HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CRESEMBA safely and effectively. See full prescribing information for CRESEMBA.

CRESEMBA® (isavuconazonium sulfate)
Capsules for oral administration
For Injection for intravenous administration
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
CRESEMBA is an azole antifungal indicated for use in the treatment of:
- Invasive aspergillosis (1.1).
- Invasive mucormycosis (1.2).

----------DOSAGE AND ADMINISTRATION----------
- CRESEMBA for injection must be administered through an in-line filter over a minimum of 1 hour (2.1).
- Loading Dose: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every 8 hours for 6 doses (48 hours) via oral (2 capsules) or intravenous administration (1 reconstituted vial) (2.2).
- Maintenance Dose: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily via oral (2 capsules) or intravenous administration (1 reconstituted vial) starting 12 to 24 hours after the last loading dose (2.2).
- Capsules can be taken with or without food (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
- CRESEMBA capsules contain 186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole) (3).
- CRESEMBA for injection is supplied in a single-dose vial as a sterile lyophilized powder containing 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) (3).

----------CONTRAINDICATIONS----------
- Hypersensitivity to CRESEMBA (4).
- Coadministration with strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir (4, 7).
- Coadministration with strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates (4, 7).
- Use in patients with familial short QT syndrome (4).

----------WARNINGS AND PRECAUTIONS----------
- Hepatic Adverse Drug Reactions: Serious hepatic reactions have been reported. Evaluate liver-related laboratory tests at the start and during the course of CRESEMBA therapy (5.1).
- Infusion-related reactions were reported during intravenous administration of CRESEMBA. Discontinue the infusion if these reactions occur (5.2).
- 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. Discontinue CRESEMBA for exfoliative cutaneous reactions (5.3).
- Embryo-Fetal Toxicity: Do not administer to pregnant women unless the benefit to the mother outweighs the risk to the fetus. Inform pregnant patients of the hazard (5.4).
- Drug Interactions: Review patient's concomitant medications. Several drugs may significantly alter isavuconazole concentrations. Isavuconazole may alter concentrations of several drugs (5.5, 7, 12.3).
- Drug Particulates: Intravenous formulation may form insoluble particulates following reconstitution. Administer CRESEMBA through an in-line filter (2.4, 5.6).

----------ADVERSE REACTIONS----------
Most frequent adverse reactions: nausea, vomiting, diarrhea, headache, elevated liver chemistry tests, hypokalemia, constipation, dyspnea, cough, peripheral edema, and back pain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- CYP3A4 inhibitors or inducers may alter the plasma concentrations of isavuconazole (7).
- Appropriate therapeutic drug monitoring and dose adjustment of immunosuppressants (i.e., tacrolimus, sirolimus, and cyclosporine) may be necessary when co-administered with CRESEMBA (7).
- Drugs with a narrow therapeutic window that are P-gp substrates, such as digoxin, may require dose adjustment when administered concomitantly with CRESEMBA (7).

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: CRESEMBA should only be used if the benefits to the mother outweigh the risk to the fetus. Inform pregnant woman of risk (8.1).
- Mothers should not breast feed children while taking CRESEMBA (8.3).
- Use in patients with severe hepatic impairment only when the benefits outweigh the risks; clinical monitoring for CRESEMBA-related adverse reactions is recommended (8.7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Invasive Aspergillosis

CRESEMBA is an azole antifungal indicated for patients 18 years of age and older for the treatment of invasive aspergillosis.

[see Clinical Studies (14.1) and Clinical Pharmacology (12.4)].

1.2 Invasive Mucormycosis

CRESEMBA is an azole antifungal indicated for patients 18 years of age and older for the treatment of invasive mucormycosis.

[see Clinical Studies (14.2) and Clinical Pharmacology (12.4)].

1.3 Usage

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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Instructions for Intravenous Administration

- Intravenous formulation must be administered via an infusion set with an in-line filter (pore size 0.2 to 1.2 micron).
- Infuse the intravenous formulation over a minimum of 1 hour in 250 mL of a compatible diluent, to reduce the risk for infusion-related reactions. Do not administer as an intravenous bolus injection.
- Do not infuse CRESEMBA with other intravenous medications.
- Flush intravenous lines with 0.9% sodium chloride injection, USP or 5% dextrose injection, USP prior to and after infusion of CRESEMBA.
- After dilution of the intravenous formulation, avoid unnecessary vibration or vigorous shaking of the solution. Do not use a pneumatic transport system.

2.2 Dosage Regimen

CRESEMBA (isavuconazonium sulfate) is the prodrug of isavuconazole, an azole antifungal drug. Prescribe CRESEMBA as shown in Table 1 below.

Table 1. Dosage Regimen for CRESEMBA

	Loading Dose	**Maintenance Dose[c]**
CRESEMBA for Injection 372 mg[a] of isavuconazonium sulfate per vial	1 reconstituted vial (372 mg[a]) intravenously every 8 hours for 6 doses (48 hours)	1 reconstituted vial (372 mg[a]) intravenously once daily
CRESEMBA Capsules 186 mg[b] of isavuconazonium sulfate per capsule	2 capsules (372 mg[a]) orally every 8 hours for 6 doses (48 hours)	2 capsules (372 mg[a]) orally once daily

[a] 372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole
[b] 186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole
[c] Start maintenance doses 12 to 24 hours after the last loading dose

Switching between the intravenous and oral formulations of CRESEMBA is acceptable as bioequivalence has been demonstrated. Loading dose is not required when switching between formulations.

With oral administration, swallow capsules whole. Do not chew, crush, dissolve, or open the capsules. CRESEMBA capsules can be taken with or without food.

2.3 Reconstitution Instructions for the Injection Formulation

Aseptic technique must be strictly observed in all handling since no preservative or bacteriostatic agent is present in CRESEMBA or in the materials specified for reconstitution. CRESEMBA is water soluble, preservative-free, sterile, and nonpyrogenic.

- Reconstitute one vial of CRESEMBA by adding 5 mL water for injection, USP to the vial.
- Gently shake to dissolve the powder completely.
- Visually inspect the reconstituted solution for particulate matter and discoloration. Reconstituted CRESEMBA should be clear and free of visible particulate.
- The reconstituted solution may be stored below 25°C for maximum 1 hour prior to preparation of the patient infusion solution.

2.4 Dilution and Preparation Instructions for the Injection Formulation

- Remove 5 mL of the reconstituted solution from the vial and add it to an infusion bag containing 250 mL (approximately 1.5 mg isavuconazonium sulfate per mL) of compatible diluent. The diluted solution may show visible translucent to white particulates of isavuconazole (which will be removed by in-line filtration).
- Use gentle mixing or roll bag to minimize the formation of particulates. Avoid unnecessary vibration or vigorous shaking of the solution.
- Apply in-line filter with a microporous membrane pore size of 0.2 to 1.2 micron and in-line filter reminder sticker to the infusion bag.
- Do not use a pneumatic transport system.
- The intravenous administration should be completed within 6 hours of dilution at room temperature. If this is not possible, immediately refrigerate (2° to 8°C / 36° to 46°F) the infusion solution after dilution and complete the infusion within 24 hours. Do not freeze the infusion solution.

2.5 Compatibility for the Injection Formulation

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

- 0.9% sodium chloride injection, USP
- 5% dextrose injection, USP

3 DOSAGE FORMS AND STRENGTHS

Each CRESEMBA capsule contains 186 mg isavuconazonium sulfate (equivalent to 100 mg of isavuconazole). Capsules are opaque and elongated, and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with “ISA” in black ink.

Each single-dose vial of CRESEMBA for injection contains 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole). CRESEMBA for injection is supplied in a single-dose vial as a sterile lyophilized white to yellow powder.

4 CONTRAINDICATIONS

- CRESEMBA is contraindicated in persons with known hypersensitivity to isavuconazole.
- Coadministration of strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir (400 mg every 12 hours), with CRESEMBA is contraindicated because strong CYP3A4 inhibitors can significantly increase the plasma concentration of isavuconazole *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.
- Coadministration of strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John’s wort, or long acting barbiturates with CRESEMBA is contraindicated because strong CYP3A4 inducers can significantly decrease the plasma concentration of isavuconazole *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.
- CRESEMBA shortened the QTc interval in a concentration-related manner. CRESEMBA is contraindicated in patients with familial short QT syndrome *[see Clinical Pharmacology (12.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Adverse Drug Reactions

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 abnormal 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 (6.1)]*.

5.2 Infusion-Related Reactions

Infusion-related reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during intravenous administration of CRESEMBA. Discontinue the infusion if these reactions occur *[see Adverse Reactions (6.1)]*.

5.3 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. Discontinue CRESEMBA if a patient develops a severe cutaneous adverse reaction. There is no information regarding cross-sensitivity between CRESEMBA and other azole antifungal agents. Caution should be used when prescribing CRESEMBA to patients with hypersensitivity to other azoles.

5.4 Embryo-Fetal Toxicity

CRESEMBA may cause fetal harm when administered to a pregnant woman. CRESEMBA should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the fetus. Women who become pregnant while receiving CRESEMBA are encouraged to contact their physician *[see Use in Specific Populations (8.1)]*.

Perinatal mortality was significantly increased in the offspring of pregnant rats dosed orally with isavuconazonium sulfate at 90 mg/kg/day (less than half the maintenance human dose based on AUC comparisons) during pregnancy through the weaning period.

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 *[see Nonclinical Toxicology (13.1)]*.

5.5 Drug Interactions

Coadministration of CRESEMBA with strong CYP3A4 inhibitors such as ketoconazole or high-dose ritonavir and strong CYP3A4 inducers such as rifampin, carbamazepine, St. John’s wort, or long acting barbiturates is contraindicated *[see Contraindications (4) and Drug Interactions (7)]*.

5.6 Drug Particulates

Following dilution, CRESEMBA intravenous formulation may form precipitate from the insoluble isavuconazole. Administer CRESEMBA through an in-line filter *[see Dosage and Administration (2.4)]*.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Hepatic Adverse Drug Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.4)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of CRESEMBA cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trial Experience

A total of 403 patients were exposed to CRESEMBA in two clinical trials. 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, neutropenia post-chemotherapy, 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 Trial 1, a randomized, double-blind, active-controlled clinical trial for treatment of invasive aspergillosis, 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. Table 2 includes selected treatment-emergent adverse reactions which were reported at an incidence of ≥ 5% during CRESEMBA therapy in Trial 1.

In Trial 2, an open-label, non-comparative trial of CRESEMBA in patients with invasive aspergillosis and renal impairment or invasive mucormycosis, treatment-emergent adverse reactions occurred in 139/146 (95%) of patients in the CRESEMBA treatment group. Adverse reactions resulting in permanent discontinuation were reported in 19 (13%) CRESEMBA-treated patients. The frequencies and types of adverse reactions observed in CRESEMBA-treated patients were similar between Trial 1 and Trial 2.

Table 2. Selected Treatment-Emergent Adverse Reactions with Rates of 5% or Greater in CRESEMBA-treated Patients in Trial 1

System Organ Class Preferred Term	Trial 1	
	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		
Edema 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		
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.

The following adverse reactions occurred in less than 5% of all CRESEMBA-treated patients in Trial 1 or 2. The list does not include reactions presented in Table 2. 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 disorders: abdominal distension, gastritis, gingivitis, stomatitis

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

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: myositis, bone pain, neck pain

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

Psychiatric disorders: confusion, hallucination, depression

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

Laboratory effects
In Trial 1, elevated liver transaminases (alanine aminotransferase or aspartate aminotransferase) greater than three times the upper limit of normal were reported at the end of study treatment in 4.4% of patients who received CRESEMBA. Elevations of liver transaminases greater than ten times the upper limit of normal developed in 1.2% of patients who received CRESEMBA.

7 DRUG INTERACTIONS

Isavuconazole is a sensitive substrate of CYP3A4. CYP3A4 inhibitors or inducers may alter the plasma concentrations of isavuconazole.

Isavuconazole is a moderate inhibitor of CYP3A4, and a mild inhibitor of P-glycoprotein (P-gp), and organic cation transporter 2 (OCT2).

Drug interaction studies were conducted to investigate the effect of co-administered drugs on pharmacokinetics of isavuconazole and the effect of isavuconazole on the pharmacokinetics of co-administered drugs *[see Clinical Pharmacology (12.3)]*.

Table 3. Drug(s) Affecting Pharmacokinetics of CRESEMBA

	Recommendation	Comments
Ketoconazole	Contraindicate coadministration of all potent CYP3A4 inhibitors	There is more than a 5-fold increase in exposure of isavuconazole upon coadministration with ketoconazole *[see Clinical Pharmacology (12.3)]*.
Lopinavir/ritonavir[a]	Caution is advised when CRESEMBA is coadministered with lopinavir/ritonavir	There is a 96% increase in exposure of isavuconazole when coadministered with lopinavir/ritonavir *[see Clinical Pharmacology (12.3)]*.
Rifampin	Contraindicate coadministration of all potent CYP3A4 inducers	There is a 97% decrease in exposure of isavuconazole upon coadministration with rifampin *[see Clinical Pharmacology (12.3)]*.

[a] 400 mg of lopinavir in combination with 100 mg of ritonavir.

Table 4. The Effect of CRESEMBA on the Pharmacokinetics of Other Drugs

	Recommendation	Comments
Lopinavir/ritonavir[a]	Use with Caution	Concomitant administration of lopinavir/ritonavir and CRESEMBA resulted in decreased exposure of lopinavir and ritonavir that could possibly result in loss of antiviral efficacy *[see Clinical Pharmacology (12.3)]*.
Atorvastatin	Use with Caution	Caution should be used when atorvastatin is used with CRESEMBA due to a potential increase in atorvastatin exposure. Monitor patients for adverse reactions that are typical of atorvastatin.
Cyclosporine	Use with Caution	Concomitant administration of CRESEMBA and cyclosporine results in increase in cyclosporine exposure. Monitor drug concentrations of cyclosporine and adjust dose as needed *[see Clinical Pharmacology (12.3)]*.
Sirolimus	Use with Caution	Concomitant administration of CRESEMBA and sirolimus results in increase in sirolimus exposure. Monitor drug concentrations of sirolimus and adjust dose as needed *[see Clinical Pharmacology (12.3)]*.
Tacrolimus	Use with Caution	Concomitant administration of CRESEMBA and tacrolimus results in increase in tacrolimus exposure. Monitor drug concentrations of tacrolimus and adjust dose as needed *[see Clinical Pharmacology (12.3)]*.
Midazolam	Use with Caution	Concomitant administration of CRESEMBA and midazolam results in increase in midazolam exposure. Consider dose reduction of midazolam when isavuconazole is coadministered *[see Clinical Pharmacology (12.3)]*.
Bupropion	Use with Caution	Concomitant administration of CRESEMBA and bupropion results in decrease in bupropion exposure. Dose increase of bupropion may be necessary when coadministered with CRESEMBA, but should not exceed the maximum recommended dose *[see Clinical Pharmacology (12.3)]*.
Mycophenolate Mofetil	Use with Caution	Concomitant administration of CRESEMBA and MMF results in increase in MMF exposure. Patients receiving CRESEMBA concurrently with MMF should be monitored for MPA-related toxicities *[see Clinical Pharmacology (12.3)]*.
Digoxin	Use with Caution	Concomitant administration of CRESEMBA and digoxin results in increase in digoxin exposure. Serum digoxin concentrations should be monitored and used for titration of when dosed concurrently with CRESEMBA *[see Clinical Pharmacology (12.3)]*.

[a] 400 mg of lopinavir in combination with 100 mg of ritonavir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C
There are no adequate and well-controlled clinical studies of CRESEMBA in pregnant women. CRESEMBA should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the fetus. Women who become pregnant during CRESEMBA treatment are encouraged to contact their physician.

Risk Summary

Based on animal data, CRESEMBA is predicted to have the potential for increasing the risk of adverse developmental outcomes above background risk.

Animal Data
Perinatal mortality was significantly increased in the offspring of pregnant rats dosed orally with isavuconazonium sulfate at 90 mg/kg/day (less than half the maintenance human dose based on AUC comparisons) during pregnancy through the weaning period.

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 *[see Nonclinical Toxicology (13.1)]*. Skeletal abnormalities have also been observed in embryo-fetal development studies of other azole antifungal agents.

8.3 Nursing Mothers

Isavuconazole is excreted in the milk of lactating rats following intravenous administration. Mothers should not breast feed while taking CRESEMBA.

8.4 Pediatric Use

The safety and efficacy of CRESEMBA in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use

Of the 547 patients who received CRESEMBA in the Phase 2 and 3 trials, 86 (16%) of patients were greater than 65 years of age and 20 (4%) were greater than 75 years of age. The pharmacokinetics of isavuconazole are comparable in young and elderly subjects (65 years of age and older) *[see Clinical Pharmacology (12.3)]*. No dose adjustment of CRESEMBA is needed in elderly patients.

8.6 Renal Impairment

Of the 403 patients who received CRESEMBA in the Phase 3 trials, 79 (20%) of patients had an estimated glomerular filtration rate (GFR) less than 60 ml/min/1.73m^2. No dose adjustment is needed in patients with mild, moderate, or severe renal impairment, including those patients with End Stage Renal Disease (ESRD) *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A and B) *[see Clinical Pharmacology (12.3)]*. CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and should be used in these patients only when the benefits outweigh the risks. Clinical monitoring for CRESEMBA-related adverse reactions is recommended when treating patients with severe hepatic impairment *[see Warnings and Precautions (5.1)]*.

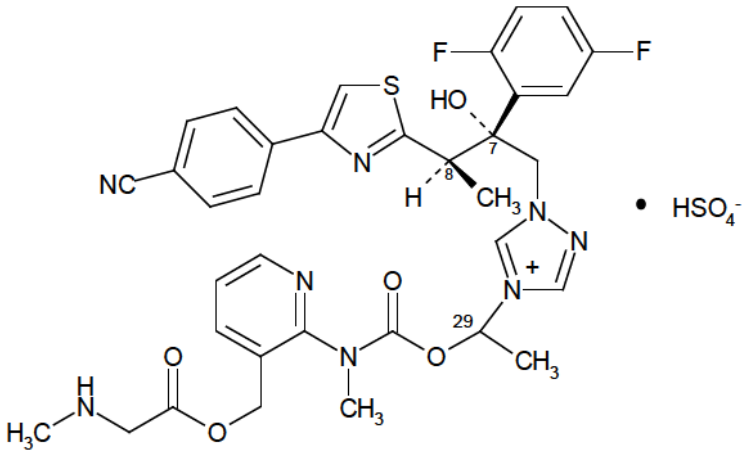
10 OVERDOSAGE

During clinical studies, total daily CRESEMBA doses higher than the recommended dose regimen were associated with an increased rate of adverse reactions. At supratherapeutic doses (three times the recommended maintenance dose) evaluated in a thorough QT study, there were proportionally more treatment-emergent adverse reactions than in the therapeutic dose group (maintenance dose) for the following: headache, dizziness, paresthesia, somnolence, disturbance in attention, dysgeusia, dry mouth, diarrhea, oral hypoesthesia, vomiting, hot flush, anxiety, restlessness, palpitations, tachycardia, photophobia and arthralgia. Treatment-emergent adverse reactions leading to discontinuation of study drug occurred in 7 of 39 (17.9%) subjects in the supratherapeutic dose group.

Isavuconazole is not removed by hemodialysis. There is no specific antidote for isavuconazole. Treatment should be supportive with appropriate monitoring.

11 DESCRIPTION

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 glycine, *N*-methyl-, [2-[[[1-[1-[(2*R*,3*R*)-3-[4-(4-cyanophenyl)-2-thiazolyl]-2-(2,5-difluorophenyl)-2- hydroxybutyl]-4*H*-1,2,4-triazolium-4-yl]ethoxy]carbonyl]methylamino]-3-pyridinyl]methyl ester, sulfate (1:1). The empirical formula is $C_{35}H_{35}F_2N_8O_5S \cdot HSO_4$, the molecular weight is 814.84 and the structural formula is:



CRESEMBA (isavuconazonium sulfate) capsules are available for oral administration. Each CRESEMBA capsule contains 186 mg isavuconazonium sulfate, equivalent to 100 mg isavuconazole. The inactive ingredients include magnesium citrate, microcrystalline cellulose, talc, colloidal silicon dioxide, stearic acid, hypromellose, red iron oxide, titanium dioxide, purified water, gellan gum, potassium acetate, disodium edetate, sodium laurylsulfate, shellac, propylene glycol, strong ammonia solution, potassium hydroxide and black iron oxide.

CRESEMBA (isavuconazonium sulfate) for injection is available for intravenous administration. CRESEMBA for injection is a white to yellow sterile lyophilized powder containing 372 mg isavuconazonium sulfate, equivalent to 200 mg isavuconazole, per vial. Inactive ingredients included in each vial are 96 mg mannitol and sulfuric acid for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Isavuconazonium sulfate is the prodrug of isavuconazole, an azole antifungal *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

Pharmacokinetic/Pharmacodynamic Relationship
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 was administered as 2 capsules (equivalent to 200 mg isavuconazole) three times daily on days 1 and 2 followed by either 2 capsules or 6 capsules (equivalent to 600 mg 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 2-capsule 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 6 capsules resulted in an LSM difference from placebo of -24.6 msec at 2 hours postdose [90% CI: -28.7, -20.4]. CRESEMBA was not evaluated in combination with other drugs that reduce the QTc interval, so the additive effects are not known.

12.3 Pharmacokinetics

General Pharmacokinetics
In healthy subjects, the pharmacokinetics of isavuconazole following oral administration of CRESEMBA capsules at isavuconazole equivalent doses up to 600 mg per day (6 capsules) are dose proportional (Table 5). Based on a population pharmacokinetics analysis of healthy subjects and patients, the mean plasma half-life of isavuconazole was 130 hours and the mean volume of distribution (V_{ss}) was approximately 450 L following intravenous administration.

Table 5. Steady State Pharmacokinetic Parameters of Isavuconazole Following Administration of CRESEMBA Capsules

Parameter	**CRESEMBA 2 Capsules[a] (n = 37)**	**CRESEMBA 6 Capsules[a] (n = 32)**
C_{max} (ng/mL)		
Mean	7499	20028
SD	1893.3	3584.3
CV %	25.2	17.9
t_{max} (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

[a] Each capsule contains the equivalent of 100 mg of isavuconazole.

Absorption
After oral administration of CRESEMBA in healthy volunteers, the active moiety, isavuconazole, generally reaches maximum plasma concentrations (C_{max}) 2 hours to 3 hours after single and multiple dosing. The absolute bioavailability of isavuconazole following oral administration of CRESEMBA is 98%. No significant concentrations of the prodrug or inactive cleavage product were seen in plasma after oral administration.

Following intravenous administration of CRESEMBA, maximal plasma concentrations of the prodrug and inactive cleavage product were detectable during infusion and declined rapidly following the end of administration. The prodrug was below the level of detection by 1.25 hours after the start of a 1 hour infusion. The total exposure of the prodrug based on AUC was less than 1% that of isavuconazole. The inactive cleavage product was quantifiable in some subjects up to 8 hours after the start of infusion. The total exposure of inactive cleavage product based on AUC was approximately 1.3% that of isavuconazole.

Effect of Food
Coadministration of CRESEMBA equivalent to isavuconazole 400 mg oral dose 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 protein bound (greater than 99%), predominantly to albumin.

Metabolism
In *in vitro* studies isavuconazonium sulfate is rapidly hydrolyzed in blood to isavuconazole by esterases, predominately by butylcholinesterase. Isavuconazole is a substrate of cytochrome P450 enzymes 3A4 and 3A5.

Following single doses of [cyano ^{14}C] isavuconazonium and [pyridinylmethyl ^{14}C] isavuconazonium 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 greater than 10% of drug related material.

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

Excretion
Following oral administration of radio-labeled isavuconazonium sulfate to healthy volunteers, a mean of 46.1% of the total radioactive dose was recovered in the feces and 45.5% was recovered in the urine.

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

The inactive cleavage product is primarily eliminated by metabolism and subsequent renal excretion of the metabolites. Renal elimination of intact cleavage product was less than 1% of the total dose administered. Following intravenous administration of radio-labeled cleavage product, 95% of the total radioactive dose was excreted in the urine.

Special populations

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

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

Pediatric Patients
The pharmacokinetics of CRESEMBA in pediatric patients have not been evaluated.

Race
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.

Gender
AUC estimates were similar between young female and male subjects (18 years to 45 years). There was a difference in AUC for elderly females, see *Geriatric* section above. No dose adjustment is required based on gender.

Renal Impairment
Total isavuconazole AUC and C_{max} were not affected to a clinically meaningful extent in subjects with mild, moderate and severe renal impairment relative to healthy controls. No dose adjustment is necessary in patients with renal impairment.

Isavuconazole is not readily dialyzable. A dose adjustment is not warranted in patients with ESRD.

Hepatic Impairment

After a single dose of CRESEMBA equivalent to 100 mg of isavuconazole was administered to 32 patients with mild (Child-Pugh Class A) hepatic impairment and 32 patients with moderate (Child-Pugh Class B) hepatic impairment (16 intravenous and 16 oral patients per Child-Pugh Class), the least squares mean systemic exposure (AUC) increased 64% and 84% in the Child-Pugh Class A group and the Child-Pugh Class B group, respectively, relative to 32 age and weight-matched healthy subjects with normal hepatic function. Mean C_{max} was 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 and moderate hepatic impairment demonstrated that the mild and moderate hepatic impairment population had 40% and 48% lower isavuconazole clearance (CL) values, respectively, compared to the healthy population. It is recommended that the standard CRESEMBA loading dose and maintenance dose regimen be utilized in patients with mild to moderate hepatic disease. CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Drug Interaction Studies

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 coadministration 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.

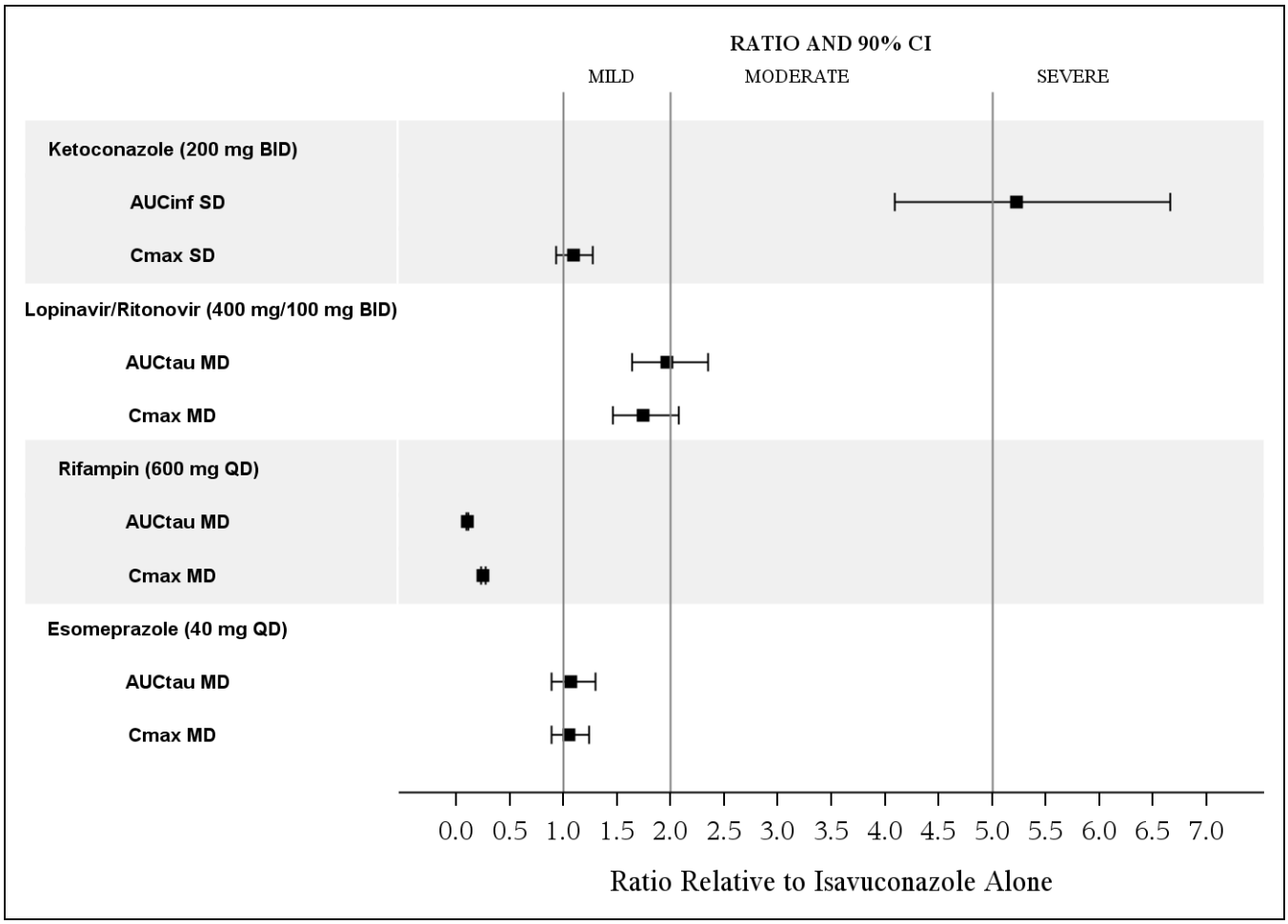
The effects of ketoconazole, rifampin, lopinavir/ritonavir, and esomeprazole on isavuconazole are shown in Figure 1.

Ketoconazole: As a strong CYP3A4 inhibitor, ketoconazole increased the isavuconazole C_{max} by 9% and isavuconazole AUC by 422% after multiple dose administration of ketoconazole (200 mg twice daily) for 24 days and a single dose of CRESEMBA equivalent to 200 mg of isavuconazole. Isavuconazole is a sensitive CYP3A4 substrate and use with strong CYP3A4 inhibitors are contraindicated per Section 4 and Figure 1.

Lopinavir/Ritonavir: Lopinavir/ritonavir (400 mg/100 mg twice daily) increased the C_{max} and AUC of isavuconazole (clinical dose) 74% and 96%, respectively, with concurrent decreases in the mean AUCs of lopinavir and ritonavir by 27% and 31%, respectively.

Rifampin: Rifampin (600 mg) decreased the mean C_{max} and AUC of isavuconazole by 75% and 97%, respectively, when coadministered with multiple doses of CRESEMBA and thus, coadministration of CRESEMBA with strong CYP3A4 inducers is contraindicated.

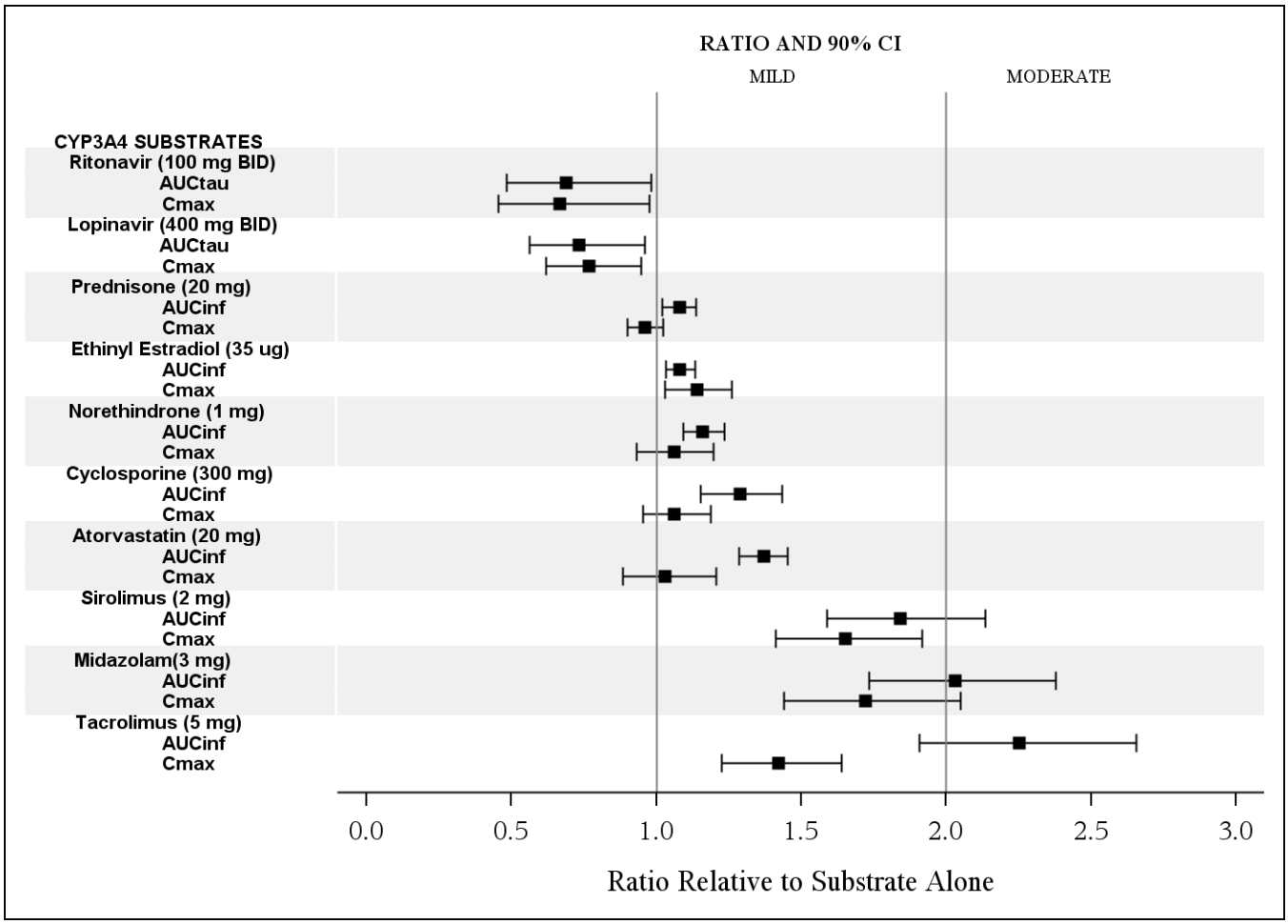
Figure 1. The Effect of Co-administered Drugs on Isavuconazole Exposure



The effects of isavuconazole on ritonavir, lopinavir, prednisone, combined oral contraceptives (ethinyl estradiol and norethindrone), cyclosporine, atorvastatin, sirolimus, midazolam, and tacrolimus are shown in Figure 2.

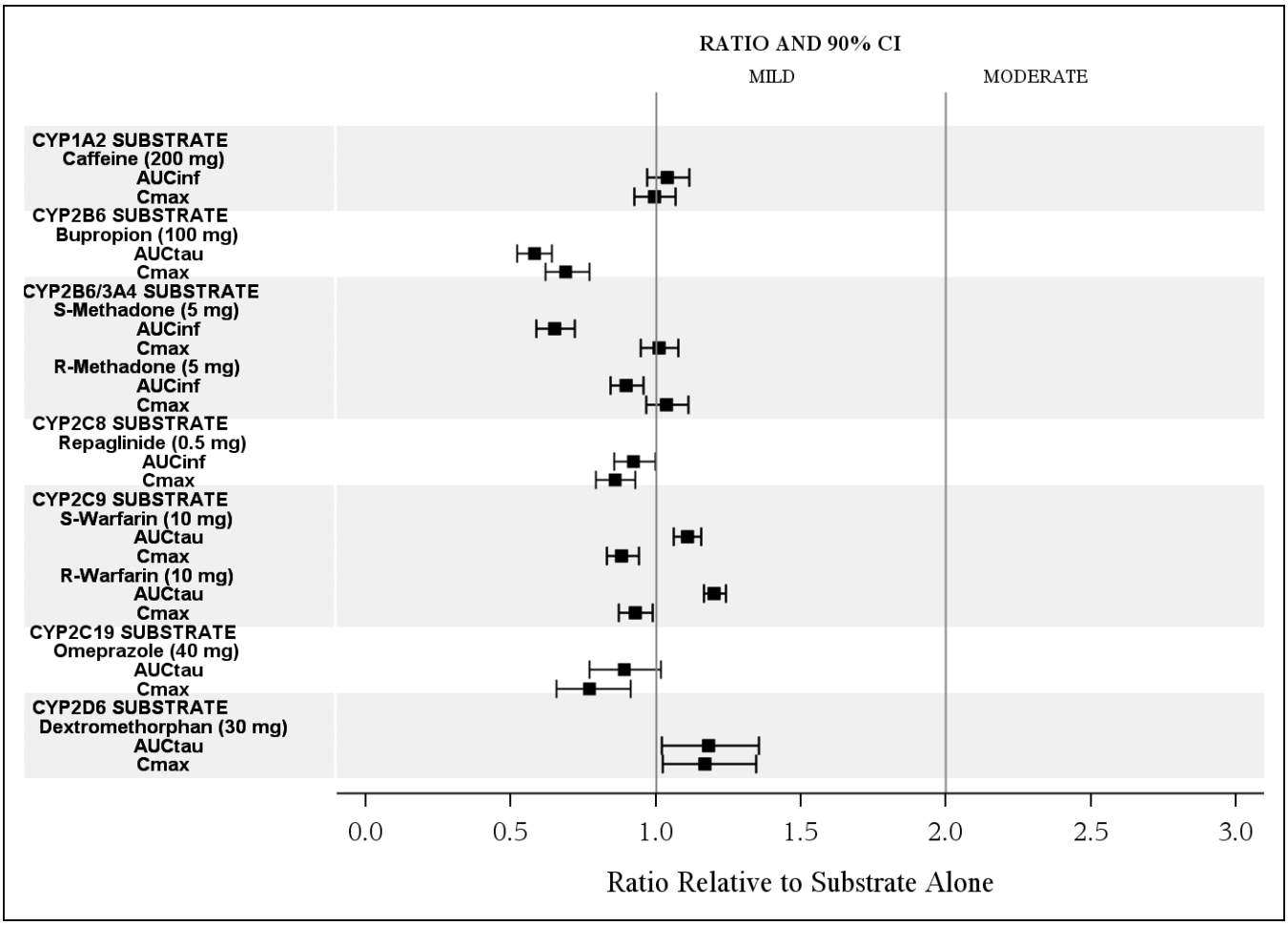
CYP3A4 Substrates: CRESEMBA increased the systemic exposure of sensitive CYP3A4 substrates midazolam, sirolimus and tacrolimus approximately 2-fold, and therefore CRESEMBA is a moderate inhibitor of CYP3A4.

Figure 2. The Effect of Isavuconazole on Co-administered CYP3A4 Substrate Medications



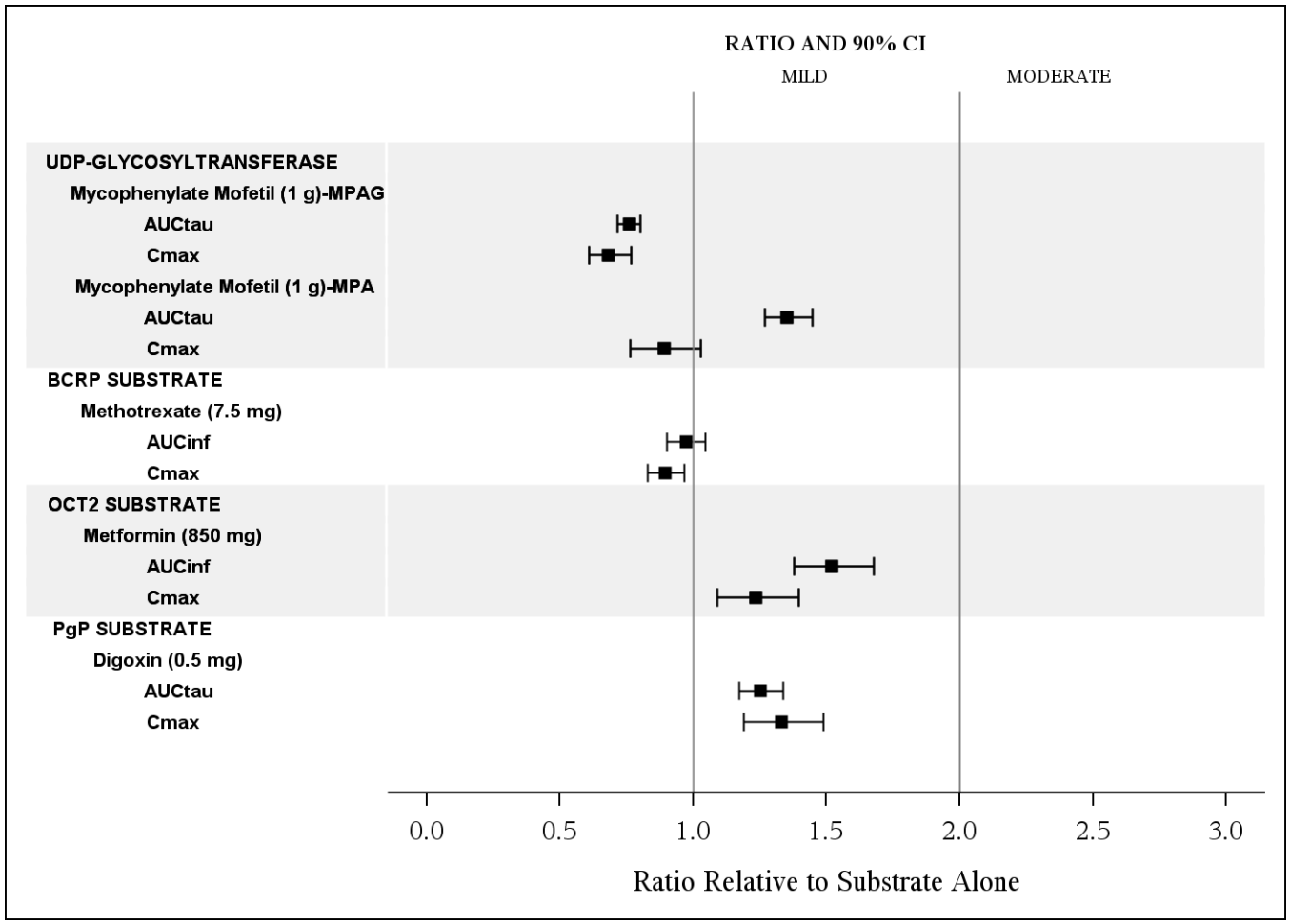
The effects of isavuconazole on other CYP substrates: caffeine, bupropion, methadone, repaglinide, warfarin, omeprazole, and dextromethorphan, are shown in Figure 3.

Figure 3. The Effect of Isavuconazole on Exposure of Co-administered CYP Substrate Medications



The effects of isavuconazole on the substrates of UGT and transporters: mycophenolate mofetil (MMF), methotrexate, metformin, and digoxin are shown in Figure 4.

Figure 4. The Effect of Isavuconazole on Exposure on the Substrates of UGT and Transporters



12.4 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. 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.

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 Mucorales such as *Rhizopus oryzae* and Mucormycetes species *[see Clinical Studies (14)]*.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies of isavuconazonium sulfate have not been performed. 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.

No mutagenic or clastogenic effects were detected in the *in vitro* bacterial reverse mutation assay and the *in vivo* bone marrow micronucleus assay in rats.

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).

14 CLINICAL STUDIES

14.1 Treatment of Invasive Aspergillosis

Trial 1 was a randomized, double-blind, non-inferiority active controlled trial which 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[1]. Patients were stratified by history of allogeneic bone marrow transplant, uncontrolled malignancy at baseline, and by geographic region. The mean age of patients was 51 years (range 17-87) and the majority were Caucasians (78%), male (60%), with fungal disease involving the lungs (95%). At least one *Aspergillus* species was identified in 30% of the subjects; *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 are presented in Table 6.

Table 6. Baseline Risk Factors in Intent To Treat (ITT[a]) Population

	CRESEMBA N=258 n (%)	**Voriconazole N=258 n (%)**
Hematologic Malignancy	211 (82)	222 (86)
Allogenic Hematopoietic Stem Cell Transplant	54 (21)	51 (20)
Neutropenia[b]	163 (63)	175 (68)
Corticosteroid Use	48 (19)	39 (15)
T-Cell Immunosuppressant Use	111 (43)	109 (42)

[a] ITT includes all randomized patients who received at least one dose of study drug.
[b] Neutropenia defined as less than 500 cells/mm^3.

Patients randomized to receive CRESEMBA treatment were administered a loading dose intravenously of 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconzole) every 8 hours for the first 48 hours. Beginning on day 3, patients received intravenous or oral therapy of 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily. Patients randomized to receive voriconazole treatment were administered voriconazole intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by 4 mg/kg intravenously every 12 hours for the following 24 hours. Therapy could then be switched to an oral formulation of voriconazole at a dose of 200 mg every 12 hours. In this trial, the protocol-defined maximum treatment duration was 84 days. Mean treatment duration was 47 days for both treatment groups, of which 8 to 9 days was by an intravenous route of administration.

All-cause mortality through Day 42 in the overall population (ITT) was 18.6% in the CRESEMBA treatment group and 20.2% in the voriconazole treatment group for an adjusted treatment difference of -1.0% with 95% confidence interval of -8.0% to 5.9%. Similar results were seen in patients with proven or probable invasive aspergillosis confirmed by serology, culture or histology (see Table 7).

Table 7. 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 randomization 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 8).

Table 8. 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 randomization factors.

14.2 Treatment of Invasive Mucormycosis

Trial 2, an open-label non-comparative trial, evaluated the safety and efficacy of a subset of patients with invasive mucormycosis. Thirty-seven (37) patients had proven or probable mucormycosis according to criteria based on those established by the European Organisation for Research and Treatment of Cancer/Mycoses Study Group[1]. *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.* The patients were white (68%), male (81%), and had a mean age of 49 years (range 22-79). 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%). Baseline risk factors are presented in Table 9. The 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.

Table 9. 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)
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.

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 Dosage and Administration (2.2)]*.

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 10. 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 10. All-Cause-Mortality 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.

15 REFERENCES

1. DePauw, B., Walsh, T.J., Donnelly, J.P., *et al.* (2008) Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer Invasive Fungal Infections Quadrature Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus group. *Clinical Infectious Diseases* **46**:1813-1821.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Capsules
CRESEMBA (isavuconazonium sulfate) capsules are available in aluminum blister packs. Each capsule contains 186 mg isavuconazonium sulfate (equivalent to 100 mg of isavuconazole). Capsules are opaque and elongated, and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with “ISA” in black ink.

Store in original container to protect from moisture.

Capsules are packaged in aluminum blister packs, seven (7) capsules per sheet with desiccant. (NDC 0469-0320-14)

Injection
CRESEMBA (isavuconazonium sulfate) for injection is supplied in a single-dose vial as white to yellow sterile lyophilized powder containing 372 mg isavuconazonium sulfate (equivalent to 200 mg isavuconazole).

Individually packaged vials are available for intravenous administration. (NDC 0469-0420-99)

16.2 Storage and Handling

Store CRESEMBA capsules at 20°C to 25°C (68°F to 77°F) in the original packaging to protect from moisture. Excursions are permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Store CRESEMBA for injection unreconstituted vials at 2° to 8°C (36° to 46°F) in a refrigerator. CRESEMBA is a single-dose vial of unpreserved sterile lyophile. Following reconstitution of the lyophile with water for injection USP, the reconstituted solution should be used immediately, or stored below 25°C for a maximum of 1 hour prior to preparation of the patient infusion solution. The prepared infusion solution should be kept for not more than 6 hours at room temperature [20°C to 25°C (68°F to 77°F)] or 24 hours at 2° to 8°C (36° to 46°F) prior to use. CRESEMBA for injection vials are for single-dose use only.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

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

Advise patients to inform their physician if they are taking other drugs or before they begin taking other drugs as certain drugs can decrease or increase the plasma concentrations of CRESEMBA.

CRESEMBA can decrease or increase the plasma concentrations of other drugs.

Advise patients to inform their physician if they are pregnant, plan to become pregnant, or are nursing.

Product of Portugal

Marketed and Distributed by:
Astellas Pharma US, Inc.
Northbrook, IL 60062

Licensed from: Basilea Pharmaceutica International Ltd.

Approved: March 2015

14D023-ISA

PATIENT INFORMATION

CRESEMBA® (Crē sem' bah)
(isavuconazonium sulfate)
Capsules, for oral administration

CRESEMBA® (Crē sem' bah)
(isavuconazonium sulfate)
For injection, for intravenous administration

Read this Patient Information before you start taking CRESEMBA and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is CRESEMBA?

CRESEMBA is a prescription medicine used to treat people 18 years of age and older with certain types of fungal infections in the blood or body called "aspergillosis," and "mucormycosis" (zygomycosis). CRESEMBA may be given as capsules or through an IV placed in your arm (intravenously).

It is not known if CRESEMBA is safe and effective in children under 18 years of age.

Who should not take CRESEMBA?

Do not take CRESEMBA if you:

- are allergic to CRESEMBA or any of the ingredients. See the end of this leaflet for a complete list of ingredients in CRESEMBA.
- have a genetic problem that affects the electrical system of the heart (familial short QT syndrome).
- are taking any of the following medicines:
  - ketoconazole
  - high-dose ritonavir
  - rifampin
  - carbamazepine
  - St. John's wort (herbal supplement)
  - long-acting barbiturates

Talk to your healthcare provider or pharmacist if you are not sure if you are taking any of these medicines or have any of the conditions listed above.

Do not start taking a new medicine without talking to your healthcare provider or pharmacist.

What should I tell my healthcare provider before taking CRESEMBA?
Before you take CRESEMBA, tell your healthcare provider if you:

- have or ever had an abnormal heart rate or rhythm. Your healthcare provider may order a test to check your heart (ECG) before starting CRESEMBA.
- have liver problems. Your healthcare provider may do blood tests to make sure you can take CRESEMBA.
- have ever had an allergic reaction to other antifungal medications such as ketoconazole, fluconazole, itraconazole, voriconazole or posaconazole.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if CRESEMBA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. CRESEMBA can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take CRESEMBA. You should not breastfeed while taking CRESEMBA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

CRESEMBA may affect the way other medicines work, and other medicines may affect how CRESEMBA works causing side effects.

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

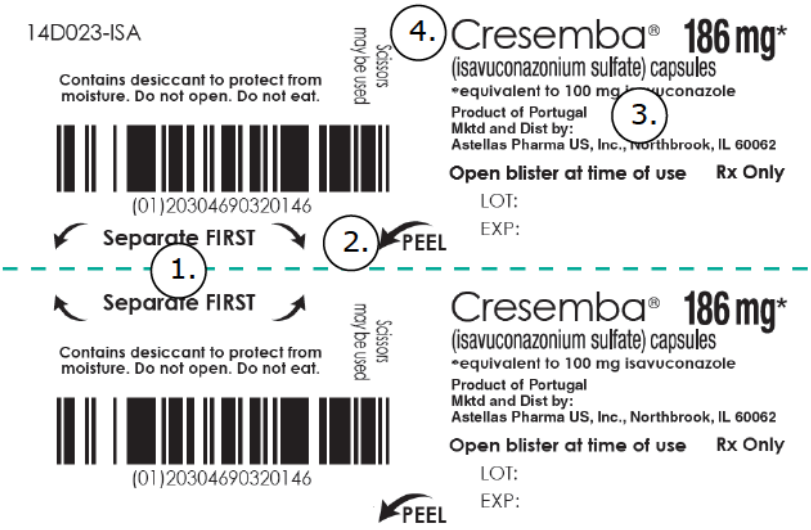
Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take CRESEMBA capsules?

- Take CRESEMBA exactly as your healthcare provider tells you to take it.
- **Do not** stop taking CRESEMBA until your healthcare provider tells you to.
- If you take too much CRESEMBA, call your healthcare provider.
- CRESEMBA capsules can be taken with or without food.
- Swallow CRESEMBA capsules whole. **Do not** chew, crush, dissolve, or open the capsules.

Instructions on opening CRESEMBA capsules blister packaging:

- CRESEMBA capsules are in child resistant blister packaging. Each blister section contains two pockets – One for the CRESEMBA capsule, and one for the desiccant to protect the capsule from moisture (located to the left of the capsule).
- Only open the blister packaging at time of use. Ensure only CRESEMBA capsule pocket is opened.
- Please refer to the picture below.



- To open the blister packaging, open from the printed side as shown above.

  1. Bend & tear along the horizontal perforated dotted line.
  2. Peel the paper away from the foil backing.
  3. Then push the capsule through the exposed foil until released.
  4. If difficult to peel, scissors may be used to open package.

What are the possible side effects of CRESEMBA?

CRESEMBA may cause serious side effects, including:

- **liver problems.** Liver problems can happen in some people taking CRESEMBA. Some people who also have other serious medical problems may get severe liver problems which can lead to hepatitis, gallbladder problems, liver failure or death. Your healthcare provider should do blood tests to check your liver before you start and while you are taking CRESEMBA. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - itchy skin
  - nausea or vomiting
  - yellowing of your eyes
  - feeling very tired
  - flu-like symptoms

- **drug interactions with cyclosporine, sirolimus, or tacrolimus.** If you take CRESEMBA with cyclosporine, sirolimus, or tacrolimus, your blood levels of cyclosporine, sirolimus, or tacrolimus may increase. Serious side effects can happen in your kidney or brain if you have high levels of cyclosporine, sirolimus, or tacrolimus in your blood. Your healthcare provider should do blood tests to check your levels of cyclosporine, sirolimus, or tacrolimus if you are taking these medicines while taking CRESEMBA. Tell your healthcare provider right away if you have swelling in your arm or leg or shortness of breath.

- **infusion reactions.** Infusion reactions can happen in people receiving CRESEMBA intravenously. If an infusion reaction happens, your infusion will be stopped. Symptoms of an infusion reaction may include:
  - low blood pressure
  - difficulty breathing
  - chills
  - dizziness
  - numbness and tingling
  - changes in your sense of touch (hypoesthesia)

- **severe allergic and skin reactions.**

- **medicine interactions. Taking CRESEMBA with some other medicines may affect the way other medicines work causing serious side effects. Other medicines may affect the way CRESEMBA works, causing serious side effects.** Tell your healthcare provider about all the medicines you take.

The most common side effects of CRESEMBA include:

- nausea
- vomiting
- diarrhea
- headache
- changes in the level of a liver enzyme in your blood
- low potassium
- back pain
- shortness of breath
- cough
- swelling of arms or legs
- constipation

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of CRESEMBA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CRESEMBA capsules?

- Store CRESEMBA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep CRESEMBA in the original package and protect it from moisture.
- **Do not** remove CRESEMBA from original packaging until your scheduled dose.
- **Do not** put CRESEMBA in pill boxes or pill organizers.
- Safely throw away medicine that is out of date or no longer needed.

Keep CRESEMBA and all medicines out of the reach of children.

General information about the safe and effective use of CRESEMBA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use CRESEMBA for a condition for which it was not prescribed. Do not give CRESEMBA to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about CRESEMBA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CRESEMBA that is written for healthcare professionals.

For more information go to www.CRESEMBA.com or call 1-800-727-7003.

What are the ingredients of CRESEMBA capsules?
Active ingredient: isavuconazonium sulfate
Inactive ingredients: magnesium citrate, microcrystalline cellulose, talc, colloidal silicon dioxide, stearic acid, hypromellose, red iron oxide, titanium dioxide, purified water, gellan gum, potassium acetate, disodium edetate, sodium laurylsulfate, shellac, propylene glycol, strong ammonia solution, potassium hydroxide, black iron oxide

This Patient Information has been approved by the U.S. Food and Drug Administration.

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/s/

JOHN J FARLEY
03/06/2015