▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – CRESEMBA® (ISAVUCONAZOLE) POWDER FOR INJECTION AND CAPSULES

1. NAME OF THE MEDICINE

Isavuconazole (as isavuconazonium sulfate).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder for injection

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

Capsules

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

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for injection

Powder for injection; white to yellow powder for intravenous administration following reconstitution and dilution.

Capsules

Swedish Orange (reddish-brown) capsule body marked with “100” in black ink and a white cap marked with “C” in black ink. For oral administration.

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 Section 4.4 Special warnings and precautions for use and Section 5.1 Pharmacodynamic properties)

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

4.2 Dose and method of administration

Dosage

Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

The recommended loading and maintenance dose for both the powder for injection and capsule formulations are shown in Table 1 below.

Table 1. Dosage Regimen for CRESEMBA

	Loading Dose	Maintenance Dose[a]
CRESEMBA Powder for injection (200 mg of isavuconazole per vial)	1 reconstituted vial (200 mg) intravenously every 8 hours for 6 doses (48 hours)	1 reconstituted vial (200 mg) intravenously once daily
CRESEMBA Capsules (100 mg of isavuconazole per capsule)	2 capsules (200 mg) orally every 8 hours for 6 doses (48 hours)	2 capsules (200 mg) orally once daily

[a] Start maintenance doses 12 to 24 hours after the last loading dose

Duration of therapy should be determined by the clinical response (see Section 5.1 Pharmacodynamic properties).

For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered (see Section 5.1 Pharmacodynamic properties and Section 5.3 Preclinical safety data).

Switching between powder for injection and capsule formulations

On the basis of the high oral bioavailability (98%, see Section 5.2 Pharmacokinetic properties), 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 Pharmacokinetic properties).

Hepatic impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B) (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties).

CRESEMBA 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 Section 4.4 Special warnings and precautions for use, Section 4.8 Adverse effects (undesirable effects) and Section 5.2 Pharmacokinetic properties.

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

Powder for injection

CRESEMBA powder for injection must be reconstituted and then further diluted to a concentration corresponding to approximately 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. 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 powder for injection must only be given as an intravenous infusion.

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 vial should be shaken to dissolve the powder completely. The reconstituted solution should be inspected visually for particulate matter and discolouration. Reconstituted concentrate should be clear and free of visible particulate. It must be further diluted prior to administration.

Dilution and administration

After reconstitution, the entire content of the reconstituted concentrate should be removed from the vial and added to an infusion bag containing at least 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 1.5 mg/mL isavuconazonium sulfate (corresponding to approximately 0.8 mg isavuconazole per mL). 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).

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

Storage conditions after reconstitution and dilution are provided in Section 6.3 Shelf life.

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 Shelf life.

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.

The product is for single use in one patient only. Discard any residue.

Capsules

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 List of excipients.

Co-administration with ketoconazole (see Section 4.5 Interactions with other medicines and other forms of interactions).

Co-administration with high dose ritonavir (> 200 mg every 12 hours) (see Section 4.5 Interactions with other medicines and other forms of interactions).

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 Interactions with other medicines and other forms of interactions).

Patients with familial short QT syndrome (see Section 4.4 Special warnings and precautions for use).

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 Adverse effects (undesirable effects)). 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 Adverse effects (undesirable effects)). 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

CRESEMBA is contraindicated in patients with familial short QT syndrome (see Section 4.3 Contraindications).

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 CRESEMBA 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 Adverse effects (undesirable effects)). The elevations in liver transaminases rarely required discontinuation of CRESEMBA. Monitoring of hepatic enzymes should be considered, as clinically indicated. Serious hepatic reactions have been reported. Evaluate liver-related laboratory tests at the start and during the course of CRESEMBA therapy.

Severe hepatic impairment

CRESEMBA 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 Section 4.2 Dose and method of administration, Section 4.8 Adverse effects (undesirable effects) and 5.2 Pharmacokinetic properties.

Concomitant use with other medicinal products

CYP3A4/5 inhibitors

Ketoconazole is contraindicated (see Section 4.3 Contraindications). 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 CRESEMBA is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see Section 4.5 Interactions with other medicines and other forms of interactions).

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 Interactions with other medicines and other forms of interactions).

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 CRESEMBA. Concomitant use of CRESEMBA 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 Interactions with other medicines and other forms of interactions).

CYP2B6 substrates

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

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 CRESEMBA (see Section 4.5 Interactions with other medicines and other forms of interactions).

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 Pharmacodynamic properties). 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.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

See Section 4.8 Adverse effects (undesirable effects) – Laboratory effects.

4.5 Interactions with other medicines and other forms of interactions

Potential of medicinal products to affect the pharmacokinetics of isavuconazole

Isavuconazole is a substrate of CYP3A4 and CYP3A5 (see Section 5.2 Pharmacokinetic properties). 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 CRESEMBA with the strong CYP3A4/5 inhibitor ketoconazole is contraindicated, since this medicinal product can significantly increase plasma concentrations of isavuconazole (see Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interactions).

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 CRESEMBA is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see Section 4.4 Special warnings and precautions for use).

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

Medicinal products that induce CYP3A4/5

Co-administration of CRESEMBA 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 Contraindications).

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 Special warnings and precautions for use).

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 Contraindications).

Potential for CRESEMBA to affect exposures of other medicines

Medicinal products metabolised by CYP3A4/5

Isavuconazole is a moderate inhibitor of CYP3A4/5; co-administration of CRESEMBA 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 CRESEMBA 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 CRESEMBA 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 CRESEMBA 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 CRESEMBA 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 CRESEMBA 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 with the recommended dose of CRESEMBA.

Table 2. Established or Potential Drug-Drug 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 CRESEMBA 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 CRESEMBA and rifampicin is contraindicated.

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**
Rifabutin (strong CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of CRESEMBA and rifabutin is contraindicated.
Nafcillin (moderate CY3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of CRESEMBA and nafcillin is contraindicated.
Clarithromycin (strong CYP3A4/5 inhibitor)	Not studied. Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	No CRESEMBA 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 CRESEMBA 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 CRESEMBA 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 CRESEMBA 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 CRESEMBA dose adjustment necessary. MMF: monitoring for MPA-related toxicities is advised.

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**
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 CRESEMBA 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 CRESEMBA 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 CRESEMBA dose adjustment necessary. Vinca alkaloids: careful monitoring for any occurrence of drug toxicity, and dose reduction if required.
Cyclophosphamide (CYP2B6 substrate)	Not studied. Cyclophosphamide concentrations may decrease. (CYP2B6 induction)	No CRESEMBA dose adjustment necessary. Cyclophosphamide: careful monitoring for any occurrence of lack of efficacy, and dose increase if required.
Methotrexate	Methotrexate: AUC_{inf}: ↓ 3%	No CRESEMBA dose adjustment necessary.

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**
(BCRP, OAT1, OAT3 substrate)	C_{max}: ↓ 11% 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 CRESEMBA 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 CRESEMBA dose adjustment necessary. Metformin: dose reduction may be required.
Repaglinide (CYP2C8 and OATP1B1 substrate)	Repaglinide: AUC_{inf}: ↓ 8% C_{max}: ↓ 14%	No CRESEMBA dose adjustment necessary. Repaglinide: no dose adjustment required.
Anticoagulants		
Dabigatran etexilate (P-gp substrate)	Not studied. Dabigatran etexilate concentrations may increase. (P-gp inhibition).	No CRESEMBA 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 CRESEMBA dose adjustment necessary. Warfarin: no dose adjustment required.

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**
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 CRESEMBA 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 CRESEMBA 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 CRESEMBA and efavirenz is contraindicated.
Etravirine (moderate CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of CRESEMBA and etravirine is contraindicated.
Indinavir (CYP3A4/5 strong inhibitor and substrate)	Indinavir[b]: AUC_{inf}: ↓ 36% C_{max}: ↓ 52% (Mechanism unknown)	No CRESEMBA dose adjustment necessary; caution is advised as adverse drug reactions may increase. Indinavir: careful monitoring for any occurrence of lack of

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**
	Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	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 CRESEMBA 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., amprenavir, nelfinavir or 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 CRESEMBA 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., delavirdine, and nevaripine) (CYP3A4/5 and 2B6 inducers and substrates)	Not studied. NNRTI concentrations may decrease (CYP2B6 induction by isavuconazole) or increase. (CYP3A4/5 inhibition)	No CRESEMBA dose adjustment necessary. NNRTIs: careful monitoring for any occurrence of drug toxicity and/or lack of anti-viral efficacy, and dose adjustment if required.
Acid lowering agents		
Esomeprazole (CYP2C19 substrate and gastric pH ↑)	Isavuconazole: AUC_{tau}: ↑ 8% C_{max}: ↑ 5%	No CRESEMBA dose adjustment necessary. Esomeprazole: no dose adjustment required.
Omeprazole (CYP2C19 substrate and gastric pH ↑)	Omeprazole: AUC_{inf}: ↓ 11% C_{max}: ↓ 23%	No CRESEMBA dose adjustment necessary. Omeprazole: no dose adjustment required.
Lipid-lowering agents		
Atorvastatin and other statins (CYP3A4 substrates	Atorvastatin : AUC_{inf}: ↑ 37% C_{max}: ↑ 3%	No CRESEMBA dose adjustment necessary.

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**
e.g., simvastatin, lovastatin, rosuvastatin) (CYP3A4/5 and/or BCRP substrates)	Other statins were not studied. Statins concentrations may increase. (CYP3A4/5 or BCRP inhibition)	Based on results with atorvastatin, no statin dose adjustment required. Monitoring of adverse reactions typical of statins is advised.
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.
Antiarrhythmics		
Digoxin (P-gp substrate)	Digoxin: AUC_{inf}: ↑ 25% C_{max}: ↑ 33% (P-gp inhibition)	No CRESEMBA dose adjustment necessary. Digoxin: serum digoxin concentrations should be monitored and used for titration of the digoxin dose.
Oral contraceptives		
Ethinyl oestradiol and norenthrindone (CYP3A4/5 substrates)	Ethinyl oestradiol: AUC_{inf}: ↑ 8% C_{max}: ↑ 14% Norenthrindone: AUC_{inf}: ↑ 16% C_{max}: ↑ 6%	No CRESEMBA dose adjustment necessary. Ethinyl oestradiol and norenthrindone: 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 CRESEMBA dose adjustment necessary. Dextromethorphan: no dose adjustment required.
Benzodiazepines		
Midazolam (CYP3A4/5 substrate)	Oral midazolam: AUC_{inf}: ↑ 103% C_{max}: ↑ 72% (CYP3A4 inhibition)	No CRESEMBA 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 CRESEMBA dose adjustment necessary. Colchicine has a narrow therapeutic index and should be monitored, dose reduction if required.

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
Natural products		
Caffeine (CYP1A2 substrate)	Caffeine: AUC_{inf}: ↑ 4% C_{max}: ↓ 1%	No CRESEMBA dose adjustment necessary. Caffeine: no dose adjustment required.
Smoking cessation aids		
Bupropion (CYP2B6 substrate)	Buproprion: AUC_{inf}: ↓ 42% C_{max}: ↓ 31% (CYP2B6 induction)	No CRESEMBA 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

Effects on fertility

There are no data on the effect of isavuconazole on human fertility. Oral administration of isavuconazonium sulfate did not affect the fertility in male or female rats treated at doses up to 90 mg/kg/day (less than a half the clinical dose based on AUC comparisons).

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

Use in pregnancy – Pregnancy Category D

There are no data from the use of CRESEMBA in pregnant women. Isavuconazonium chloride administration was associated with dose-related increases in the incidences of rudimentary cervical ribs in rats and rabbits at 30 and 45 mg/kg, respectively, doses equivalent to about one fifth and one tenth of the clinical exposures based on AUC comparisons. In rats, dose-related increases in the incidences of zygomatic arch fusion and supernumerary ribs/rudimentary supernumerary ribs were also noted at 30 mg/kg and above, equivalent to one fifth the clinical dose based on AUC comparisons. 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 fetus.

Use in lactation

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

A risk to newborns and infants cannot be excluded.

Breast-feeding should be discontinued during treatment with CRESEMBA.

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 Adverse effects (undesirable effects)

Summary of the safety profile

The frequency of adverse reactions shown in Table 3 is based on data from 403 patients with invasive fungal infections treated with CRESEMBA in Phase 3 studies.

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 CRESEMBA 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 3 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 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

System Organ Class	Adverse Drug Reactions
Uncommon	Hypomagnesaemia; Hypoglycaemia; Hypoalbuminaemia; Malnutrition^
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, hyperbilirubinaemia, 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 CRESEMBA. Marked elevations of liver transaminases > 10 × ULN developed in 1.2% of patients on isavuconazole.

Table 4 includes selected treatment-emergent adverse reactions which were reported at an incidence of more than 5% during CRESEMBA therapy in Study 9766-CL-0104 (Invasive Aspergillosis).

Table 4. Selected Treatment-Emergent Adverse Reactions with Rates of 5% or Greater in CRESEMBA-treated Patients in Study 9766-CL-0104 (Invasive Aspergillosis)

System Organ Class Preferred Term	**CRESEMBA (N=257) n (%)**	**Voriconazole (N=259) n (%)**
Gastrointestinal disorders		
Nausea	71 (27.6)	78 (30.1)
Vomiting	64 (24.9)	73 (28.2)
Diarrhea	61 (23.7)	60 (23.2)
Abdominal pain	43 (16.7)	59 (22.8)
Constipation	36 (14.0)	54 (20.8)
Dyspepsia	16 (6.2)	14 (5.4)
General disorders and administration site conditions		
Oedema peripheral	39 (15.2)	46 (17.8)
Fatigue	27 (10.5)	18 (6.9)
Chest pain	23 (8.9)	16 (6.2)
Injection site reaction	16 (6.2)	4 (1.5)
Hepatobiliary disorders		
Elevated liver laboratory tests[a]	44 (17.1)	63 (24.3)
Metabolism and nutrition disorders		
Hypokalemia	49 (19.1)	58 (22.4)
Decreased appetite	22 (8.6)	28 (10.8)
Hypomagnesemia	14 (5.4)	27 (10.4)
Musculoskeletal and connective tissue disorders		

System Organ Class Preferred Term	CRESEMBA (N=257) n (%)	Voriconazole (N=259) n (%)
Back pain	26 (10.1)	19 (7.3)
Nervous system disorders		
Headache	43 (16.7)	38 (14.7)
Psychiatric disorders		
Insomnia	27 (10.5)	25 (9.7)
Delirium[b]	22 (8.6)	30 (11.6)
Anxiety	21 (8.2)	18 (6.9)
Renal and urinary disorders		
Renal failure	26 (10.1)	21 (8.1)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	44 (17.1)	35 (13.5)
Acute respiratory failure	19 (7.4)	22 (8.5)
Skin and subcutaneous tissue disorders		
Rash	22 (8.6)	36 (13.9)
Pruritus	21 (8.2)	15 (5.8)
Vascular disorders		
Hypotension	21 (8.2)	28 (10.8)

[a] Elevated liver laboratory tests include reactions of increased alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, blood bilirubin, and gamma-glutamyltransferase.

[b] Delirium includes adverse reactions of agitation, confusional state, delirium, disorientation, and mental status changes.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms

Symptoms reported more frequently at supratherapeutic doses of CRESEMBA (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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC05

Mechanism of action

Isavuconazonium sulfate is the prodrug of isavuconazole, an azole antifungal drug. Isavuconazole inhibits 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. This enzyme is responsible for the conversion of lanosterol to ergosterol. An accumulation of methylated sterol precursors and a depletion of ergosterol within the fungal cell membrane weakens the membrane structure and function. Mammalian cell demethylation is less sensitive to isavuconazole inhibition.

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).*

Drug resistance

There is a potential for development of resistance to isavuconazole. The mechanism of resistance to isavuconazole, like other azole antifungals, is likely due to multiple mechanisms that include substitutions in the target gene CYP51. Changes in sterol profile and elevated efflux pump activity were observed, however, the clinical relevance of these findings is unclear. *In vitro* and animal studies suggest cross-resistance between isavuconazole and other azoles. The relevance of cross resistance to clinical outcome has not been fully characterised. However, patients failing prior azole therapy may require alternative antifungal therapy.

Breakpoints

EUCAST MIC breakpoints are defined for the following species (susceptible S; resistant R):

- *Aspergillus fumigatus:* S ≤ 1 mg/L, R > 1 mg/L
- *Aspergillus nidulans:* S ≤ 0.25 mg/L, R > 0.25 mg/L
- *Aspergillus terreus:* S ≤ 1 mg/L, R > 1 mg/L

There are currently insufficient data to set clinical breakpoints for other *Aspergillus* species or for any *Mucorales* species.

Clinical trials

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. CRESEMBA 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 (isavuconazole−voriconazole) was −4.0 (95% confidence interval: −16.3, 8.4).

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: −13.6, 8.2) (see Table 5).

Table 5. All-Cause Mortality Through Day 42

	CRESEMBA		**Voriconazole**		
	N	**All-cause Mortality n (%)**	**N**	**All-cause Mortality n (%)**	**Difference[a] (95% CI)%**
ITT	258	48 (18.6)	258	52 (20.2)	-1.0 (-8.0, 5.9)
Proven or Probable Invasive Aspergillosis	123	23 (18.7)	108	24 (22.2)	-2.7 (-13.6, 8.2)

[a] Adjusted treatment difference (CRESEMBA-voriconazole) by Cochran-Mantel-Haenszel method stratified by the randomisation factors.

Overall success at End-of-Treatment (EOT) was assessed by a blinded, independent Data Review Committee (DRC) using pre-specified clinical, mycological, and radiological criteria. In the subgroup of patients with proven or probable invasive aspergillosis confirmed by serology, culture or histology, overall success at EOT was seen in 35% of CRESEMBA-treated patients compared to 38.9% of voriconazole-treated patients (see Table 6).

Table 6. Overall Response Success at End-of-Treatment

	CRESEMBA		**Voriconazole**		
	N	**Success n (%)**	**N**	**Success n (%)**	**Difference[a] (95% CI)%**
Proven or Probable Invasive Aspergillosis	123	43 (35.0)	108	42 (38.9)	-4.0 (-16.3, 8.4)

[a] Adjusted treatment difference (CRESEMBA-voriconazole) by Cochran-Mantel-Haenszel method stratified by the randomisation factors.

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). Baseline risk factors are presented in Table 7.

Table 7. Baseline Risk Factors in Mucorales Patients

	Primary N=21 n (%)	**Refractory N=11 n (%)**	**Intolerant N=5 n (%)**	**Total N=37 n (%)**
Hematologic Malignancy	11 (52)	7 (64)	4 (80)	22 (60)
Allogeneic Hematopoietic Stem Cell Transplant	4 (19)	4 (36)	5 (100)	13 (35)
Neutropenia[a]	4 (19)	5 (46)	1 (20)	10 (27)
Corticosteroid Use	5 (24)	3 (27)	2 (40)	10 (27)
T-Cell Immunosuppressant Use	7 (33)	6 (55)	5 (100)	18 (49)
Diabetic	4 (19)	0	0	4 (11)

Therapy status assessed by independent Data Review Committee: Primary = patients received CRESEMBA as primary treatment; refractory = patient's underlying infection not adequately treated by prior therapy; intolerant = patients unable to tolerate prior therapy.

[a] Neutropenia is defined as less than 500 cells/mm^3.

Patients were treated with CRESEMBA intravenously or via oral administration at the recommended doses. Median treatment duration was 102 days for patients classified as primary, 33 days for refractory, and 85 days for intolerant (see Section 4.2 Dose and method of administration).

For patients with invasive mucormycosis, all-cause mortality through day 42 and success in overall response at the End-of-Treatment as assessed by the independent Data Review Committee is shown in Table 8. These results provide evidence that CRESEMBA is effective for the treatment for mucormycosis, in light of the natural history of untreated mucormycosis. However, the efficacy of CRESEMBA for the treatment for invasive mucormycosis has not been evaluated in concurrent, controlled clinical trials.

Table 8. All-Cause Mortality through Day 42 and Overall Response Success in Mucorales Patients

	Primary N=21	Refractory N=11	Intolerant N=5	Total N=37
All-cause Mortality Through Day 42	7 (33%)	5 (46%)	2 (40%)	14 (38%)
Overall Response Success Rate at End-of-Treatment	6/19[a] (32%)	4/11 (36%)	1/5 (20%)	11/35[a] (31%)

[a] Two primary mucormycosis patients were not assessed at End-of-Treatment due to ongoing treatment.

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 9).

Table 9. 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	7499	20028
SD	1893.3	3584.3
CV %	25.2	17.9
t_{max} (h)		
Median	3.0	4.0
Range	2.0 – 4.0	2.0 – 4.0
AUC (h•ng/mL)		
Mean	121402	352805
SD	35768.8	72018.5
CV %	29.5	20.4

As shown in Table 10 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 10. 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.

Metabolism

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.

Excretion

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 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 CRESEMBA 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 Dose and method of administration).

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.

CRESEMBA 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 Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use.

5.3 Preclinical safety data

Genotoxicity

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.

Carcinogenicity

Isavuconazole has demonstrated carcinogenic potential in liver, thyroid, skin and endometrium when administered to rodents in long term (2 years) carcinogenicity studies.

Hepatocellular adenomas and carcinomas were noted in mice and rats, and thyroid follicular cell adenomas and carcinomas in rats at exposures below the clinical exposure at the maintenance dose of 200 mg isovuconazole, based on AUC. This pattern of tumours is known to result from prolonged hepatocellular enzyme induction in rodents, and is considered an adaptive response that is not relevant to humans.

A significant increase in the incidence of skin fibromas was noted in male rats (exposure below the clinical exposure based on AUC) but not in female rats or mice. Similarly, the incidence of uterine adenocarcinoma was significantly increased in rats (but not mice) at exposure below the clinical exposure. Given that these findings occurred in only one sex (fibromas) or one species (uterine carcinomas) after close to lifetime exposure, and the limited treatment duration in patients, the carcinogenic risk in humans for these tumours is considered low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for injection

Mannitol
Sulfuric acid (for pH-adjustment)

Capsules

Capsule contents: Magnesium citrate, microcrystalline cellulose, purified talc, colloidal anhydrous silica, stearic acid

Capsule shell: hypromellose, purified water, iron oxide red (E172) (capsule body only), titanium dioxide (E171), gellan gum, potassium acetate, disodium edetate, sodium lauryl sulfate

Printing ink: shellac, propylene glycol, potassium hydroxide, iron oxide black (E172)

6.2 Incompatibilities

See Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 Shelf life

Powder for injection

Unoponed vials: In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Reconstituted soluton: 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.

Capsules

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Powder for injection

Unoponed vials: Store in a refrigerator (2°C to 8°C).

For storage conditions after reconstitution and dilution of the medicinal product, see Section 6.3 Shelf life.

Capsules

Store below 25°C. Store in the original packaging in order to protect from moisture.

6.5 Nature and contents of container

Powder for injection

One 10 mL Type I glass vial with teflon coated butyl rubber stopper and an aluminium flip-off cap with plastic seal.

Capsules

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

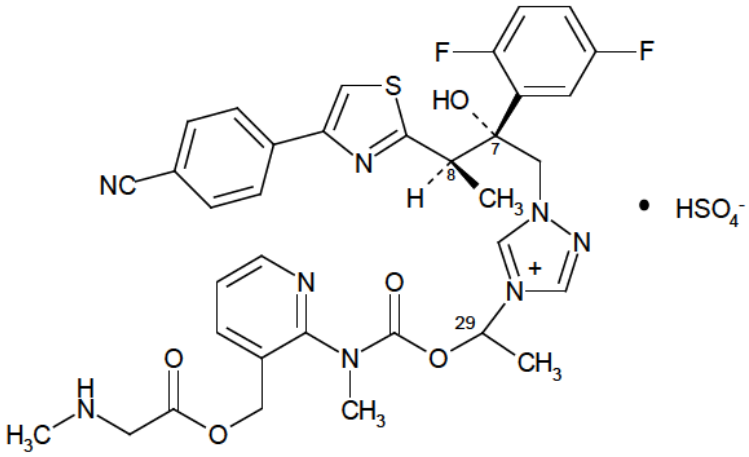
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

CRESEMBA contains isavuconazonium sulfate, which is the prodrug of isavuconazole, an azole antifungal drug. Isavuconazonium sulfate drug substance is an amorphous, white to yellowish-white powder. The chemical name of isavuconazonium sulfate is 1-{(2*R*,3*R*)-3-[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl}-4-[(1*RS*)-1-({methyl[3-({[(methylamino)acetyl]oxy}methyl)pyridin-2-yl]carbamoyl}oxy)ethyl]-1*H*-1,2,4-triazol-4-ium monosulfate. The empirical formula is $C_{35}H_{35}F_2N_8O_5S \cdot HSO_4$, the molecular weight is 814.84

Chemical structure



CAS number

946075-13-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

17 May 2019

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® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
All	Minor editorial updates
4.4 and 4.8	Update to include warning and ADR on ‘anaphylactic reaction’