CRESEMBA™

Isavuconazonium sulfate

1. NAME OF THE MEDICINAL PRODUCT

CRESEMBA 100 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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 is indicated in adults 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.

Loading dose

The recommended loading dose is two capsules (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours (6 administrations in total).

Maintenance dose

The recommended maintenance dose is two capsules (equivalent to 200 mg of isavuconazole) once daily, starting 12 to 24 hours after the last loading dose.

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 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.

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 patients with renal impairment, including patients with end-stage renal disease (see section 5.2).

Hepatic impairment

No dose adjustment is necessary in 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 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).

Paediatric population

The safety and efficacy of CRESEMBA in children aged below 18 years has not yet been established. No data are available.

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).

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 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 1 (increase is indicated as "↑", decrease as "↓"), ordered by therapeutic class. Unless otherwise stated, studies detailed in Table 1 have been performed with the recommended dose of isavuconazole.

Table 1 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 CYP3A4/5 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.
Immunosuppressants		
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 (alfentanil, fentanyl) (CYP3A4/5 substrate)	Not studied. Short-acting opiate concentrations may increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary. Short-acting opiates (alfentanil, 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.
Anticancer		
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. Concentrations of active metabolites of cyclophosphamide 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. 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% (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% (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) 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. 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.
[a)] % decrease of the mean trough level values.
[b)] Indinavir was only studied after a single dose of 400 mg isavuconazole.

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 childbearing 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 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 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 2 presents adverse reactions with isavuconazole in the treatment of invasive fungal infections, 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); uncommon (≥1/1,000 to <1/100); and not known (frequency cannot be estimated from available data).

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

Table 2 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

System Organ Class	Adverse Drug Reactions
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, randomised, 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.

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.

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 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 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).

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 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 3).

Table 3 Steady state pharmacokinetic parameters of isavuconazole following oral administration of CRESEMBA

Parameter Statistic	**Isavuconazole 200 mg (n = 37)**	**Isavuconazole 600 mg (n = 32)**
C_{max} (ng/mL)		
Mean SD CV %	7499 1893.3 25.2	20028 3584.3 17.9
t_{max} (h)		
Median Range	3.0 2.0 – 4.0	4.0 2.0 – 4.0
AUC (h•ng/mL)		
Mean SD CV %	121402 35768.8 29.5	352805 72018.5 20.4

As shown in table 4 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 4 Pharmacokinetic comparison for oral and intravenous dose (Mean)

	ISA 400 mg oral	**ISA 400 mg i.v.**
AUC (h•ng/mL)	189462.8	193906.8
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/day.

Pharmacokinetics in special populations

Paediatric patients

The pharmacokinetics in paediatric patients (<18 years) have not yet been evaluated. No data are available.

Renal impairment

No clinically relevant changes were observed in the total C_{max} and AUC of isavuconazole in 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).

Hepatic impairment

After a single 100 mg dose of isavuconazole was administered to 32 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 patients with mild to moderate 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 (see sections 4.2 and 4.4).

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 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).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
magnesium citrate (anhydrous)
microcrystalline cellulose
talc
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
propylene glycol
potassium hydroxide
black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store below 30°C. Store in the original packaging in order to protect from moisture.

6.5 Nature and contents of container

14 hard capsules (in two aluminium 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. PRODUCT OWNER

Basilea Pharmaceutica International Ltd., Allschwil
Allschwil
Switzerland

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