site of infusion.
To obtain the final concentration, the appropriate volume of the reconstituted concentrate based on paediatric dosing recommendations (see section 3) should be removed from the vial and added to an

infusion bag containing the appropriate amount of diluent. The appropriate volume of the infusion bag is calculated as follows:

[Required dose (mg)/final concentration (mg/mL)] – Volume of the concentrate (mL)

The concentrate can be diluted with either 9 mg/mL (0.9%) sodium chloride solution for injection or 50 mg/mL (5%) dextrose solution.

Administration

After the reconstituted concentrate is further diluted, the diluted solution may show fine white-to-translucent particulates of isavuconazole that do not sediment (but will be removed by in-line filtration). The diluted solution should be mixed gently, or the bag should be rolled to minimise the formation of particulates. Unnecessary vibration or vigorous shaking of the solution should be avoided. The solution for infusion must be administered via an infusion set with an in-line filter (pore size 0.2 µm to 1.2 µm) made of polyether sulfone (PES). Infusion pumps can be used and must be placed before the infusion set. Regardless of the infusion solution container size used, the entire volume of the container should be administered to ensure the complete dose is administered.

Isavuconazole should not be infused into the same line or cannula concomitantly with other intravenous products.

Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 2 °C to 8 °C, or 6 hours at room temperature.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

If possible, the intravenous administration of isavuconazole should be completed within 6 hours after reconstitution and dilution at room temperature. If this is not possible, the infusion solution should be immediately refrigerated after dilution, and infusion should be completed within 24 hours.

An existing intravenous line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) dextrose solution.

This medicinal product is for single use only. Discard partially-used vials.

Package leaflet: Information for the patient

Cresemba 40 mg hard capsules
Cresemba 100 mg hard capsules
isavuconazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cresemba is and what it is used for

What Cresemba is
Cresemba is an anti-fungal medicine that contains the active substance isavuconazole.

How Cresemba works
Isavuconazole works by killing or stopping the growth of the fungus, which causes the infection.

What Cresemba is used for
Cresemba is used in adults and in paediatric patients from 6 years of age to treat the following fungal infections:
- invasive aspergillosis, caused by a fungus in the 'Aspergillus' group;
- mucormycosis, caused by a fungus belonging to the 'Mucorales' group in patients for whom a treatment with amphotericin B is not appropriate.

2. What you need to know before you take Cresemba

Do not take Cresemba:
- if you are allergic to isavuconazole or any of the other ingredients of this medicine (listed in section 6),
- if you have a heart beat problem called 'familial short QT syndrome',
- **if you are using any of the following medicines:**
  - ketoconazole, used for fungal infections,
  - high doses of ritonavir (more than 200 mg every 12 hours), used for HIV,
  - rifampicin, rifabutin, used for tuberculosis,
  - carbamazepine, used for epilepsy,
  - barbiturate medicines like phenobarbital, used for epilepsy and sleep disorders,
  - phenytoin, used for epilepsy,
  - St John's wort, a herbal medicine used for depression,
  - efavirenz, etravirine, used for HIV,
  - nafcillin, used for bacterial infections.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Cresemba:
- if you have had an allergic reaction to other 'azole' anti-fungal treatments in the past, such as ketoconazole, fluconazole, itraconazole, voriconazole or posaconazole,
- if you are suffering from severe liver disease. Your doctor should monitor you for possible side effects.

Look out for side effects

Stop taking Cresemba and tell your doctor straight away if you notice any of the following side effects:
- sudden wheezing, difficulty breathing, swelling of the face, lips, mouth or tongue, severe itching, sweating, dizziness or fainting, fast heartbeat or pounding in the chest – these may be signs of a severe allergic reaction (anaphylaxis).

Changes in your liver function
Cresemba can sometimes affect your liver function. Your doctor may carry out blood tests while you are taking this medicine.

Skin problems
Tell your doctor straight away if you get severe blistering of the skin, mouth, eyes or genitals.

Children and adolescents
Do not give Cresemba capsules to children between the age of one year and 6 years, because this form of the medicine has not been tested in this age group. For children over 6 years and adolescents who wheigh at least 32 kg your doctor may prescribe Cresemba 100 mg capsules. Other forms of this medicine are more suitable for children or adolescents who cannot swallow capsules; ask your doctor or pharmacist.

Other medicines and Cresemba
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. Some medicines may affect the way Cresemba works or Cresemba may affect the way they work, if they are taken at the same time.

In particular, do not take this medicine and tell your doctor or pharmacist if you are taking any of the following medicines:
- ketoconazole, used for fungal infections,
- high doses of ritonavir (more than 200 mg every 12 hours), used for HIV,
- rifampicin, rifabutin, used for tuberculosis,
- carbamazepine, used for epilepsy,
- barbiturate medicines like phenobarbital, used for epilepsy and sleep disorders,
- phenytoin, used for epilepsy,
- St John's wort, a herbal medicine used for depression,
- efavirenz, etravirine, used for HIV,
- nafcillin, used for bacterial infections.

Unless your doctor tells you otherwise, do not take this medicine and tell your doctor or pharmacist if you are taking any of the following medicines:
- rufinamide or other medicines which decrease the QT interval on the heart tracing (ECG),
- aprepitant, used to prevent nausea and vomiting by cancer treatment,
- prednisone, used for rheumatoid arthritis,
- pioglitazone, used for diabetes.

Tell your doctor or pharmacist if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines are still having the desired effect:
- ciclosporin, tacrolimus and sirolimus, used to prevent rejection of a transplant,
- cyclophosphamide, used for cancer,

- digoxin, used to treat heart failure or an uneven heart beat,
- colchicine, used for gout attack,
- dabigatran etexilate, used to stop blood clots after hip or knee replacement surgery,
- clarithromycin, used for bacterial infections,
- saquinavir, fosamprenavir, indinavir, nevirapine, lopinavir/ritonavir combination, used for HIV,
- alfentanil, fentanyl, used against strong pain,
- vincristine, vinblastine, used for cancer,
- mycophenolate mofetil (MMF), used in transplant patients,
- midazolam, used for severe insomnia and stress,
- bupropion, used for depression,
- metformin, used for diabetes,
- daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan, used for different sorts of cancer.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Do not take Cresemba if you are pregnant, unless your doctor tells you otherwise. This is because it is not known if it may affect or harm your unborn baby.

Do not breast-feed if you are taking Cresemba.

Driving and using machines
Cresemba may make you feel confused, tired or sleepy. It can also make you pass out. Therefore, be very careful when driving or operating machinery.

3. How to take Cresemba

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is as follows:

Adult patients		
Starting dose (three times daily)[1]		**Usual dose after the first two days: Once per day[2]**
every 8 hours during Days 1 and 2	**total daily dose during Days 1 and 2**	
Two 100 mg capsules	Six 100 mg capsules	Two 100 mg capsules
[1] Six doses in total. [2] This is started 12 to 24 hours after your last starting dose.		

Paediatric patients aged from 6 years to less than 18 years			
Bodyweight (kg)	**Starting dose (three times daily)[1]**		**Usual dose after the first two days: Once per day [2]**
	every 8 hours during Days 1 and 2	**total daily dose during Days 1 and 2**	
16 kg to < 18 kg	Two 40 mg capsules	Six 40 mg capsules	Two 40 mg capsules
18 kg to < 25 kg	Three 40 mg capsules	Nine 40 mg capsules	Three 40 mg capsules
25 kg to < 32 kg	Four 40 mg capsules	Twelve 40 mg capsules	Four 40 mg capsules
32 kg to < 37 kg	One 100 mg capsule **and** two 40 mg capsules	Three 100 mg capsules **and** six 40 mg capsules	One 100 mg capsule **and** two 40 mg capsules
≥ 37 kg	Five 40 mg capsules **or** two 100 mg capsules	Fifteen 40 mg capsules **or** six 100 mg capsules	Five 40 mg capsules **or** two 100 mg capsules
[1] Six doses in total. [2] This is started 12 to 24 hours after your last starting dose.			

Use in children and adolescents
The use of Cresemba 100 mg capsules in children and adolescents is not studied. Your doctor may give Cresemba 100 mg capsules to children and adolescents who weigh at least 32 kg.

Other forms of this medicine are suitable for children and adolsecents who cannot swallow capsules; ask your doctor or pharmacist.

You will take this dose until your doctor tells you otherwise. The duration of treatment with Cresemba may be longer than 6 months if your doctor considers this necessary.

Capsules can be taken with or without food. Swallow the capsules whole. Do not chew, crush, dissolve or open the capsules.

If you take more Cresemba than you should
If you take more Cresemba than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you so the doctor knows what you have taken.
You may have more side effects such as:
- headache, feeling dizzy, restless or sleepy,
- tingling, reduced sense of touch or sensation in the mouth,
- problems being aware of things, hot flushes, anxiety, joint pain,
- changes in the way things taste, dry mouth, diarrhoea, vomiting,
- feeling your heart beat, faster heart rate, being more sensitive to light.

If you forget to take Cresemba
Take the capsules as soon as you remember. However, if it is nearly time for the next dose, skip the missed dose.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Cresemba
Do not stop taking Cresemba unless you doctor has told you to do so. It is important to keep taking this medicine as long as your doctor tells you. This is to make sure that the fungal infection has gone.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Cresemba and tell your doctor straight away if you notice any of the following side effects:

- a severe allergic reaction (anaphylaxis) such as sudden wheezing, breathing problems, swelling of the face, lips, mouth or tongue, severe itching, sweating, dizziness or fainting, fast heartbeat or pounding in the chest.

Tell your doctor straight away if you notice any of the following side effects:

- severe blistering of the skin, mouth, eyes or genitals.

Other side effects

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common: may affect up to 1 in 10 people

- low potassium in your blood,
- decreased appetite,
- confusion (delirium),
- headache,
- sleepiness,
- inflamed veins that could lead to blood clots,
- shortness of breath or sudden and severe difficulty breathing,
- feeling sick (nausea), being sick (vomiting), diarrhoea, stomach pain,
- changes in blood tests of liver function,
- rash, itching,
- kidney failure (symptoms could include swelling of legs),
- chest pain, feeling tired or sleepy.

Uncommon: may affect up to 1 in 100 people

- reduced white blood cells - can increase your risk of infection and fever,
- reduced blood cells called 'platelets' - can increase your risk for bleeding or bruising,
- reduced red blood cells - can make you feel weak or short of breath or make your skin pale,
- severe reduction in blood cells - can make you feel weak, cause bruising or make infections more likely,
- rash, swelling of your lips, mouth, tongue or throat with difficulty breathing (hypersensitivity),
- low blood sugar levels,
- low blood levels of magnesium,
- low levels in the blood of a protein called 'albumin',
- not getting the right goodness from your diet (malnutrition),
- low blood levels of sodium (hyponatraemia),
- depression, difficulty sleeping,
- seizure, fainting or feeling faint, dizziness,
- sensation of tingling, tickling, or pricking of the skin (paraesthesia),
- altered mental state (encephalopathy),
- changes in taste (dysgeusia),
- feeling of 'spinning' or being dizzy (vertigo),
- heart beat problems - may be too fast or uneven, or extra heart beats – this may show in your heart tracing (electrocardiogram or ECG),
- problems with the blood circulation,
- low blood pressure,
- wheezing, very fast breathing, coughing up blood or blood-stained sputum, nose bleeding,
- indigestion,
- constipation,
- feeling bloated (abdominal distension),
- enlarged liver,

- inflammation of the liver,
- problems with the skin, red or purple spots on the skin (petechiae), inflamed skin (dermatitis), hair loss,
- back pain,
- swelling of the extremities,
- feeling weak, very tired, or sleepy or generally out of sorts (malaise).

Side effects with frequency not known:
- anaphylaxis (a severe allergic reaction).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cresemba

Keep this medicine out of the sight and reach of children.

Do not take this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Store in the original packaging in order to protect from moisture.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cresemba contains
- The active substance is isavuconazole. Each capsule contains either 74.5 mg isavuconazonium sulfate, corresponding to 40 mg isavuconazole (for Cresemba 40 mg hard capsules) or 186.3 mg isavuconazonium sulfate, corresponding to 100 mg isavuconazole (for Cresemba 100 mg hard capsules).
- The other ingredients are:
  - Capsule content: magnesium citrate (anhydrous), microcrystalline cellulose (E460), talc (E553b), anhydrous colloidal silica, stearic acid.
  - Caspule shell for Cresemba 40 mg hard capsules: hypromellose, red iron oxide (E172), titanium dioxide (E171).
  - Capsule shell for Cresemba 100 mg hard capsules: hypromellose, red iron oxide (E172) (capsule body only), titanium dioxide (E171), gellan gum, potassium acetate, disodium edetate, sodium laurilsulfate.
  - Printing ink: shellac (E904), propylene glycol (E1520), potassium hydroxide, black iron oxide (E172).

What Cresemba looks like and contents of the pack

Cresemba 40 mg hard caspsules are reddish-brown capsules with a cap marked with “CR40” in black ink.

Cresemba 100 mg hard capsules are capsules with a reddish-brown body marked with “100” in black ink and a white cap marked with “C” in black ink.

Cresemba 40 mg hard capsules are available in cartons that contain 35 capsules. Each carton contains seven aluminium blisters with 5 capsules each.

Cresemba 100 mg hard capsules are available in cartons that contain 14 capsules. Each carton contains 2 aluminium blisters with 7 capsules each.

Each capsule pocket is connected to a pocket that contains ‘desiccant’ to protect the capsule from moisture.

Do not puncture the blister containing the desiccant.

Do not swallow or use the desiccant.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for isavuconazole, the scientific conclusions of PRAC are as follows:

In view of available data on hyponatraemia from clinical trials, the literature, spontaneous reports including 23 cases with a close temporal relationship, 11 cases with positive de-challenge and 1 case with positive re-challenge, the PRAC considers that a causal relationship between isavuconazole and hyponatraemia is at least a reasonable possibility. The PRAC concluded that the product information of products containing isavuconazole should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for isavuconazole the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing isavuconazole is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.