PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr CRESEMBA®

Isavuconazole Capsules
100 mg isavuconazole (as isavuconazonium sulfate)

Isavuconazole for injection
200 mg/vial isavuconazole (as isavuconazonium sulfate)
Powder for solution, intravenous

Oral, Intravenous

Antifungal Agent

J02AC05

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RECENT MAJOR LABEL CHANGES

Not applicable.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CRESEMBA (isavuconazole, as isavuconazonium sulfate) is an azole antifungal indicated for use in adults for the treatment of:

- Invasive aspergillosis;
- Invasive mucormycosis.

1.1 Pediatrics (< 18 years of age)

The safety and efficacy of CRESEMBA in children aged below 18 years has not yet been established. As no data are available, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics (≥ 65 years of age)

The clinical experience in elderly patients is limited. See DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics.

2 CONTRAINDICATIONS

CRESEMBA is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Co-administration with strong CYP3A4 inhibitor ketoconazole because this strong CYP3A4 inhibitor can significantly increase the plasma concentration of isavuconazole. See DRUG INTERACTIONS.
- Co-administration with strong CYP3A4 inducers, such as rifampin, rifabutin, carbamazepine, St. John's wort, high-dose ritonavir (>400mg every 12 hours), or long acting barbiturates because strong CYP3A4 inducers can significantly decrease the plasma concentration of isavuconazole. See DRUG INTERACTIONS.
- Co-administration with moderate CYP3A4/5 inducers such as efavirenz and etravirine. See DRUG INTERACTIONS.
- Patients with familial short QT syndrome. See WARNINGS AND PRECAUTIONS.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Embryo-Fetal Toxicity:

CRESEMBA may cause fetal harm when administered to a pregnant woman. CRESEMBA should not be used during pregnancy unless the potential benefit to the patient outweighs the risk to the fetus.

CRESEMBA is not recommended for women of childbearing potential who are not using contraception. Women who become pregnant while receiving CRESEMBA are encouraged to contact their physician. See WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women and NON-CLINICAL TOXICOLOGY.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

CRESEMBA is available with two routes of administration: oral (capsules) and intravenous (powder for solution).

- Capsules: 100 mg isavuconazole, equivalent to 186.3 mg isavuconazonium sulfate.
- Powder for solution (for intravenous infusion): 200 mg isavuconazole, equivalent to 372.6 mg isavuconazonium sulfate.
    - Precautions are to be taken before handling or administering CRESEMBA (isavuconazole for injection). See Reconstitution section for instructions on reconstitution, dilution and filtration.
- On the basis of the high oral bioavailability (98%), switching between intravenous and oral administration is appropriate when clinically indicated. See ACTION AND CLINICAL PHARMACOLOGY. Loading dose is not required when switching between formulations. Start maintenance doses 12 to 24 hours after the last loading dose.
- Duration of therapy should be determined by the clinical response. Safety and efficacy data of isavuconazole use for longer than 6 months is limited. Therefore, the benefit-risk balance should be carefully considered. See ACTION AND CLINICAL PHARMACOLOGY, and MICROBIOLOGY.
- 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 WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and ACTION AND CLINICAL PHARMACOLOGY.
- Specimens for fungal culture and other relevant laboratory studies (including histopathology) to isolate and identify causative organism(s) should be obtained prior to initiating antifungal therapy. 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.

4.2 Recommended Dose and Dosage Adjustment

Table 1: Dosing regimen for CRESEMBA

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

[a] 100 mg of isavuconazole is equivalent to 186.3 mg of isavuconazonium sulfate
[b] 200 mg of isavuconazole is equivalent to 372.6 mg of isavuconazonium sulfate

- Health Canada has not authorized an indication for pediatric use. See WARNINGS AND PRECAUTIONS.
- No dose adjustment is necessary for elderly patients.
- No dose adjustment is necessary in patients with renal impairment, including patients with end-stage renal disease. See WARNINGS AND PRECAUTIONS, and ACTION AND CLINICAL PHARMACOLOGY.
- No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B). See WARNINGS AND PRECAUTIONS, and ACTION AND CLINICAL PHARMACOLOGY.

4.3 Administration

CRESEMBA (isavuconazole 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.

CRESEMBA (isavuconazole for injection)

- CRESEMBA (isavuconazole for injection) must be reconstituted and then further diluted in 250 mL of a compatible diluent to a concentration corresponding to approximately 0.8 mg/mL of 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 (isavuconazole for injection) must only be given as an intravenous infusion. For reconstitution, dilution and filtration instructions, see Reconstitution.
- Do not administer as an intravenous bolus injection.
- CRESEMBA (isavuconazole for injection) should not be infused into the same line or cannula concomitantly with other intravenous products.
- Flush intravenous lines with 0.9% sodium chloride solution for injection, or 5% dextrose solution for injection prior to and after infusion of CRESEMBA (isavuconazole for injection).
- This medicinal product is for single use only. Discard partially-used vials.

4.4 Reconstitution

Aseptic technique must be strictly observed in all handling since no preservative or bacteriostatic agent is present in CRESEMBA (isavuconazole for injection) or in the materials specified for reconstitution.

One vial of CRESEMBA (isavuconazole for injection) should be reconstituted by addition of 5 mL water for injections to the vial. The vial should be gently shaken to dissolve the powder completely. See Table 2.

The reconstituted solution should be inspected visually for particulate matter and discoloration. Reconstituted concentrate should be clear and free of visible particulate. It must be further diluted prior to administration. The reconstituted solution may be stored below 25°C for maximum 1 hour prior to preparation of the patient infusion solution.

Table 2: Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration
10 mL	5 mL water	5 mL	40 mg/mL isavuconazole

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 0.9% solution for injection or 5% dextrose solution. See Table 3. The infusion solution contains approximately 0.8 mg isavuconazole per mL (corresponding to approximately 1.5 mg/mL isavuconazonium sulfate).

Table 3: Dilution

Infusion Bag size	Volume of Diluent to be Added to Reconstituted Concentrate	Approximate Available Volume	Nominal Concentration
≥ 250 mL	250 mL, 0.9% sodium chloride solution for injection or 250 mL, 5% dextrose solution for injection	255 mL	0.8 mg/mL isavuconazole

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 minimize the formation of particulates. Unnecessary vibration or vigorous shaking of the solution should be avoided. Do not use a pneumatic transport system.

The solution or 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).

If possible, the intravenous administration of CRESEMBA (isavuconazole for injection) 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. Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 2 - 8 °C, or 6 hours at room temperature.

CRESEMBA (isavuconazole for injection) should only be administered with the following diluents:

- 0.9% sodium chloride solution for injection
- 5% dextrose solution for injection

4.5 Missed Dose

If a dose of CRESEMBA (isavuconazole capsules) is missed, it should be taken as soon as possible, unless it is almost time for the next dose. A patient should not take a double dose to make up for a forgotten one.

5 OVERDOSAGE

Symptoms

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

Management of Overdose

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules / 100 mg isavuconazole (as 186.3 mg isavuconazonium sulfate)	Capsule contents: magnesium citrate (anhydrous), microcrystalline cellulose, silica (colloidal anhydrous), stearic acid, talc Capsule shell: disodium edetate, gellan gum, hypromellose, potassium acetate, red iron oxide, sodium lauryl sulfate, titanium dioxide, water Printing ink: black iron oxide, potassium hydroxide, propylene glycol, shellac

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (infusion)	Powder for solution / 200 mg isavuconazole (as 372.6 mg isavuconazonium sulfate)	Mannitol Sulfuric acid (pH adjustment)

Capsules

CRESEMBA capsules have a Swedish orange (reddish-brown) capsule body marked with ”100” in black ink and a white cap marked with "C" in black ink. Capsule length: 24.2 mm.

CRESEMBA capsules are packaged in carton containing 14 capsules. Each carton contains 2 blister cards of 7 capsules each, and each capsule pocket is connected to a pocket with desiccant.

Powder for solution

CRESEMBA (isavuconazole for injection) is a white to yellow powder supplied in a 10 mL Type 1 glass vial with rubber stopper and an aluminum cap with plastic seal. CRESEMBA (isavuconazole for injection) is water soluble, preservative-free, sterile, and nonpyrogenic.

7 WARNINGS AND PRECAUTIONS

Please see the SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

During intravenous administration of isavuconazole, infusion-related reactions including hypotension, dyspnea, dizziness, paraesthesia, nausea, and headache were reported. See ADVERSE REACTIONS. The infusion should be stopped if these reactions occur.

Limitations of the clinical data for invasive mucormycosis

The clinical experience for isavuconazole in the treatment of invasive mucormycosis is limited to one prospective non-comparative clinical study in 37 patients with proven or probable mucormycosis (mITT-Mucorales) who received isavuconazole for primary treatment, or because other antifungal treatments (predominantly amphotericin B) were not effective.

For individual Mucorales species, the clinical efficacy data are very limited. Susceptibility data indicate that concentrations of isavuconazole required for inhibition *in vitro* are variable between genera/species within the order of Mucorales, and generally higher than concentrations required to inhibit *Aspergillus* species. No dose-finding study has been conducted for isavuconazole use in mucormycosis and patients were administered the same dose of isavuconazole as was used for the treatment of invasive aspergillosis (See CLINICAL TRIALS and MICROBIOLOGY).

Cardiovascular

CRESEMBA is contraindicated in patients with familial short QT syndrome. See CONTRAINDICATIONS. In a QT study in healthy human subjects, isavuconazole shortened the QTc interval in a concentration-related manner. See ACTION AND CLINICAL PHARMACOLOGY.

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

Drug Interactions

Co-administration of CRESEMBA with strong CYP3A4 inhibitor ketoconazole and strong inducers (such as rifampin, rifabutin and high-dose ritonavir) is contraindicated (see CONTRAINDICATIONS). See SERIOUS DRUG INTERACTIONS and Drug-Drug Interactions for warnings and precautions regarding co-administration with CYP3A4/5 inhibitors and inducers, CYP3A4/5 substrates including immunosuppressants, CYP2B6 substrates, and P-gp substrates.

Driving and Operating Machinery

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.

Hepatic/Biliary/Pancreatic

Hepatic adverse drug reactions (e.g., elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin) have been reported in clinical trials. The elevations in liver-related laboratory tests were generally reversible and did not require discontinuation of CRESEMBA. Cases of more severe hepatic adverse drug reactions including hepatitis, cholestasis or hepatic failure including death have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with azole antifungal agents, including CRESEMBA.

Evaluate liver-related laboratory tests at the start and during the course of CRESEMBA therapy. Monitor patients who develop abnormality in liver-related laboratory tests during CRESEMBA therapy for the development of more severe hepatic injury. Discontinue CRESEMBA if clinical signs and symptoms consistent with liver disease develop that may be attributable to CRESEMBA. See ADVERSE REACTIONS.

Hypersensitivity Reactions

Serious hypersensitivity and severe skin reactions, such as anaphylaxis or Stevens-Johnson syndrome, have been reported during treatment with other azole antifungal agents. Hypersensitivity to CRESEMBA may result in adverse reactions that include: hypotension, respiratory failure, dyspnea, drug eruption, pruritus, and rash. There is no information regarding cross-sensitivity between CRESEMBA and other azole antifungal agents. However, caution should be used in prescribing CRESEMBA to patients with hypersensitivity to other azole antifungal agents.

Sexual Health

Reproduction

Not applicable.

Function

No data are available.

Fertility

CRESEMBA did not affect the fertility of male or female rats treated with oral doses equivalent to less than half the maintenance human dose (200 mg) based on AUC comparisons.

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 such as exfoliative cutaneous reactions, CRESEMBA should be discontinued.

7.1 Special Populations

7.1.1 Pregnant Women

CRESEMBA may cause fetal harm when administered to a pregnant woman. CRESEMBA should not be used during pregnancy unless the potential benefits to the patient outweigh the risk to the fetus. There are no adequate or well-controlled clinical studies of CRESEMBA in pregnant women.

CRESEMBA is not recommended for women of childbearing potential who are not using effective contraception. Women who become pregnant, or wish to become pregnant, during CRESEMBA treatment are encouraged to contact their physician.

Perinatal mortality was significantly increased in the offspring of pregnant rats dosed orally with isavuconazonium sulfate at levels that were less than half the maintenance human dose based on AUC comparisons during pregnancy through the weaning period.

Isavuconazonium chloride administration in rats and rabbits was associated with dose-related increases in the incidences of rudimentary cervical ribs at 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 levels equivalent to one fifth the clinical dose based on AUC comparisons. See NON-CLINICAL TOXICOLOGY.

7.1.2 Breast-feeding

Mothers should not breast-feed while taking CRESEMBA. Isavuconazole is excreted in the milk of lactating rats following intravenous administration. A risk to newborns and infants cannot be excluded. See NON-CLINICAL TOXICOLOGY.

7.1.3 Pediatrics (< 18 years of age)

No data are available to establish the safety and efficacy of CRESEMBA in children below 18 years of age. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

The clinical experience in elderly patients is limited. See INDICATIONS, and DOSAGE AND ADMINISTRATION.

7.1.5 Patients with 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 DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS, and ACTION AND CLINICAL PHARMACOLOGY.

7.1.6 Patients with Renal Impairment

CRESEMBA has been studied in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. No dose adjustment is required in patients with renal impairment, including those patients with end-stage renal disease.

Isavuconazole is not readily dialyzable. See DOSAGE AND ADMINISTRATION.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The Phase 3 clinical trials involved 403 patients with invasive fungal infections treated with CRESEMBA. The most frequently reported adverse reactions among CRESEMBA-treated patients were nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver chemistry tests (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%). Serious adverse reactions occurred in 223/403 (55%) of patients and 56/403 (14%) of patients permanently discontinued treatment with CRESEMBA due to an adverse reaction in the two trials. The adverse reactions which most often led to permanent discontinuation of CRESEMBA therapy during the clinical trials were: confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnea (0.5%), epilepsy (0.5%), respiratory failure (0.5%), and vomiting (0.5%).

Patients in the clinical trials were immunocompromised with underlying conditions including hematological malignancy, post-chemotherapy neutropenia, graft-versus-host disease, and hematopoietic stem cell transplant. The patient population was 61% male, had a mean age of 51 years (range 17-92, including 85 patients aged greater than 65 years), and was 79% white and 3% black. One hundred forty-four (144) patients had a duration of CRESEMBA therapy of greater than 12 weeks, with 52 patients receiving CRESEMBA for over six months.

In a randomized, double-blind, active-controlled clinical trial for treatment of invasive aspergillosis (9766-CL-0104), treatment-emergent adverse reactions occurred in 247/257 (96%), and 255/259 (99%) patients in the CRESEMBA and voriconazole treatment groups, respectively. Treatment-emergent adverse reactions resulting in permanent discontinuation were reported in 37 (14%) CRESEMBA-treated patients and 59 (23%) voriconazole-treated patients.

In an open-label, non-comparative trial of CRESEMBA in patients with invasive aspergillosis and renal impairment or invasive mucormycosis (9766-CL-0103), treatment-emergent adverse reactions occurred in 139/146 (95%) of patients receiving CRESEMBA. Adverse reactions resulting in permanent discontinuation were reported in 19 (13%) of these patients.

The frequencies and types of adverse reactions observed in CRESEMBA-treated patients were similar between these two trials.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table **5** 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). Study details including dosing regimen and treatment duration are described in CLINICAL TRIALS. The trial design and study demographics of Invasive Aspergillosis study (9766-CL-0104) and Invasive Mucormycosis study (9766-CL-0103) are presented in Table 9).

Table 5: 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 (%)**	**Voriconazole N=259 (%)**
Gastrointestinal disorders		
Nausea	27.6	30.1
Vomiting	24.9	28.2
Diarrhea	23.7	23.2
Abdominal pain	16.7	22.8
Constipation	14.0	20.8
Dyspepsia	6.2	5.4
General disorders and administration site conditions		
Edema peripheral	15.2	17.8
Fatigue	10.5	6.9
Chest pain	8.9	6.2
Injection site reaction	6.2	1.5
Hepatobiliary disorders		
Elevated liver laboratory tests[a]	17.1	24.3
Metabolism and nutrition disorders		
Hypokalemia	19.1	22.4
Decreased appetite	8.6	10.8
Hypomagnesemia	5.4	10.4
Muskuloskeletal and connective tissue disorders		
Back pain	10.1	7.3
Nervous system disorders		
Headache	16.7	14.7
Psychiatric disorders		
Insomnia	10.5	9.7
Delirium[b]	8.6	11.6
Anxiety	8.2	6.9
Renal and urinary disorders		
Renal failure	10.1	8.1
Respiratory, thoracic and mediastinal disorders		
Dyspnea	17.1	13.5

System Organ Class Preferred Term	CRESEMBA N=257 (%)	Voriconazole N=259 (%)
Acute respiratory failure	7.4	8.5
Skin and subcutaneous tissue disorders		
Rash	8.6	13.9
Pruritus	8.2	5.8
Vascular disorders		
Hypotension	8.2	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.

8.3 Less Common Clinical Trial Adverse Reactions

Additional adverse reactions reported in less than 5% of all CRESEMBA-treated patients in both clinical trials, not listed in Table 5 above, are presented below. This listing includes adverse reactions where a causal relationship to isavuconazole cannot be ruled out or those which may help the physician in managing the risks to the patients.

Blood and lymphatic system disorders: agranulocytosis, leukopenia, pancytopenia

Cardiac disorders: atrial fibrillation, atrial flutter, bradycardia, reduced QT interval on electrocardiogram, palpitations, supraventricular extrasystoles, supraventricular tachycardia, ventricular extrasystoles, cardiac arrest

Ear and labyrinth disorders: tinnitus, vertigo

Eye disorders: optic neuropathy

Gastrointestinal: abdominal distension, gastritis, gingivitis, stomatitis

General disorders and administration site conditions: catheter thrombosis, chills, malaise

Hepatobiliary disorders: cholecystitis, cholelithiasis, hepatitis, hepatomegaly, hepatic failure

Immune System Disorders: hypersensitivity

Injury, poisoning and procedural complications: fall

Metabolism and nutrition disorders: hypoalbuminemia, hypoglycemia, hyponatremia

Musculoskeletal and connective tissue disorders: bone pain, myositis, neck pain

Nervous system disorders: convulsion, dysgeusia, encephalopathy, hypoesthesia, migraine, peripheral neuropathy, paraesthesia, somnolence, stupor, syncope, tremor

Psychiatric disorders: confusion, depression, hallucination

Renal and urinary disorders: hematuria, proteinuria

Respiratory, thoracic and mediastinal disorders: bronchospasm, tachypnea

Skin and subcutaneous tissue disorders: alopecia, dermatitis, exfoliative dermatitis, erythema, petechiae, urticaria

Vascular disorders: thrombophlebitis

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

In Study 9766-CL-0104, 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 CRESEMBA. See CLINICAL TRIALS.

8.5 Post-Market Adverse Reactions

The following additional adverse reactions have been reported during clinical studies and/or marketed use as uncommon (≥1/1,000 to <1/100):

Blood and lymphatic system disorders: neutropenia, thrombocytopenia, anemia

General disorders and administration site conditions: asthenia

Metabolism and nutrition disorders: malnutrition

Nervous System Disorders: dizziness

Respiratory, thoracic and mediastinal disorders: hemoptysis, epistaxis

Skin and subcutaneous tissue disorders: drug eruption

Vascular disorders: circulatory collapse.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Due to the effect on plasma concentrations, isavuconazole is contraindicated with the following drugs:

- Strong CYP3A4 inhibitor ketoconazole
- Strong CYP3A4/5 inducers such as rifampin, rifabutin, carbamazepine, high-dose ritonavir (> 400mg every 12 hours), long-acting barbiturates (e.g. phenobarbital) phenytoin and St. John's wort
- Moderate CYP3A4/5 inducers such as efavirenz and etravirine

See Table 6 for further information regarding drug-drug interactions with these drugs.

9.2 Overview

Isavuconazole is a substrate of CYP3A4 and CYP3A5. See ACTION AND CLINICAL PHARMACOLOGY. 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.

9.3 Drug-Drug Interactions

Isavuconazole is a substrate of CYP3A4 and CYP3A5. *In vitro*, isavuconazole is an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Isavuconazole is also an inhibitor of P-gp-, BCRP-and OCT2-mediated drug transporters. *In vitro*, isavuconazole is also an inducer of CYP3A4, CYP2B6, CYP2C8, and CYP2C9.

The effect of co-administration of drugs on the pharmacokinetics of isavuconazole and the effect of isavuconazole on the pharmacokinetics of co-administered drugs were studied after single and multiple doses of isavuconazole in healthy subjects.

Appropriate therapeutic drug monitoring and dose adjustment of some products (e.g immunosuppressants (i.e., tacrolimus, sirolimus, and cyclosporine)) may be necessary when co-administered with CRESEMBA. Drugs with a narrow therapeutic window that are P-gp substrates, such as digoxin, may require dose adjustment when administered concomitantly with CRESEMBA. See Table 6: Established or Potential Drug-Drug Interactions.

Potential of medicinal products to affect the pharmacokinetics of isavuconazole

CYP3A4/5 Inhibition

Co-administration of CRESEMBA with the strong CYP3A4/5 inhibitor ketoconazole is contraindicated. This medicinal product can significantly increase plasma concentrations of isavuconazole. See CONTRAINDICATIONS and DRUG 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 these strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase. See WARNINGS AND PRECAUTIONS.

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

CYP3A4/5 Induction

Co-administration of CRESEMBA with potent CYP3A4/5 inducers such as rifampin, rifabutin, carbamazepine, high dose ritonavir (>400mg every 12 hours), long-acting barbiturates (e.g., phenobarbital), phenytoin and St. John's wort, or with moderate CYP3A4/5 inducers such as efavirenz and etravirine, is contraindicated, since these medicinal products can significantly decrease plasma concentrations of isavuconazole. See 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 WARNINGS AND PRECAUTIONS.

Potential for CRESEMBA to affect exposures of other medicines

Medicines metabolized by CYP3A4/5

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

Medicines metabolized by CYP2B6

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

Medicines 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.

Medicines transported by BCRP

In vitro, isavuconazole is an inhibitor 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.

Medicines renally excreted via transport proteins

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

Uridine diphosphate-glucuronosyltransferases (UGT) substrates

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

Table 6: Established or Potential Drug-Drug Interactions

Isavuconazole **Co-administered medicines by therapeutic area**	**Source of Evidence**	**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)	T	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.

Isavuconazole Co-administered medicines by therapeutic area	Source of Evidence	Effects on drug concentrations / Geometric Mean Change (%) in AUC, C_{max} (Mode of action)	Recommendation concerning co-administration
Antibacterials			
Rifampin (strong CYP3A4/5 inducer)	CT	Isavuconazole: AUC_{tau}: ↓ 90% C_{max}: ↓ 75% (CYP3A4/5 induction)	As this medicinal product can significantly decrease plasma concentrations of isavuconazole, the concomitant administration of CRESEMBA and rifampin is contraindicated.
Rifabutin (strong CYP3A4/5 inducer)	T	Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of CRESEMBA and rifabutin is contraindicated.
Clarithromycin (strong CYP3A4/5 inhibitor)	T	Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	Based on relative potency, no CRESEMBA dose adjustment necessary; caution is advised as adverse drug reactions may increase.
Antifungals			
Ketoconazole (strong CYP3A4/5 inhibitor)	CT	Isavuconazole: AUC_{tau}: ↑ 422% C_{max}: ↑ 9% (CYP3A4/5 inhibition)	This medicinal product can significantly increase plasma concentrations of isavuconazole. The concomitant administration of CRESEMBA and ketoconazole is contraindicated.
Herbal medicines			
St John's wort (Hypericum perforatum) (strong CYP3A4/5 inducer)	T	Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction).	The concomitant administration of CRESEMBA and St John's wort is contraindicated.
Immunosuppressants			
Cyclosporine, sirolimus, tacrolimus (CYP3A4/5 substrates)	CT	Cyclosporine: $AUC_{0-\infty}$: ↑ 29% C_{max}: ↑ 6% Sirolimus: AUC_{inf}: ↑ 84% C_{max}: ↑ 65% Tacrolimus: $AUC_{0-\infty}$: ↑ 125% C_{max}: ↑ 42% (CYP3A4 inhibition)	Systemic exposure to these medicinal products metabolised by CYP3A4 may be increased when co-administered with CRESEMBA. No CRESEMBA dose adjustment necessary. Cyclosporine, sirolimus, tacrolimus: monitoring of plasma levels and appropriate dose adjustment if required.
Mycophenolate mofetil (MMF) (UGT substrate)	CT	Mycophenolic acid (MPA, active metabolite): $AUC_{0-\infty}$: ↑ 35% C_{max}: ↓ 11% (UGT inhibition)	No CRESEMBA dose adjustment necessary. MMF: monitoring for MPA-related toxicities is advised.

Isavuconazole Co-administered medicines by therapeutic area	Source of Evidence	Effects on drug concentrations / Geometric Mean Change (%) in AUC, C_{max} (Mode of action)	Recommendation concerning co-administration
Prednisone (CYP3A4 substrate)	CT	Prednisolone (active metabolite): $AUC_{0-\infty}$: ↑ 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)	T	Short-acting opiate concentrations may increase. (CYP3A4/5 inhibition).	No CRESEMBA 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)	CT	S-methadone (inactive opiate isomer) $AUC_{0-\infty}$: ↓ 35% C_{max}: ↑ 1% 40% reduction in terminal half-life R-methadone (active opiate isomer). $AUC_{0-\infty}$: ↓ 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)	T	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)	T	Isavuconazole is an inducer of CYP2B6. Cyclophosphamide has a narrow therapeutic index. 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 (BCRP, OAT1, OAT3 substrate)	CT	Methotrexate: $AUC_{0-\infty}$: ↓ 3% C_{max}: ↓ 11% 7-hydroxymetabolite: $AUC_{0-\infty}$: ↑ 29% C_{max}: ↑ 15% (Mechanism unknown)	No CRESEMBA dose adjustment necessary. Methotrexate: no dose adjustment required.

Isavuconazole Co-administered medicines by therapeutic area	Source of Evidence	Effects on drug concentrations / Geometric Mean Change (%) in AUC, C_{max} (Mode of action)	Recommendation concerning co-administration
Other anticancer agents (daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan) (BCRP substrates)	T	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)	T	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)	CT	Metformin: $AUC_{0-\infty}$: ↑ 52% C_{max}: ↑ 23% (OCT2 inhibition)	No CRESEMBA dose adjustment necessary. Metformin: dose reduction may be required.
Repaglinide (CYP2C8 and OATP1B1 substrate)	CT	Repaglinide: $AUC_{0-\infty}$: ↓ 8% C_{max}: ↓ 14%	No CRESEMBA dose adjustment necessary. Repaglinide: no dose adjustment required.
Anticoagulants			
Dabigatran etexilate (P-gp substrate)	T	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)	CT	S-warfarin $AUC_{0-\infty}$: ↑ 11% C_{max}: ↓ 12% R-warfarin $AUC_{0-\infty}$: ↑ 20% C_{max}: ↓ 7%	No CRESEMBA dose adjustment necessary. Warfarin: no dose adjustment required.
Antiretroviral agents			
Lopinavir / Ritonavir (CYP3A4/5 strong inhibitors and substrates)	CT	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)	For this strong CYP3A4 inhibitor, a two-fold increase in isavuconazole exposure was observed. 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.

Isavuconazole **Co-administered medicines by therapeutic area**	**Source of Evidence**	**Effects on drug concentrations / Geometric Mean Change (%) in AUC, C_{max} (Mode of action)**	**Recommendation concerning co-administration**
Ritonavir (at doses >400 mg every 12 hours) (strong CYP3A4/5 inducer)	T	Ritonavir at high doses may significantly decrease isavuconazole concentrations. (CYP3A4/5 induction)	The concomitant administration of CRESEMBA and high doses of ritonavir (>400 mg every 12 hours) is contraindicated.
Efavirenz (CYP3A4/5 moderate inducer and CYP2B6 substrate)	T	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)	T	Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of CRESEMBA and etravirine is contraindicated.
Indinavir (CYP3A4/5 strong inhibitor and substrate)	CT	Indinavir:[b] $AUC_{0-\infty}$: ↓ 36% C_{max}: ↓ 52% (Mechanism unknown) Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	Based on relative potency, no CRESEMBA 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)	T	Saquinavir concentrations may decrease (as observed with lopinavir/ritonavir) or increase (CYP3A4 inhibition). Isavuconazole concentrations may increase. (CYP3A4/5 inhibition).	Based on relative potency, 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., fosamprenavir, nelfinavir) (CYP3A4/5 strong or moderate inhibitors and substrates)	T	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.

Isavuconazole Co-administered medicines by therapeutic area	Source of Evidence	Effects on drug concentrations / Geometric Mean Change (%) in AUC, C_{max} (Mode of action)	Recommendation concerning co-administration
Other Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) (e.g., delavirdine, and nevirapine) (CYP3A4/5 and 2B6 inducers and substrates)	T	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.
Antacids			
Esomeprazole (CYP2C19 substrate and gastric pH ↑)	CT	Isavuconazole: AUC_{tau}: ↑ 8% C_{max}: ↑ 5%	No CRESEMBA dose adjustment necessary. Esomeprazole: no dose adjustment required.
Omeprazole (CYP2C19 substrate and gastric pH ↑)	CT	Omeprazole: $AUC_{0-\infty}$: ↓ 11% C_{max}: ↓ 23%	No CRESEMBA dose adjustment necessary. Omeprazole: no dose adjustment required.
Lipid-lowering agents			
Atorvastatin and other statins (CYP3A4 substrates e.g., simvastatin, lovastatin, pravastatin, cilastatin, rosuvastatin) (CYP3A4/5 and/or BCRP substrates)	CT	Atorvastatin: $AUC_{0-\infty}$: ↑ 37% C_{max}: ↑ 3% Other statins were not studied. Statins concentrations may increase. (CYP3A4/5 or BCRP inhibition)	No CRESEMBA dose adjustment necessary. Based on results with atorvastatin, no statin dose adjustment required. Monitoring of adverse reactions typical of statins is advised.
Pioglitazone (mild CYP3A4/5 inducer)	T	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)	CT	Digoxin: $AUC_{0-\infty}$: ↑ 25% C_{max}: ↑ 33% (P-gp inhibition)	No CRESEMBA dose adjustment necessary. Isavuconazole may increase the exposure of digoxin which has a narrow therapeutic index. Digoxin: serum digoxin concentrations should be monitored and used for titration of the digoxin dose.
Oral contraceptives			
Ethinyl estradiol and norethindrone (CYP3A4/5 substrates)	CT	Ethinyl estradiol $AUC_{0-\infty}$: ↑ 8% C_{max}: ↑ 14% Norethindrone $AUC_{0-\infty}$: ↑ 16% C_{max}: ↑ 6%	No CRESEMBA dose adjustment necessary. Ethinyl estradiol and norethindrone: no dose adjustment required.

Isavuconazole Co-administered medicines by therapeutic area	Source of Evidence	Effects on drug concentrations / Geometric Mean Change (%) in AUC, C_{max} (Mode of action)	Recommendation concerning co-administration
Antitussives			
Dextromethorphan (CYP2D6 substrate)	CT	Dextromethorphan: $AUC_{0-\infty}$: ↑ 18% C_{max}: ↑ 17% Dextrorphan (active metabolite): $AUC_{0-\infty}$: ↑ 4% C_{max}: ↓ 2%	No CRESEMBA dose adjustment necessary. Dextromethorphan: no dose adjustment required.
Benzodiazepines			
Midazolam (CYP3A4/5 substrate)	CT	Oral midazolam: $AUC_{0-\infty}$: ↑ 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)	T	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.
Natural products			
Caffeine (CYP1A2 substrate)	CT	Caffeine: $AUC_{0-\infty}$: ↑ 4% C_{max}: ↓ 1%	No CRESEMBA dose adjustment necessary. Caffeine: no dose adjustment required.
Smoking cessation aids			
Bupropion (CYP2B6 substrate)	CT	Buproprion: $AUC_{0-\infty}$: ↓ 42% C_{max}: ↓ 31% (CYP2B6 induction)	No CRESEMBA dose adjustment necessary. Bupropion: dose increase if required.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical, has not been studied; NNRTI = non-nucleoside reverse-transcriptase inhibitor; P-gp = P-glycoprotein.

[a] % decrease of the mean trough level values

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

$AUC_{0-\infty}$ = 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.

9.4 Drug-Food Interactions

CRESEMBA can be administered with or without food.

9.5 Drug-Herb Interactions

Concomitant administration of CRESEMBA with St. John's wort is contraindicated as isavuconazole concentrations may significantly decrease. Interactions with other herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established. See ADVERSE REACTIONS.

9.7 Drug-Lifestyle Interactions

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.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Isavuconazonium sulfate is the prodrug of isavuconazole, an azole antifungal.

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.

10.2 Pharmacodynamics

In patients treated with CRESEMBA for invasive aspergillosis in a controlled trial, there was no significant association between plasma AUC or plasma isavuconazole concentration and efficacy.

Cardiac Electrophysiology

The effect on QTc interval of multiple doses of CRESEMBA capsules was evaluated. CRESEMBA capsules was administered as 2 capsules (equivalent to 200 mg of isavuconazole) three times daily on days 1 and 2 followed by either 2 capsules or 6 capsules (equivalent to 600 mg of isavuconazole) once daily for 13 days in a randomized, placebo- and active-controlled (moxifloxacin 400 mg single dose), four-treatment-arm, parallel study in 160 healthy subjects.

Isavuconazole resulted in dose-related shortening of the QTc interval. For the 200 mg dosing regimen, the least squares mean (LSM) difference from placebo was -13.1 msec at 2 hours postdose (90% CI: -17.1, -9.1 msec). Increasing the dose to 600 mg resulted in an LSM difference from placebo of -24.6 msec at 2 hours postdose (90% CI: -28.7, -20.4). CRESEMBA capsules was not evaluated in combination with other drugs that reduce the QTc interval, so the additive effects are not known.

10.3 Pharmacokinetics

CRESEMBA contains isavuconazonium sulfate, a water-soluble prodrug of isavuconazole. CRESEMBA can be administered both parenterally as intravenous infusion and orally as capsules. Following administration, isavuconazonium sulfate is rapidly hydrolyzed by plasma esterases to the active moiety isavuconazole.

Table 7: Steady State Pharmacokinetic Parameters of Isavuconazole Following Oral Administration of CRESEMBA (isavuconazole capsules)

Parameter	CRESEMBA (isavuconazole capsules) 200 mg (n = 37)	CRESEMBA (isavuconazole capsules) 600 mg (n = 32)
Cmax (ng/mL)		
Mean	7499	20028
SD	1893.3	3584.3
CV %	25.2	17.9
tmax (h)		
Median	3.000	4.000
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 8, the absolute bioavailability of isavuconazole following oral administration of a single dose of CRESEMBA capsules was 98%. Based on these findings, intravenous and oral dosing can be used interchangeably.

Table 8: Pharmacokinetic Comparison for Oral and IV Dose (Mean)

	CRESEMBA (isavuconazole capsules 400 mg Oral	CRESEMBA (isavuconazole for injection 400 mg IV
AUC (h•ng/ml)	189462.8	193906.8
CV (%)	36.5	37.2
Half-life (h)	110	115

Absorption: Following oral administration of CRESEMBA capsules 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 7.

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

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

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.

Special Populations and Conditions

Geriatrics: The AUC of isavuconazole following a single oral dose of CRESEMBA capsules equivalent to 200 mg isavuconazole in elderly subjects (65 years and older) was similar to that in younger volunteers (18 to 45 years). The AUC was similar between younger female and male subjects and between elderly and younger males.

AUC estimates in elderly females were 38% and 47% greater than AUC estimates obtained in elderly males and younger females, respectively. The pharmacokinetic differences in elderly females receiving CRESEMBA are not considered to be clinically significant. Therefore, no dose adjustment is required based on age and gender.

Sex: AUC estimates were similar between young female and male subjects (18 to 45 years). There was a difference in AUC for elderly females. See Geriatrics above. No dose adjustment is required based on gender.

Ethnic origin: A 2-compartment population pharmacokinetic model was developed to assess the pharmacokinetics of isavuconazole between healthy Western and Chinese subjects. Chinese subjects were found to have on average a 40% lower clearance compared to Western subjects (1.6 L/hr for Chinese subjects as compared to 2.6 L/hr for Western subjects) and therefore approximately 50% higher AUC than Western subjects. Body mass index (BMI) did not play a role in the observed differences. No dose adjustment is recommended for Chinese patients.

Hepatic Insufficiency: 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 did 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 DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS.

Renal Insufficiency: 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 dialyzable. See DOSAGE AND ADMINISTRATION.

11 STORAGE, STABILITY AND DISPOSAL

Keep out of reach and sight of children.

CRESEMBA (isavuconazole capsules)

Store at room temperature (15 - 30 °C). Store in the original packaging in order to protect from moisture.

CRESEMBA (isavuconazole for injection)

Powder vial

Store powder vial in refrigerator (2 to 8 °C).

Reconstituted vial

The reconstituted solution may be stored below 25°C for maximum 1 hour prior to preparation of the patient infusion solution.

Diluted solution for infusion

If possible, the intravenous administration of CRESEMBA (isavuconazole for injection) should be completed within 6 hours after reconstitution and dilution at room temperature (15 - 30 °C). If this is not possible, the infusion solution should be refrigerated immediately after dilution, and infusion should be completed within 24 hours. Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 2 - 8 °C, or 6 hours at room temperature (15 - 30 °C).

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: isavuconazonium sulfate

Chemical name:

USAN:

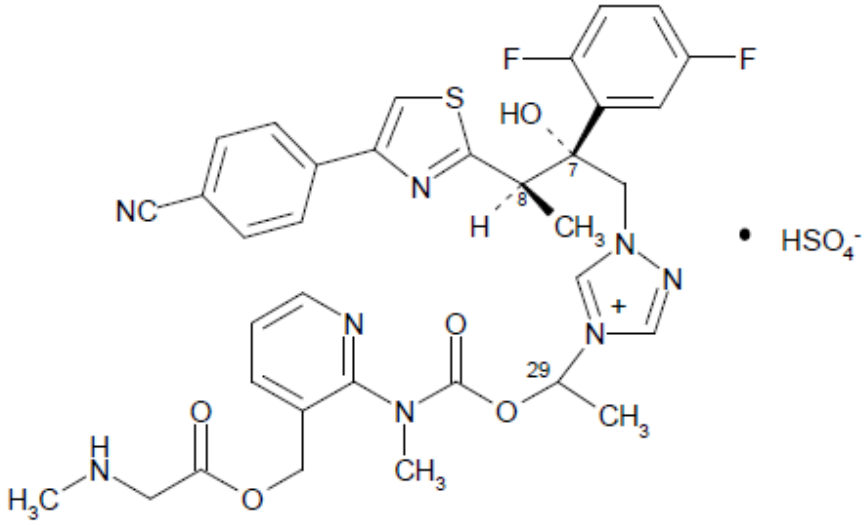
1-{(2R,3R)-3-[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl}- 4-[(1RS)-1-({methyl[3-({[(methylamino)acetyl]oxy}methyl)pyridin-2-yl]carbamoyl}oxy)ethyl]-1H-1,2,4-triazol-4-ium monosulfate

IUPAC:

1-{(2R,3R)-3-[4-(4-Cyanophenyl)-1,3-thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl}- 4-[(1RS)-1-({methyl[3-({[(methylamino)acetyl]oxy}methyl)pyridin-2-yl]carbamoyl}oxy)ethyl]-1H-1,2,4-triazol-4-ium monosulfate

Molecular formula and molecular mass: $C_{35}H_35F_2N_8O_5S•HSO_4$ and molecular weight of 814.84

Structural formula:



Physicochemical properties: Isavuconazonium sulfate is a white amorphous powder with a pKa of 7.3 that is very soluble in water, methanol, dimethyl sulfoxide, and pH 1,3,5,7; and sparingly soluble in absolute ethanol.

Isavuconazonium has three chiral centres and is a mixture of two epimers. After administration both epimers are rapidly converted to the active moiety, isavuconazole.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

The trial design and study demographics of Invasive Aspergillosis study (9766-CL-0104) and Invasive Mucormycosis study (9766-CL-0103) are presented in Table 9.

Table 9: Summary of Patient Demographics for Clinical Trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N)	Mean age (Range)	Sex
Invasive Aspergillosis					
9766-CL-0104	Randomized, Multi-centre, double-blind, noninferiority, comparative, active-controlled	• CRESEMBA (isavuconazole for injection) IV, 200mg[a] • CRESEMBA (isavuconazole capsules) Oral, 200mg[a] Comparator: • Voriconazole IV, 200mg[b] • Voriconazole Oral, 200mg[b] Maximum treatment period: 84 days	516 (ITT) 231 (myITT)[d] 95% with fungal disease involving lungs Caucasians (78%)	51.1 (17 – 87)	M: 59.7% F: 40.3%
Invasive Mucormycosis					
9766-CL-0103	Open-Label, multi-centre, uncontrolled	• CRESEMBA (isavuconazole for injection) IV, 200mg[c] • CRESEMBA(isavuconazole capsules) Oral, 200mg[c] Maximum treatment period: 84 days or 180 days	37 (mITT-Mucorales) Caucasians (68%)	48.5 (22 - 79)	M: 81.1% F: 18.9%

EoT = End of Treatment; F = Female; ITT = Intent-to-Treat; IV = Intravenous; M = Male; QD = once daily; TID = 3 times daily; q12h = every 12 hours

[a] Loading dose (day 1,2): 200 mg TID IV; Maintenance dose (day 3 to EoT): 200mg QD IV or oral

[b] Loading dose (day 1): 6 mg/kg q12h IV; Maintenance dose (day 2 to EoT): 4 mg/kg q12h IV or 200 mg q12h oral

[c] Loading dose (day 1,2): 200 mg TID IV or oral; Maintenance dose (day 3 to EoT): 200mg QD IV or oral

[d] myITT: patients with proven or probable invasive aspergillosis confirmed by serology, culture or histology.

Patients in the clinical trials were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, graft-versus-host disease, and hematopoietic stem cell transplant.

Invasive Aspergillosis (Study 9766-CL-0104)

Study 9766-CL-0104 evaluated the safety and efficacy of CRESEMBA versus voriconazole for primary treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi. Eligible patients had proven, probable, or possible invasive fungal infections per European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria. At least one *Aspergillus* species was identified in 30% of the patients; *A. fumigatus* and *A. flavus* were the most common pathogens identified. There were few patients with other *Aspergillus* species: *A.niger*, *A. sydowi*, *A. terreus*, and *A. westerdijkiae*. Baseline risk factors for ITT and myITT (patients with proven or probable invasive aspergillosis confirmed by serology, culture or histology) populations are presented in Table 10.

Table 10: Baseline Risk Factors in ITT and myITT Populations

	CRESEMBA		**voriconazole**	
	N=258 (ITT) n (%)	N=123 (myITT) n (%)	N=258 (ITT) n (%)	N=108 (myITT) n (%)
Hematologic Malignancy	211 (82)	100 (81)	222 (86)	90 (83)
Allogenic Hematopoietic Stem Cell Transplant	54 (21)	32 (26)	51 (20)	22 (20)
Neutropenia[a]	163 (63)	78 (63)	175 (68)	64 (59)
Corticosteroid Use	48 (19)	25 (20)	39 (15)	27 (25)
T-Cell Immunosuppressant Use	111 (43)	52 (42)	109 (42)	52 (48)

ITT = Intent-to-Treat; myITT = mycological Intent-to-Treat
[a]Neutropenia is defined as less than 500 cells/mm^3

Invasive Mucormycosis (Study 9766-CL-0103)

Study 9766-CL-0103 evaluated the safety and efficacy of a subset of ITT patients (n=146) with invasive mucormycosis. Thirty-seven (37) patients had proven or probable mucormycosis (mITT-Mucormorales) (EORTC/MSG based criteria). *Rhizopus oryzae* and Mucormycetes were the most common pathogens identified. There were few patients with other Mucorales: *Lichtheimia corymbifera, Mucor amphibiorum, Mucor circinelloides, Rhizomucor pusillus, Rhizopus azygosporus,* and *Rhizopus microspores.*

Patients were administered either CRESEMBA IV infusion or oral capsules at the same dose regimen as that used to treat invasive aspergillosis. Median treatment duration was 84 days (2 to 882 days) for the overall mucormycosis patient population (the median duration for IV dosing was 10 days, and 80 days for oral dosing); 102 days for the 21 patients not previously treated for mucormycosis, 33 days for the 11 patients refractory to, and 85 days for the 5 patients intolerant of other antifungal therapy. There were 7 patients with mucormycosis dosed for longer than 6 months.

Fifty-nine percent (59%) of patients had pulmonary disease involvement, half of whom also had other organ involvement. The most common non-pulmonary disease locations were sinus (43%), eye (19%), CNS (16%) and bone (14%). An independent Data Review Committee classified patients receiving CRESEMBA as primary therapy, or for invasive mold disease refractory to, or patients intolerant of other antifungal therapy (e.g., 11/37 patients with prior Amphotericin B based therapy). Baseline risk factors are presented in Table 11.

Table 11: Baseline Risk Factors in Mucormycosis

	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)
Allogenic 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 = patients 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.

13.2 Study Results

Invasive Aspergillosis (Study 9766-CL-0104)

Efficacy endpoints included the assessment of all-cause mortality through day 42 in the overall population (ITT) and the myITT, as well as the overall response at end-of-treatment (EoT) in the myITT population. These results are shown in Table 12.

Table 12: Results of study 9766-CL-0104 in Aspergillosis

Endpoints (population)	CRESEMBA 200 mg	Voriconazole 200 mg	Adjusted Treatment Difference (%) (95% CI) [a]
Primary Endpoint			
All-cause mortality, Day 42 (ITT)	18.6% (n=258)	20.2% (n=258)	-1.0 (-8.0, 5.9)
Key Secondary Endpoints			
All-cause mortality, Day 42 (Proven or Probable Invasive Aspergillosis)	18.7% (n=123)	22.2% (n=108)	-2.7 (-13.6, 8.2)
Overall Response = Success at EoT (Proven or Probable Invasive Aspergillosis)	35.0% (n=123)	38.9% (n=108)	-4.0 (-16.3, 8.4)

CI = Confidence Interval; EoT = End of Treatment, ITT = Intent-to-Treat;
[a] Cochran-Mantel-Haenszel method stratified by the randomization factors.

This study demonstrated that CRESEMBA is effective for the treatment of invasive aspergillosis. CRESEMBA is noninferior relative to voriconazole since the upper bound of the 95% CI around the adjusted treatment difference is lower than the prespecified non-inferiority margin of 10%. The Data Review Committee assessed overall response at EoT showed similar success rates in the CRESEMBA and voriconazole treatment groups.

Invasive Mucormycosis (Study 9766-CL-0103)

Efficacy endpoints, including the all-cause mortality through day 42, 84 and success in overall response at EoT as assessed by the Data Review Committee, are shown in Table 13.

Table 13: Results of study 9766-CL-0103 in Mucormycosis

Endpoints	CRESEMBA 200 mg
Primary Endpoint	
All-cause Mortality Through Day 42	
- All patients	38% (n = 37)
- Primary therapy setting	33% (n = 21)
- Refractory or intolerant therapy setting	44% (n = 16)
Key Secondary Endpoint	
All-cause Mortality Through Day 84 (secondary endpoint)	
- All patients	43% (n = 37)
- Primary therapy setting	43% (n = 21)
- Refractory or intolerant therapy setting	44% (n = 16)
Overall Response Rate at EoT (i.e. Success)	
- All patients	31% (n = 35 [a])
- Primary therapy setting	32% (n = 19 [a])
- Refractory or intolerant therapy setting	31% (n = 16)

EoT = End of Treatment

[a] Two primary mucormycosis patients were not assessed at EoT due to ongoing treatment.

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.

14 MICROBIOLOGY

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.

Activity *in vitro* and in clinical infections

Isavuconazole has activity against most strains of the following microorganisms, both *in vitro* and in clinical infections: *Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger,* and pathogenic members of the order Mucorales such as *Rhizopus* spp., *Lichtheimia* spp., *Mucor* spp., and Mucormycetes species. See CLINICAL TRIALS.

In animal models of disseminated and pulmonary aspergillosis and mucormycosis, 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 different species of *Aspergillus* and genera/species of the order Mucorales could be established.

Activity *in vitro*

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.

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 characterized. However, patients failing prior azole therapy may require alternative antifungal therapy.

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.

15 NON-CLINICAL TOXICOLOGY

General Toxicity

Repeat-dose toxicity after oral administration was studied in mice, rats and Cynomolgus monkeys for up to 13, 26 and 39 weeks, respectively.

Isavuconazole resulted in toxicological changes in the liver, thyroid and adrenals. An increase in liver weights associated with centrilobular hepatocyte hypertrophy was observed which was attributable to induction of CYP enzymes and was reversible after cessation of treatment. In addition, reversible effects considered secondary to isavuconazole metabolism, were observed in the thyroid (increased weights associated with cellular hypertrophy and considered to be rat specific) and adrenals (increased adrenal weight associated with cortical vacuolation, and thickening of zona fasciculate, considered due to CYP2B induction).

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 levels that were 0.8 fold those of the human exposure at the maintenance dose of 200 mg per day).

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

Two-year carcinogenicity studies of isavuconazonium sulfate have been initiated, though data are not yet available.

Hepatocellular adenomas and carcinomas have been reported in mice and rats in carcinogenicity studies for other drugs in the azole class at near human recommended doses.

Reproductive and Developmental Toxicology

Isavuconazonium chloride administration was associated with dose-related increases in the incidences of rudimentary cervical ribs in rats and rabbits at 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 levels equivalent to one fifth the clinical dose based on AUC comparisons. Skeletal abnormalities have also been observed in embryo-fetal development studies of other azole antifungal agents.

Perinatal mortality was significantly increased in the offspring of pregnant rats dosed orally with isavuconazonium sulfate at less than half the maintenance human dose based on AUC comparisons during pregnancy through the weaning period. *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 less than half the maintenance human dose (200 mg) based on AUC comparisons.