CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

207500Orig1s013

Trade Name:	CRESEMBA
Generic or Proper Name:	Isavuconazonium Sulfate; 186 MG, 74.5 MG, Capsule
Sponsor:	Advanced Accelerator Applications USA, Inc.
Approval Date:	November 22, 2022
Indication:	For the use in the treatment of invasive aspergillosis and invasive mucormycosis.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 207500/S-013
NDA 207501/S-011

SUPPLEMENT APPROVAL

Astellas Pharma US Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your supplemental new drug applications (sNDAs) dated and received July 28, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cresemba (isavuconazonum sulfate) capsules, 186 mg (NDA 207500\S-013) and Cresemba (isavuconazonium sulfate) for injection, 372 mg (NDA 207501\S-011).

These Prior Approval sNDAs provide for information in support of a new capsule strength (74.5 mg of isavuconazonium sulfate). Accordingly, the following sections and subsections of the Prescribing Information (PI) have been updated:

- **HIGHLIGHTS OF PRESCRIBING INFORMATION: RECENT MAJOR CHANGES, DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS**
- **FULL PRESCRIBING INFORMATION: DOSAGE AND ADMINISTRATION (2)** section, **Dosage Regimen (2.2)** subsection, **DOSAGE FORMS AND STRENGTHS (3)** section**, DESCRIPTION (11**) section**, CLINICAL PHARMACOLOGY (12)** section**, Pharmacokinetics (12.3)** subsection, ***General Pharmacokinetics*** (subheading), and the **HOW SUPPLIED/STORAGE AND HANDLING (16)** section.

Additionally, minor editorial revisions have been made throughout the PI and the Patient Package Insert (PPI) and the carton and container labeling was updated to reflect the changes made to the PI.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and the Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for these NDAs, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in these supplemental applications, as well as annual reportable changes. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labeling for approved NDAs 207500/S-013, 207501/S-011**." Approval of this submission by FDA is not required before the labeling is used.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53 (f)(2)(iv).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at 301-796-0797.

Sincerely,

{See appended electronic signature page}

Dmitri Iarikov, MD, PhD
Deputy Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207500Orig1s013

LABELING

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 use
CRESEMBA® (isavuconazonium sulfate) for injection, for intravenous use
Initial U.S. Approval: 2015

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration, Dosing Regimen (2.2)	11/2022
Warnings and Precautions, Hypersensitivity Reactions (5.3)	12/2021

---------- 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, 2.4)
- CRESEMBA capsules can be taken with or without food. (2.2)
- Dosage Regimen for CRESEMBA (2.2)

	Loading Dose	Maintenance Dose[1]
CRESEMBA for Injection, 372 mg/vial 372 mg of isavuconazonium sulfate per vial	One reconstituted vial (372 mg) intravenously every 8 hours for 6 doses (48 hours)	One reconstituted vial (372 mg) intravenously once daily
CRESEMBA Capsules, 186 mg 186 mg of isavuconazonium sulfate per capsule	Two 186 mg capsules (372 mg) orally every 8 hours for 6 doses (48 hours)	Two 186 mg capsules (372 mg) orally once daily
CRESEMBA Capsules, 74.5 mg 74.5 mg of isavuconazonium sulfate per capsule	Five 74.5 mg capsules (372 mg) orally every 8 hours for 6 doses (48 hours)	Five 74.5 mg capsules (372 mg) orally once daily

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

---------- DOSAGE FORMS AND STRENGTHS ----------

- CRESEMBA capsules: 74.5 mg of isavuconazonium sulfate (equivalent to 40 mg of isavuconazole), 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: Anaphylactic reactions, with fatal outcome, have been reported during treatment with CRESEMBA. Serious skin reactions, such as Stevens-Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA if anaphylactic or serious skin reactions occur, and initiate supportive treatment as needed. (5.3)
- Embryo-Fetal Toxicity: CRESEMBA may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective method of contraception. (5.4, 8.1, 8.3)
- 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 coadministered 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 ----------

- Breastfeeding should be discontinued during treatment with CRESEMBA. (8.2)
- 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: 11/2022

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[1]
CRESEMBA for Injection, 372 mg/vial	One reconstituted vial (372 mg[2]) intravenously	One reconstituted vial (372 mg[2]) intravenously

	Loading Dose	Maintenance Dose[1]
372 mg[2] of isavuconazonium sulfate per vial	every 8 hours for 6 doses (48 hours)	once daily
CRESEMBA Capsules, 186 mg 186 mg[3] of isavuconazonium sulfate per capsule	Two 186 mg capsules (372 mg[2]) orally every 8 hours for 6 doses (48 hours)	Two 186 mg capsules (372 mg[2]) orally once daily
CRESEMBA Capsules, 74.5 mg 74.5 mg[4] of isavuconazonium sulfate per capsule	Five 74.5 mg capsules (372 mg[2]) orally every 8 hours for 6 doses (48 hours)	Five 74.5 mg capsules (372 mg[2]) orally once daily

1. Start maintenance doses 12 to 24 hours after the last loading dose
2. 372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole
3. 186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole
4. 74.5 mg of isavuconazonium sulfate is equivalent to 40 mg of isavuconazole

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 a maximum of 1 hour prior to preparation of the patient intravenous infusion solution *[see Dosage and Administration (2.4)]*.
- For nasogastric tube administration, the reconstituted solution should be administered within 1 hour of reconstitution *[see Dosage and Administration (2.5)]*.

2.4 Dilution and Preparation Instructions for the Intravenous Administration of 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°C to 8°C / 36°F to 46°F) the infusion solution after dilution and complete the infusion within 24 hours. Do not freeze the infusion solution.

2.5 Preparation Instructions for the Nasogastric Tube Administration of the Injection Formulation

- Utilizing aseptic technique, reconstitute one vial of CRESEMBA for injection (equivalent to 200 mg isavuconazole) with 5 mL of water for injection, USP *[see Dosage and Administration (2.3)]*.

- Withdraw the entire contents (5 mL) of the vial using an appropriate syringe and needle. Discard the needle and cap the syringe.
- To administer, remove the cap from the syringe containing the reconstituted solution and connect the syringe to the nasogastric (NG) tube to deliver the dose. After administering the dose, administer three 5 mL rinses to the NG tube with water *[see Clinical Pharmacology (12.3)]*.
- The reconstituted solution should be administered via nasogastric tube within 1 hour of reconstitution.

2.6 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

CRESEMBA Capsules

CRESEMBA 74.5 mg isavuconazonium sulfate (equivalent to 40 mg of isavuconazole) capsules are opaque and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a Swedish orange cap imprinted with "557" in black ink.

CRESEMBA 186 mg isavuconazonium sulfate (equivalent to 100 mg of isavuconazole) capsules are opaque, elongated and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with "766" in black ink.

CRESEMBA for Injection

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

Anaphylactic Reactions

Anaphylactic reactions, with fatal outcome, have been reported during treatment with CRESEMBA. Symptoms including dyspnea, hypotension, generalized erythema with flushing, and urticaria have been reported in such cases often soon after the initiation of treatment.

Severe Skin Reactions

Severe skin reactions, such as Stevens-Johnson syndrome, have been reported during treatment with other azole antifungal agents.

Discontinue CRESEMBA if a patient develops an anaphylactic or severe cutaneous adverse reaction and initiate supportive treatment as needed. There is no information regarding cross-sensitivity between CRESEMBA and other azole antifungal agents though cross-sensitivity between other triazole agents has been reported. When prescribing CRESEMBA to patients with hypersensitivity to other azoles, monitor for signs and symptoms of hypersensitivity reactions.

5.4 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies, CRESEMBA may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

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 0.2 and 0.1 of the human maintenance dose 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 maintenance human dose based on AUC comparisons *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use an effective method of contraception during treatment with CRESEMBA and for 28 days after the final dose *[see Use in Specific Populations (8.3)]*.

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 (%)	Trial 1 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[1]	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[2]	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)

1. Elevated liver laboratory tests include reactions of increased alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, blood bilirubin, and gamma-glutamyl transferase.
2. 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 CRESEMBA 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, paresthesia, 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.

6.2 Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of CRESEMBA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Immune system disorders: anaphylactic reaction

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 coadministered drugs on the pharmacokinetics of isavuconazole and the effect of isavuconazole on the pharmacokinetics of coadministered 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[1]	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)]*.

1. 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[1]	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 *[see Clinical Pharmacology (12.3)]*.
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 when dosed concurrently with CRESEMBA *[see Clinical Pharmacology (12.3)]*.

1. 400 mg of lopinavir in combination with 100 mg of ritonavir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, CRESEMBA may cause fetal harm when administered to a pregnant woman. There are no available human data on the use of CRESEMBA in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, perinatal mortality was increased in the offspring of pregnant rats dosed orally with isavuconazonium sulfate at approximately 0.5 times the clinical exposure during pregnancy through the weaning period. In animal studies when isavuconazonium chloride was administered by oral gavage to pregnant rats and rabbits during organogenesis at exposures corresponding to less than the human maintenance dose, increases in the incidences of multiple skeletal abnormalities, including rudimentary cervical ribs and fused zygomatic arches, were observed *(see Data)*. Advise pregnant women of the potential risk to a fetus *[see Warnings and Precautions (5.4)]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Isavuconazonium chloride administration during organogenesis (gestational days 6-17 in rats and gestational days 6-18 in rabbits) was associated with dose-related increases in the incidences of rudimentary cervical ribs in rats and rabbits at 30 and 45 mg/kg, respectively, equivalent to about 0.2 and 0.1 times of the clinical exposure 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 0.2 times the human AUC. Skeletal abnormalities have also been observed in embryo-fetal development studies of other azole antifungal agents.

Isavuconazonium sulfate increased perinatal mortality in the pups when orally administered to pregnant rats during pregnancy and lactation (gestational day 6 through postpartum day 20) at doses up to 90 mg/kg/day (approximately 0.5 times the clinical exposure based on AUC comparison). No effect on the duration of pregnancy or delivery was seen in the pups at this same dose.

8.2 Lactation

Risk Summary

There are no data on the presence of isavuconazole in human milk, the effects on the breastfed infant or the effects on milk production. Isavuconazole was present in the milk of lactating rats following intravenous administration. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Therefore, breastfeeding should be discontinued during treatment with CRESEMBA.

8.3 Females and Males of Reproductive Potential

Contraception

CRESEMBA may cause embryo-fetal harm when administered to pregnant women *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with CRESEMBA and for 28 days after the final dose.

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/1.73 m^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)]*.

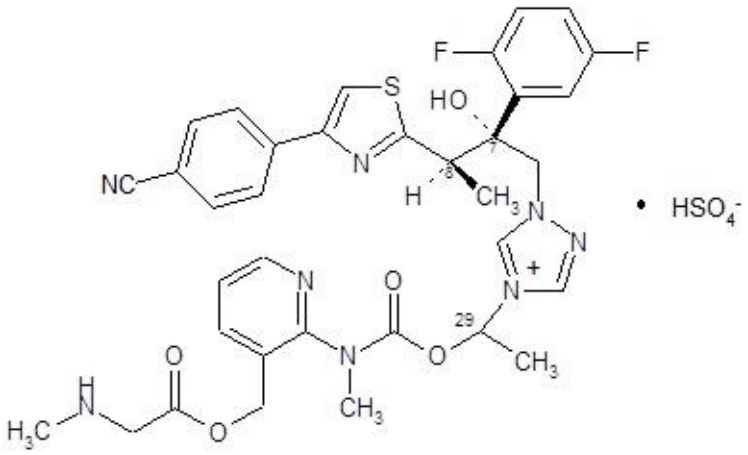
10 OVERDOSAGE

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 Capsules

CRESEMBA (isavuconazonium sulfate) 74.5 mg capsules are available for oral administration. Each CRESEMBA capsule contains 74.5 mg isavuconazonium sulfate, equivalent to 40 mg isavuconazole. The inactive ingredients include black iron oxide, colloidal silicon dioxide, disodium edetate, gellan gum, hypromellose, magnesium citrate, microcrystalline cellulose, potassium acetate, potassium hydroxide, propylene glycol, purified water, red iron oxide, shellac, sodium lauryl sulfate, stearic acid, strong ammonia solution, talc and titanium dioxide.

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

CRESEMBA for Injection

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 Microbiology (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 186 mg CRESEMBA Capsules

Parameter	CRESEMBA 186 mg 2 Capsules[1] (n = 37)	CRESEMBA 186 mg 6 Capsules[1] (n = 32)
C_{max} (ng/mL)		
Mean	7499	20028
SD	1893.3	3584.3
CV %	25.2	17.9
t_{max} (hr)		
Median	3.000	4.000
Range	2.0 – 4.0	2.0 – 4.0
AUC (hr•ng/mL)		
Mean	121402	352805
SD	35768.8	72018.5
CV %	29.5	20.4

1. Each capsule contains the equivalent of 100 mg of isavuconazole.

Following oral administration of CRESEMBA capsules at an isavuconazole equivalent dose of 200 mg in 66 fasted healthy male subjects, a single dose administration of two 186 mg CRESEMBA capsules and five 74.5 mg CRESEMBA capsules exhibited a mean (SD) C_{max} and AUC of 3296 (614) ng/mL and 112229 (30289) ng·hr/mL, respectively, and 3277 (576) ng/mL and 117913 (33142) ng·hr/mL, respectively.

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 one-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.

CRESEMBA given orally as an intravenous solution administered via nasogastric (NG) tube provides systemic isavuconazole exposure that is similar to the oral capsule (Table 6).

Table 6. Statistical Comparison of Plasma Pharmacokinetics of Isavuconazole Following Single Oral Dose Administration of 2 Capsules of 186 mg (Equivalent to 200 mg Isavuconazole) and Single Intravenous Solution Dose Administration of 372 mg (Equivalent to 200 mg Isavuconazole) via Nasogastric (NG) Tube in Healthy Subjects Under Fasted Conditions

	CRESEMBA IV Solution via NG Tube		CRESEMBA Oral Capsules		NG Tube/Oral Capsule
Pharmacokinetic Parameter	**N**	**Mean (%CV)**	**N**	**Mean (%CV)**	**GMR (90% CI)**
C_{max} (ng/mL)	13	2295 (23.6)	13	2185 (26.7)	105.34 (89-124)
$AUC_{0\text{-}72hr}$ (hr·ng/mL)	13	34885 (22.1)	13	35777 (24.6)	97.81 (93-103)
$AUC_{0\text{-}\infty}$ (hr·ng/mL)	12	98142 (44.5)	12	100050 (46.8)	99.27 (93-106)
GMR = Geometric least-squares mean ratio; CI = confidence interval					

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, predominantly 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 coadministered 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 by 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.

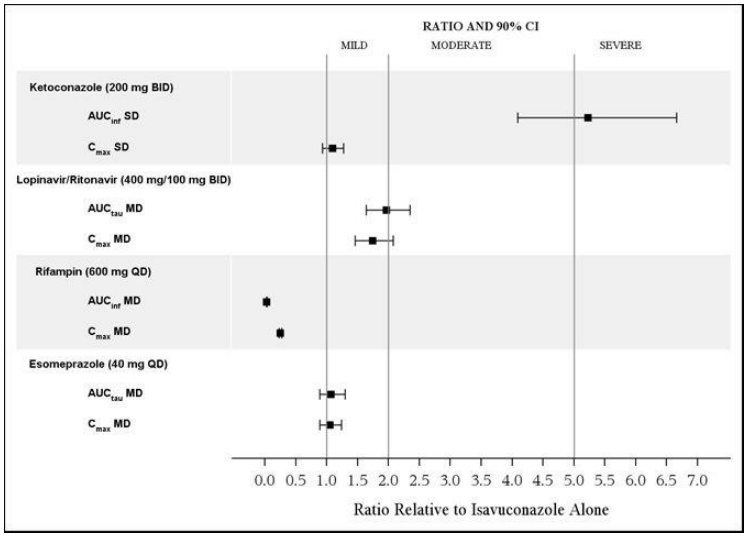


Figure 1. The Effect of Coadministered Drugs on Isavuconazole Exposure

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.

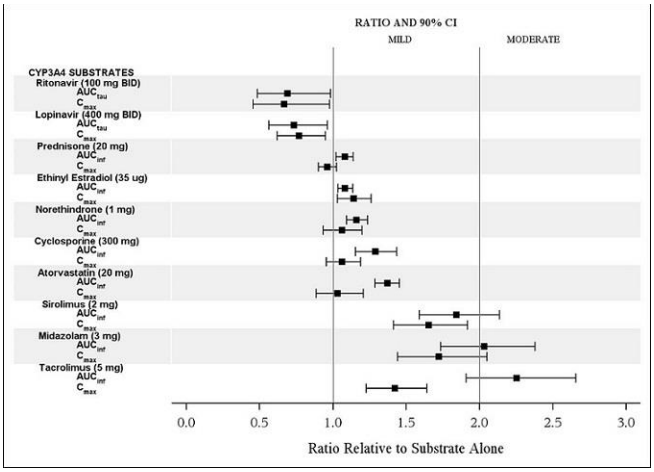


Figure 2. The Effect of Isavuconazole on Coadministered CYP3A4 Substrate Medications

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

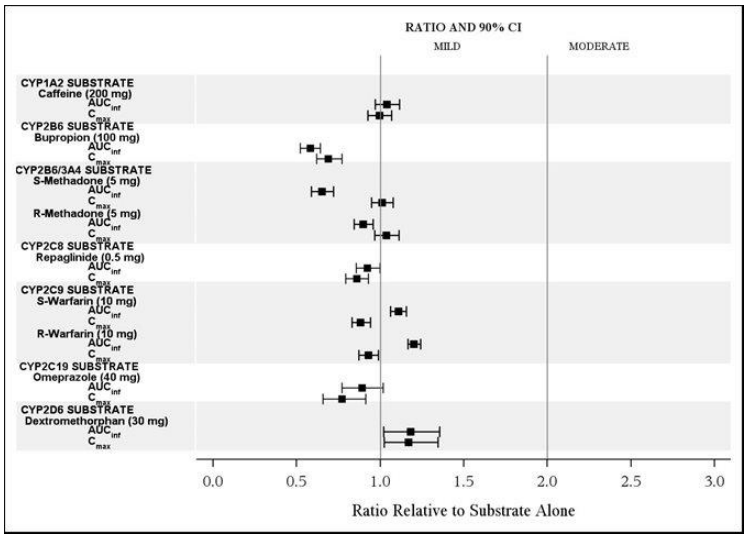


Figure 3. The Effect of Isavuconazole on Exposure of Coadministered CYP Substrate Medications

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

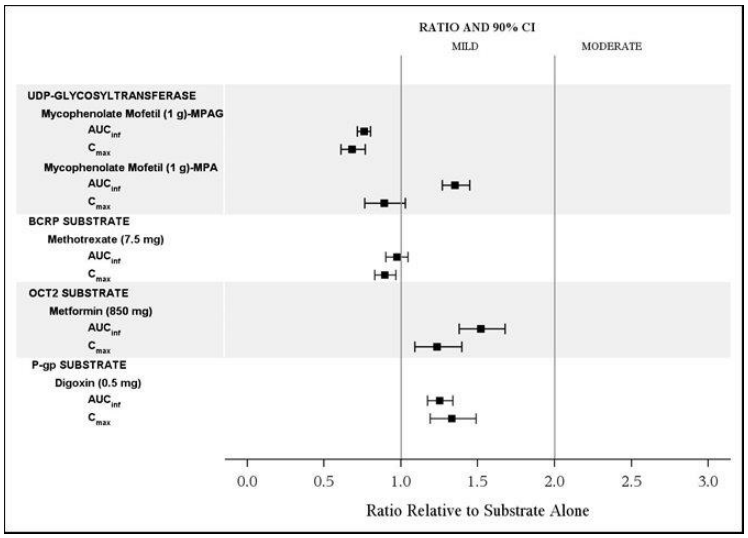


Figure 4. The Effect of Isavuconazole on Exposure on the Substrates of UGT and Transporters

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.

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.

Antimicrobial Activity

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)]*.

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat carcinogenicity study and a 2-year mouse carcinogenicity study, dose-related increases in hepatocellular adenomas and/or carcinomas were observed in male and female B6C3F1/Crl mice, and male, but not female Han Wistar rats at doses as low as 0.1 times the exposure seen in humans administered the maintenance dose. Hepatic hemangiomas were increased in female mice at 300 mg/kg, at an exposure similar to the maintenance dose. Hepatoblastoma were increased in male mice at 100 mg/kg, about 0.4 times the systemic exposures based on AUC comparisons.

Thyroid follicular cell adenomas were observed in male and female rats at doses as low as 60 mg/kg in male rats (about 0.2 times the human clinical maintenance dose). The relevance of the rat thyroid tumors to human carcinogenic risk remains unclear.

A significant increase in the incidence of skin fibromas was seen in male rats at 300 mg/kg, exposures 0.8 times the human exposure at the human clinical maintenance dose. Uterine adenocarcinomas were observed in female rats at 200 mg/kg, at systemic exposures similar to the human exposure at the human clinical maintenance dose.

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 (approximately 0.3 times the systemic exposure at the human clinical maintenance dose).

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. sydowii*, *A. terreus,* and *A. westerdijkiae*. Baseline risk factors are presented in Table 7.

Table 7. Baseline Risk Factors in Intent-To-Treat (ITT[1]) Population

	CRESEMBA N=258 n (%)	Voriconazole N=258 n (%)
Hematologic Malignancy	211 (82)	222 (86)
Allogeneic Hematopoietic Stem Cell Transplant	54 (21)	51 (20)
Neutropenia[2]	163 (63)	175 (68)
Corticosteroid Use	48 (19)	39 (15)
T-Cell Immunosuppressant Use	111 (43)	109 (42)

1. ITT includes all randomized patients who received at least one dose of study drug.
2. 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 isavuconazole) 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 8).

Table 8. All-Cause Mortality Through Day 42

	CRESEMBA		Voriconazole		
	N	All-cause Mortality n (%)	N	All-cause Mortality n (%)	Difference[1] (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)

1. 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 9).

Table 9. Overall Response Success at End-of-Treatment

	CRESEMBA		Voriconazole		
	N	**Success n (%)**	**N**	**Success n (%)**	**Difference[1] (95% CI)%**
Proven or Probable Invasive Aspergillosis	123	43 (35.0)	108	42 (38.9)	-4.0 (-16.3, 8.4)

1. 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 microsporus.* 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 10. 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 10. Baseline Risk Factors in Mucorales Patients

	Primary N=21 n (%)	**Refractory N=11 n (%)**	**Intolerant N=5 n (%)**	**Total N=37 n (%)**
Hematologic Malignancy	11 (52)	7 (64)	4 (80)	22 (60)
Allogeneic Hematopoietic Stem Cell Transplant	4 (19)	4 (36)	5 (100)	13 (35)
Neutropenia[1]	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 the Independent Data Review Committee: Primary = patients received CRESEMBA as primary treatment; refractory = patient's underlying infection not adequately treated by prior therapy; intolerant = patients unable to tolerate prior therapy.

1. 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 11. These results provide evidence that CRESEMBA is effective for the treatment of mucormycosis, in light of the natural history of untreated mucormycosis. However, the efficacy of CRESEMBA for the treatment of invasive mucormycosis has not been evaluated in concurrent, controlled clinical trials.

Table 11. 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[1] (32%)	4/11 (36%)	1/5 (20%)	11/35[1] (31%)

1. 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

CRESEMBA Capsules

CRESEMBA (isavuconazonium sulfate) 74.5 mg capsules are supplied as opaque capsules and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a Swedish orange cap imprinted with “557” in black ink. Each capsule contains 74.5 mg isavuconazonium sulfate (equivalent to 40 mg of isavuconazole) and is packaged as follows:

35-count carton (contains seven individual aluminum child-resistant blister packs of 5 capsules per sheet with desiccant)	**NDC 0469-2860-35**

CRESEMBA (isavuconazonium sulfate) 186 mg capsules are supplied as opaque and elongated capsules and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with “766” in black ink. Each capsule contains 186 mg isavuconazonium sulfate (equivalent to 100 mg of isavuconazole) and is packaged as follows:

14-count carton (contains two individual aluminum child-resistant blister packs of 7 capsules per sheet with desiccant)	**NDC 0469-0520-02**

CRESEMBA for Injection

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

Individually packaged single-dose vial	**NDC 0469-0420-01**

16.2 Storage and Handling

CRESEMBA Capsules

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].

CRESEMBA for Injection

Store CRESEMBA for injection unreconstituted vials at 2°C to 8°C (36°F to 46°F) in a refrigerator. CRESEMBA for injection 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 *[see Dosage and Administration (2.3)]*. 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°C to 8°C (36°F to 46°F) prior to use *[see Dosage and Administration (2.4)]*. For nasogastric tube use, the reconstituted solution should be used within 1 hour of reconstitution *[see Dosage and Administration (2.5)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient 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.

Advise patients to inform their physician immediately if they have ever had an allergic reaction to isavuconazole or other antifungal medicines such as ketoconazole, fluconazole, itraconazole, posaconazole, or voriconazole. Advise patients to discontinue CRESEMBA and seek immediate medical attention if any signs or symptoms of severe allergic reaction occur *[see Warnings and Precautions (5.3)]*.

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Northbrook, IL 60062

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327375-ISA-USA

Patient Information

CRESEMBA® (Crē sem' bah)

(isavuconazonium sulfate)

capsules, for oral use

CRESEMBA® (Crē sem' bah)

(isavuconazonium sulfate)

for injection, for intravenous use

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).

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

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 new medicines without talking to your healthcare provider or pharmacist.

Before you take CRESEMBA, tell your healthcare provider about all of your medical conditions, including 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 medicines such as ketoconazole, fluconazole, itraconazole, voriconazole or posaconazole.
- are pregnant or plan to become pregnant. CRESEMBA may harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant. Women who can become pregnant should use effective birth control while taking CRESEMBA and for 28 days after the last CRESEMBA dose. Talk to your healthcare provider about birth control methods that may be right for you.
- 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.

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 and can cause 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 pocket for the CRESEMBA capsule and one pocket 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. Make sure only the CRESEMBA capsule pocket is opened.
- Do not puncture the pocket containing the desiccant.
- Do not swallow or use the desiccant.

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
  - yellowing of your eyes
  - flu-like symptoms
  - nausea or vomiting
  - feeling very tired
- **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
  - chills
  - numbness and tingling
  - difficulty breathing
  - dizziness
  - changes in your sense of touch (hypoesthesia)
- **severe allergic reactions.** Severe allergic reactions including death can happen in some people taking CRESEMBA. Symptoms of a severe allergic reaction may include:
  - swelling of your face, lips, mouth, or tongue
  - trouble breathing
  - wheezing
  - severe itching
  - skin rash redness, or swelling
  - dizziness or fainting
  - fast heartbeat or pounding in your chest
  - sweating

  Stop taking CRESEMBA and call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the symptoms listed above.
- **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.
- **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
- changes in the level of a liver enzyme in your blood
- cough
- vomiting
- low potassium
- swelling of arms or legs
- diarrhea
- constipation
- back pain
- headache
- shortness of breath

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.
- 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 health professionals.

What are the ingredients of CRESEMBA capsules?
Active ingredient: isavuconazonium sulfate.

Inactive ingredients: black iron oxide, colloidal silicon dioxide, disodium edetate, gellan gum, hypromellose, magnesium citrate, microcrystalline cellulose, potassium acetate, potassium hydroxide, propylene glycol, purified water, red iron oxide, shellac, sodium lauryl sulfate, stearic acid, strong ammonia solution, talc and titanium dioxide.

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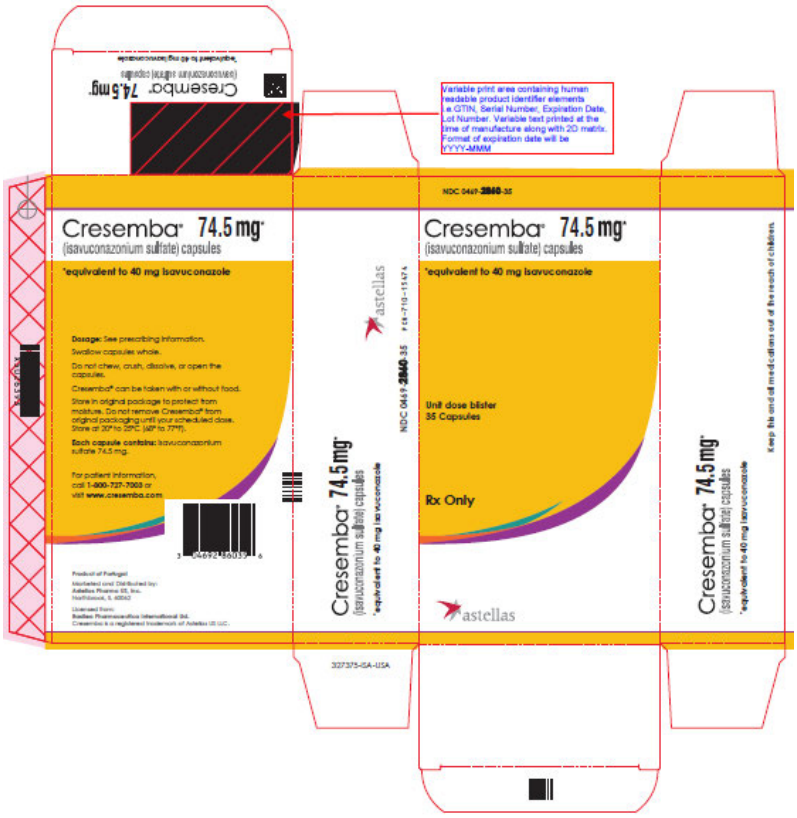
For more information go to www.CRESEMBA.com or call 1-800-727-7003.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 11/2022


Variable print area containing human readable product identifier elements i.e GTIN, Serial Number, Expiration Date, Lot Number. Variable text printed at the time of manufacture along with 2D matrix. Format of expiration date will be YYYY-MMM
Cresemba® 74.5 mg*
(isavuconazonium sulfate) capsules
*equivalent to 40 mg isavuconazole
Dosage: See prescribing information.
Swallow capsules whole.
Do not chew, crush, dissolve, or open the capsules.
Cresemba® can be taken with or without food.
Store in original package to protect from moisture. Do not remove Cresemba® from original packaging until your scheduled dose.
Store at 20° to 25°C (68° to 77°F).
Each capsule contains: isavuconazonium sulfate 74.5 mg.
For patient information, call 1-800-727-7003 or visit www.cresemba.com
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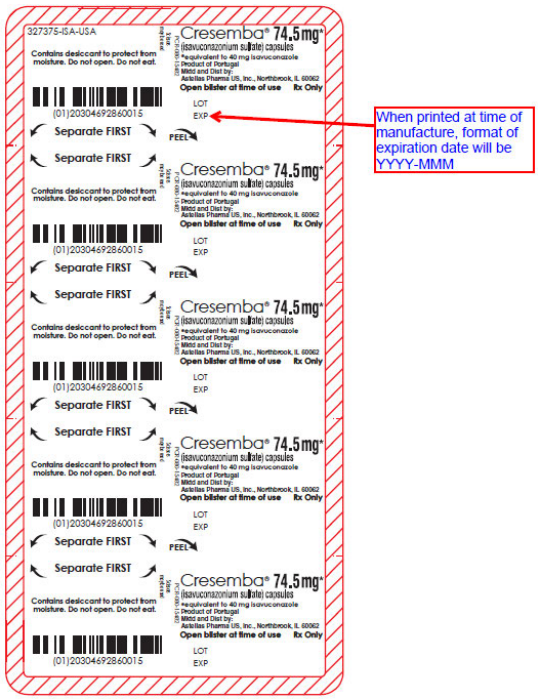
Astellas Pharmaceutica International Ltd.
Cresemba is a registered trademark of Astellas US LLC.
NDC 0469-2860-35
astellas
Unit dose blister
35 Capsules
Rx Only
Keep this and all medications out of the reach of children.
327375-GA-USA


327375-ISA-USA
Contains desiccant to protect from moisture. Do not open. Do not eat.
Cresemba® 74.5mg*
(isavuconazonium sulfate) capsules
*equivalent to 40 mg isavuconazole
Product of Portugal
Manufactured and Distributed by:
Astellas Pharma US, Inc., Northbrook, IL 60062
Open blister at time of use Rx Only
(01)20304692860015
LOT
EXP
Separate FIRST
PEEL
When printed at time of manufacture, format of expiration date will be YYYY-MMM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207500Orig1s013

SUMMARY REVIEW

NDA Summary Review

NDA #	NDAs 207500/S-013 and 207501/S-011
Applicant	Astellas Pharma US Inc.
Date of Submission	July 28, 2022
PDUFA Goal Date	November 28, 2022
Proprietary Name / Established (USAN) names	Cresemba (isavuconazonium sulfate)
Dosage forms/Strength	Cresemba capsules, 186 mg; Cresemba for injection, 372 mg
Proposed Indication(s)	Treatment of invasive aspergillosis and invasive mucormycosis
Regulatory Action:	Approval

1. Background

NDA 207500 for Cresemba (isavuconazonium sulfate) capsules, 186 mg and NDA 207501 for Cresemba (isavuconazonium sulfate) powder for injection, 372 mg (NDA 207501) were approved on March 6, 2015.

These supplemental applications provide for information in support of a new capsule strength (74.5 mg isavuconazonium sulfate) and include the final study report and associated datasets for a phase 1 bioequivalence study.

2. Current Submission

OPQ: The new lower strength Cresemba capsules are formulated with the same excipients as those used in the approved 186.3 mg capsule. (b) (4) [redacted]

The manufacturing processes used for the approved 186.3 mg capsules and the proposed 74.5 mg capsules are the same. The manufacturing equipment line is also similar for both strengths. The Office of Pharmaceutical Manufacturing Assessment (OPMA) approved the manufacturing facilities responsible for the commercial production of Cresemba capsules, 74.5 mg. (b) (4) Analytical methods, previously approved for testing the 186.3 mg capsules, were adequately validated/verified for testing the new 74.5 mg capsules. The container closure system proposed for the new lower strength Cresemba capsules, 74.5 mg is similar to the one approved for the currently approved 186.3 mg capsules. The components of the blister packaging are identical for both strengths.

Batch release and stability data provided for the registration/primary stability batches indicate that all batches met the drug product specification with batch-to-batch consistency. Based on the adequate stability data, the proposed initial shelf life of 24 months for Cresemba capsules 74.5 mg, when stored in aluminum/aluminum blister with desiccant at controlled room temperature, is acceptable in accordance with ICH Q1E guidelines. Based on the adequate product quality information provided along with the necessary labeling updates, and the OPMA approval of the manufacturing facilities, the addition of Cresemba (isavuconazonium sulfate) capsules, 74.5 mg is approvable from a CMC perspective.

Clinical: The safety data submitted with the bioequivalence study were reviewed. All safety data were in line with the current drug labelling and no further revisions were requested by either the sponsor or this reviewer. From a clinical standpoint, the supplement can be approved. Please refer to the Clinical Review signed into DARRTS 11/2/2022 for additional details.

Clinical Pharmacology: The bioequivalence (BE) study conducted by the Applicant was reviewed, and it is agreed that the test formulation exposures ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}) met the BE criterion; therefore, test formulation has shown equivalent bioavailability to the reference formulation. Please refer to the Clinical Pharmacology review signed into DARRTS on 11/4/2022 for additional details.
In addition, the Applicant's proposed label required minor edits to Section 12 (CLINICAL PHARMACOLOGY). For additional information, see the Labeling section below (12 CLINICAL PHARMACOLOGY).

Labeling:

Prescribing Information

Summary of Significant Labeling Changes made to the Prescribing Information submitted on July 28, 2022

Section/Subsection	Applicant's Proposed Labeling	FDA Recommended Labeling
HIGHLIGHTS OF PRESCRIBING INFORMATION	Information on dosing of CRESEMBA Capsules, 74.5 mg was in the text format.	A table for dosage regimen of the 74.5 mg 186 mg CRESEMBA capsules and the 372 mg CRESEMBA for injection has been added to the Highlights section for Dosage and Administration in lieu of text. This tabular format was made to enhance accessibility of the information as per the labeling recommendations in the Guidance for Industry: Labeling for Human Prescription Drug and Biological Products-Implementing the PLR Content and Format Requirements.
FULL PRESCRIBING INFORMATION		
2. DOSAGE AND ADMINISTRATION **Subsection 2.2 Dosage Regimen**	Information on dosing CRESEMBA Capsules, 74.5 mg is added to Table 1: (b) (4) [redacted]	Revised as follows to promote safe use of CRESEMBA from a medication error perspective (Refer to DMEPA review dated October 24,2022 for additional details): **Loading dose**: Five 74.5 mg capsules (372 mg) orally every 8 hours for 6 doses (48 hours) **Maintenance dose:** Five 74.5 mg capsules (372 mg) orally once daily. Similar revisions were made to the text of the dosing information for CRESEMBA capsules 186 mg and CRESEMBA for Injection 372 mg in Table 1.

11 DESCRIPTION	Description of CRESEMBA Capsules, 74.5 mg is added.	Accepted with minor editorial changes.
12 CLINICAL PHARMACOLOGY Subsection 12.3 Pharmacokinetics	Applicant added a paragraph summarizing the bioequivalence between the test formulation and reference formulation, and they added a table (Table 6 in label) summarizing the pharmacokinetic parameters of the bioequivalence study.	(b) (4) [redacted]
16 HOW SUPPLIED/STORAGE AND HANDLING Subsection 16.1 How Supplied	(b) (4) [redacted]	Accepted with minor editorial changes to the text.
Subsection 16.2 Storage and Handling		Nasogastric handling was added within the post-reconstitution and dilution storage and handling text of subsection 16.2 to provide clarity and reduce the risk of deteriorated product medication errors. Refer to DMEPA review dated October 24,2022 for additional details.

Carton and Container Labeling Changes

The revisions applied to the carton and container labeling are based on the recommendations of the Division of Medication Error Prevention and Analysis-1 (DMEPA). The DMEPA review was signed into DARRTS on October 24, 2022.

3. Regulatory Action

These supplemental applications for Cresemba (isavuconazonium sulfate) capsules, 74.5 mg will receive an approval action.

Reviewers:

CMC: Ramesh Gopalaswamy, PhD
CMC Team Leader: David Lewis, PhD
Clinical Pharmacology Reviewer: Anthony Nicasio, PharmD
Clinical Pharmacology Team Leader: Dakshina Chilukuri, PhD
Associate Director for Labeling: Abimbola Adebowale, PhD
Clinical: Shrimant Mishra, MD
Clinical Team Leader: Heidi Smith, MD, PhD
Deputy Division Director: Dmitri Iarikov, MD, PhD
Division Director: Peter Kim, MD, MS

Signatures: *{See appended electronic signature page}*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALISON K RODGERS
11/22/2022 08:49:55 AM

RAMESH N GOPALASWAMY
11/22/2022 08:52:35 AM
Please note that I am also signing for Dr. David Lewis.

DAKSHINA M CHILUKURI
11/22/2022 09:00:45 AM
I am signing for Anthony Nicasio (primary reviewer) and myself (Team Leader).

ABIMBOLA O ADEBOWALE
11/22/2022 09:05:48 AM

SHRIMANT MISHRA
11/22/2022 09:07:18 AM

HEIDI L SMITH
11/22/2022 09:10:31 AM

DMITRI IARIKOV
11/22/2022 10:08:25 AM

PETER W KIM
11/22/2022 10:11:51 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207500Orig1s013

MEDICAL REVIEW(S)

NDA: 207500 (oral formulation)

Sponsor: Astellas

Submission: Labeling Supplement

Receipt Date: 7/28/22

Goal Date: 11/28/22

Reviewer: Shrimant Mishra MD MPH

Background:

The Sponsor has submitted a labeling supplement in support of a new oral capsule formulation – 74.5mg of isavuconazonium sulfate. Currently, the Sponsor manufactures a 186mg oral capsule and each dose consists of two capsules (372 mg). In support of this new formulation, the Sponsor has conducted a bioequivalence trial between the current and new oral formulation. The purpose of this review is to evaluate the clinical safety information associated with this study/labeling supplement.

The bioequivalence trial consisted of 70 healthy, Japanese adult males that were enrolled and tested in an open-label format. The 70 subjects were randomly assigned to 2 groups in 35 patients per group, using a single dose, 2-group, 2-period crossover method. In the first group (Group A), subjects would receive the standard formulation (two 186 capsules) followed by the new formulation (five 74.5 mg capsules). In the second group (Group B), the reverse occurred. The drug holiday period from the date of administration of the investigational drug in Period 1 to the date of administration of the investigational drug in Period 2 was 35 days. After collecting a blood sample from the subjects over time for pharmacokinetic examination, the plasma isavuconazole concentration was measured, the pharmacokinetic parameters were calculated, and the bioequivalence between the two formulations was evaluated. Safety parameters measured included adverse events, 12-lead ECGs, laboratory tests, and vital signs.

Results:

The evaluation of the pharmacokinetic/bioequivalence results are deferred to the Clinical Pharmacology reviewer.

The safety population included 35 subjects in Group A (35 subjects in Period 1, 34 subjects in Period 2) and 35 subjects in Group B (35 subjects in Period 1, 33 subjects in Period 2). This was equivalent to 68 subjects receiving the standard formulation and 69 subjects receiving the test formulation. The subjects were all Asian males with a mean age in the late 20s and mean BMI around 21 kg/m^2; the distribution of these demographic characteristics was roughly equivalent between the two groups.

TEAEs were observed in 16 of 68 subjects (23.5%) with the standard formulation and 24 of 69 (34.8%) patients with the test formulation. TEAEs judged to have had a causal relationship with the

investigational drug ("adverse reaction") were observed in 3 of 68 (4.4%) patients with the standard formulation and 2 of 69 (2.9%) patients with the test formulation. No serious TEAEs including death were observed.

The TEAEs associated with the standard formulation consisted of upper respiratory tract inflammation 10.3% (7 subjects), ALT increased 2.9% (2 subjects), blood creatine phosphokinase increased 2.9% (2 subjects), urinary blood positive 2.9. % (2 subjects), dizziness (1 subject), headache (1 subject), pre-syncope (1 subject), diarrhea (1 subject), nausea (1 subject), epidermolysis (1 subject), fatigue (1 subject), increased blood glucose (1 subject), and positive urinary protein (1 subject). Of these, related adverse reactions were increased ALT, headache, and diarrhea. It should be noted that almost all of these AEs (or a related AE) appear in the current labeling for isavuconazole. Upper respiratory tract inflammation and increased blood glucose are not approximated by current labeling, however all such reactions were considered not related to study drug and in the case of the subject with increased blood glucose, this occurred 35 days after study drug administration.

The TEAEs associated with the test formulation consisted of upper respiratory tract inflammation 13.0% (9 subjects), headache 8.7% (6 subjects), increased blood triglyceride 2.9% (2 subjects), urinary blood positive 2.9% (2 subjects) and urinary protein positive 2.9% (2 subjects), rhinitis (1 subject), abdominal discomfort (1 subject) , diarrhea (1 subject), hypoesthesia of the mouth (1 subject), nausea (1 subject), vomiting (1 subject), fatigue (1 subject), increased ALT (1 subject), and blood creatine phosphokinase increased (1 subject). The related adverse reactions were headache, diarrhea, nausea, and vomiting. As noted for the standard formulation, almost all of these AEs (or a related AE) appear in the current labeling for isavuconazole. Notably, there were 6 subjects with headache with the test formulation compared to just 1 subject with the standard formulation, however just one test formulation subject was deemed to have a drug-related headache. Upper respiratory tract infection, rhinitis, and increased blood triglycerides are not approximated by current labeling, however all such cases were considered not related to study drug; one triglyceride increase occurred 35 days after administration of study drug.

No severe AEs were noted with either formulation. For the standard formulation, 2 subjects had moderate AEs - pre syncope and epidermolysis. A pre-syncope AE developed within 6 hours after the administration of the standard formulation and the patient recovered about 30 minutes after onset without treatment. The epidermolysis AE occurred 27 days after the administration of the standard formulation and the patient recovered 13 days after onset without treatment. For the test formulation, one subject had 2 moderate AEs (nausea and vomiting; occurred 11 hours after drug administration) that resulted in the discontinuation of the clinical trial. All other AEs for both formulations were mild.

No significant differences were noted between the formulations in terms of laboratory values, vital signs, and ECG findings.

Conclusion:

No safety differences were noted between the two formulations, and the AEs that were noted are appropriately described in current labeling (please note that the Sponsor has not proposed any changes to safety labeling). From a clinical standpoint, the supplement should be approved.

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/s/

SHRIMANT MISHRA
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207500Orig1s013

CHEMISTRY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA-207500-SUPPL-13 and NDA-207501-SUPPL-11
   sNDA Recommendation: Approval
   sNDA Managed by: OND

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	07/28/2022	07/28/2022	08/18/2022	11/28/2022	11/07/2022
Amendment		09/29/2022	09/29/2022	09/30/2022		11/04/2022
Amendment		11/01/2022	11/01/2022	11/03/2022		11/07/2022
Amendment		11/14/2022	11/14/2022	11/14/2022		11/14/2022

3. **Provides For From Cover Letter:** Addition of a new formulation for Cresemba capsules containing 74.5 mg isavuconazonium sulfate and associated labeling changes.

4. **Review #**: 1

5. **Clinical Review Division**: OID/DAI

6. **Name and Address of Applicant**:

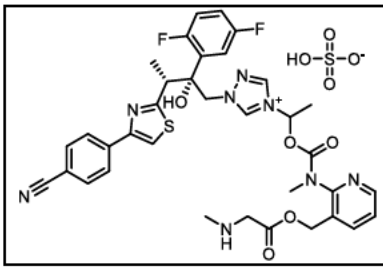
Astellas Pharma US Inc.
1 Astellas way
Northbrook, IL 60062

Phone: (b) (6)
Email: robert.reed@astellas.com

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
CRESEMBA® (isavuconazonium sulfate) capsules	Capsule	186 mg	Oral	Rx	No
CRESEMBA® (isavuconazonium sulfate) for injection	Powder for Injection	372 mg	Intravenous	Rx	No

8. **Chemical Name and Structure of Drug Substance**:



USAN: Isavuconazonium sulfate,
Chemical Name: Glycine, N-methyl-, [2-[[[1-[1-[(2R,3R)-3-[4-(4-cyanophenyl)-2-thiazolyl]-2-(2,5difluorophenyl)-2-hydroxybutyl]-4H-1,2,4-triazolium-4-yl]ethoxy]carbonyl]methylamino]-3-pyridinyl]methyl ester, sulfate (1:1)
Molecular Formula: $C_{35}H_{35}F_2N_8O_5S \cdot HSO_4$
MW: 814.84

9. Indication: Treatment of invasive aspergillosis, and invasive mucormycosis.

10. Supporting/Related Documents: N/A

11. Disciplines/Consults:

Disciplines/Consults	Recommendation	Date	Reviewer
Biopharmaceutics	Adequate	08-NOV-2022	Payal Agarwal, Ph. D.
OPMA/Facility	Approval	02-NOV-2022	Mark Johnson

12. Executive Summary:

With this OND managed PAS submission, the applicant proposes to add a new strength for Cresemba capsules containing 74.5 mg isavuconazonium sulfate (equivalent to 40 mg isavuconazole) (b) (4)

The Office of Pharmaceutical Manufacturing Assessment (OPMA) approved the manufacturing facilities responsible for the commercial production of Cresemba capsules, 74.5 mg based on file review. An overall manufacturing inspection recommendation (OMIR) was issued on 02-SEP-2022 for approval for all the facilities registered in the NDA.

The new lower strength Cresemba capsules are formulated with the same excipients as those used in the approved 186.3 mg capsule. Quantitatively, the amounts of excipients- Isavuconazonium sulfate, (b) (4) but color (Swedish Orange) and components of the capsule shell are the same; the imprint design on the cap was changed from "766" to "557".

The manufacturing processes used for the approved 186.3 mg capsules and the proposed 74.5 mg capsules are the same. The manufacturing equipment line is also similar for both strengths (b) (4) . Overall, the drug product specification is unchanged (b) (4) Analytical methods, previously approved for testing the 186.3 mg capsules, were adequately validated/verified for testing the new 74.5 mg capsules.

Batch release data provided for four registration / primary stability batches indicate that all batches met the drug product specification with batch-to-batch consistency. Based on the dose proportionality of the active ingredient and the excipients, and similarity of capsule shell components, non-testing of elemental impurities in the drug product, approved for the 186.3 mg capsules, is also applicable for the new 74.5 mg capsules.

The container closure system proposed for the new lower strength Cresemba capsules, 74.5 mg is similar to the one approved for the currently approved 186.3 mg capsules. The components of the blister packaging are identical for both strengths.

Stability data provided - long-term storage (25°C/60% RH; 18 months stability data for 2 batches, and 12 months for one batch), and accelerated storage (40°C/75%RH; 6 months for all registration batches) - indicate that acceptance criteria were met for all attributes with batch-to-batch consistency. No significant trends were observed. Based on the adequate stability data, along with the supporting information provided in the statistical analyses, the proposed initial shelf life of 24 months for Cresemba capsules 74.5 mg, when stored in aluminum/aluminum blister with desiccant at controlled room temperature, is acceptable in accordance with ICH Q1E guidelines.

The Prescribing Information (PI) and Patient Information (PPI) were updated for revisions to include information on the proposed Cresemba Capsules, 74.5 mg. Also submitted were carton and blister pack labels for Cresemba Capsules, 74.5 mg. Editorial changes were proposed to improve clarity of information and readability. With the Agency recommended changes adequately implemented, the updated labeling is adequate from the product quality standpoint.

Based on the adequate calculation showing that the expected introduction concentration (EIC) for isavuconazonium sulfate is significantly lower than 1 ppb, the applicant's request for a categorical exclusion from the requirement to submit an environmental assessment for this supplemental application may be granted.

Based on the adequate product quality information provided along with the necessary labeling updates, and the OPMA approval of the manufacturing facilities, the addition of Cresemba (isavuconazonium sulfate) capsules, 74.5 mg is approvable from a CMC perspective.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Ramesh Gopalaswamy, Ph.D., CMC reviewer, Branch 2, DPMAI, OLDP, OPQ

16. Secondary Reviewer:

David B. Lewis, Ph.D., Branch Chief, Branch 2, DPMAI, OLDP, OPQ

CMC Assessment

I. Background Information

CRESEMBA® (isavuconazonium sulfate) drug products (Cresemba capsules – NDA 207500 and Cresemba for injection - NDA 207501, both approved on 15-MAR-2015) contain isavuconazonium sulfate, which is the prodrug of isavuconazole, an azole antifungal drug.

Cresemba capsules are available for oral administration. Each 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 for injection (Cresemba IV) is available for intravenous administration ss 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.

With supplemental application NDA-207500-SUPPL-13, assessed in this review, the applicant introduces a new formulation for Cresemba capsules containing 74.5 mg isavuconazonium sulfate and associated labeling changes. Since the Prescribing Information (PI) is shared by both Cresemba products, the same labeling changes are also proposed in supplements NDA-207501-SUPPL-11. Hence, this is a common review for both supplements. However, all product quality updates are made only to NDA-207500 (Cresemba capsules).

II. Proposed Changes

The Applicant, Astellas Pharma US, Inc., proposes to add a new strength for Cresemba capsules containing 74.5 mg isavuconazonium sulfate (equivalent to 40 mg isavuconazole).

III. Assessment of Data Submitted to Support the Proposed Changes

(b) (4)

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(b) (4)

1.14 Labeling:

Updated Prescribing Information (PI) and Patient Information (PPI) - clean and annotated versions – were submitted with the original supplement submission for revisions to include information on the proposed Cresemba Capsules, 74.5 mg. Also included are carton and blister pack labels for Cresemba Capsules, 74.5 mg.

HIGHLIGHTS

The Dosage Forms and Strengths section of the Highlights portion of the PI was revised to include information on the new 74.5 mg capsule strength as shown below, reproduced from the annotated version of the PI:

--- **DOSAGE FORMS AND STRENGTHS** ---

CRESEMBA capsules: 74.5 mg of isavuconazonium sulfate (equivalent to 40 mg of isavuconazole), (b) (4) -186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole). (3)

The above information, including the equivalence statement, is verified to be accurate, and is acceptable. There are no other CMC relevant changes to the Highlights.

Section 3. Dosage Forms and Strengths

This section of the full prescribing information (FPI) was updated to include information on the new 74.5 mg capsule strength as shown below, reproduced from the annotated version of the PI:

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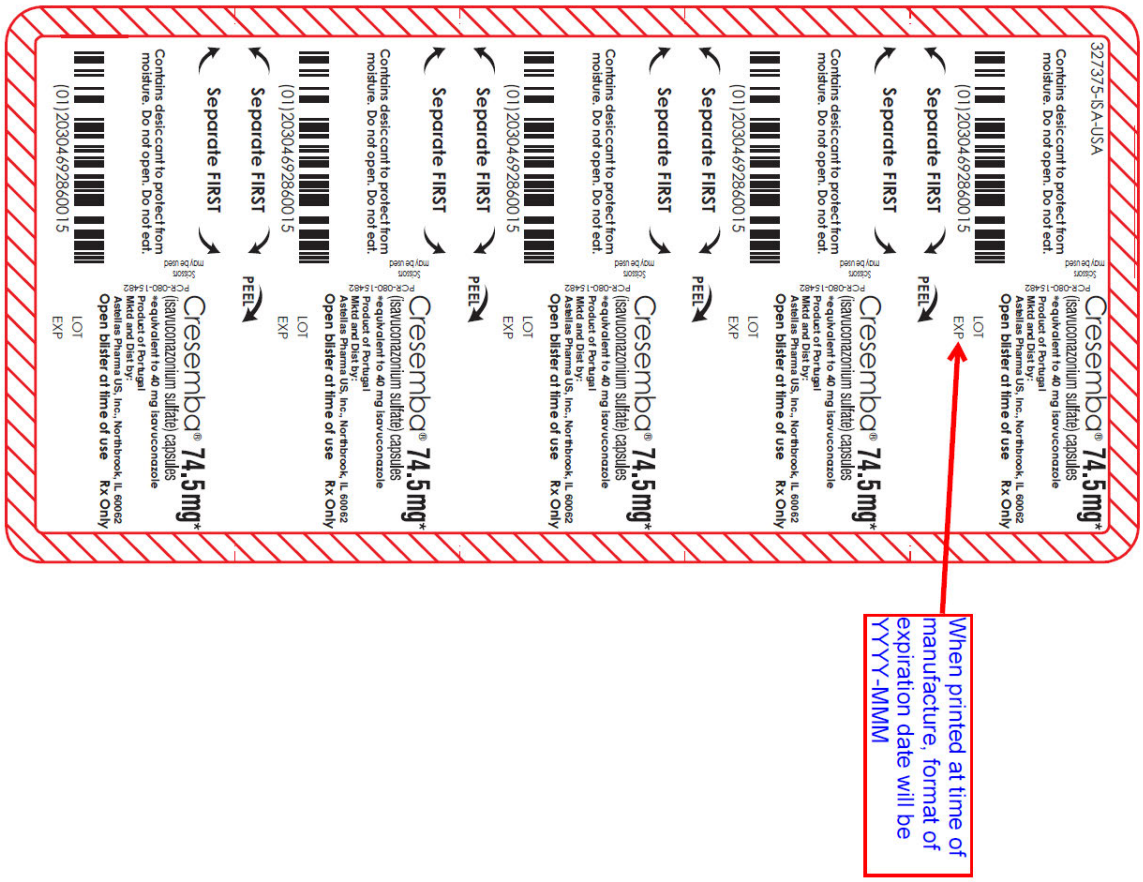
Container Label

Updated blister pack label was submitted on 01-NOV-2022 (eCTD 0127) in response to recommendations provided DMEPA. An image of the updated carton labeling is shown below.

Cresemba 74.5 mg Container Label (Blister Pack)



The updated blister label contains all necessary information such as product title, strength, equivalency information, manufacturer information and place holder for product lot number and expiry date. The updated blister label is adequate from a CMC perspective.

Overall Labeling Assessment: *Adequate*

The updated labeling (PI, PPI, and container and carton) provided to support the introduction of Cresemba (isavuconazonium sulfate) Capsules 74.5 mg is adequate from the product quality standpoint. It is noted that DMEPA reviewer found the updated container label and carton labeling acceptable from a medication error prevention perspective (DMEPA Memo: 2022-908-1 Cresemba (isavuconazonium sulfate) Label and Labeling Review NDAs 207500 and 207501 Memo.pdf; 02-NOV-2022).

Environmental Assessment

The applicant requested a categorical exclusion of the requirement to submit an environmental assessment with justification provided in Section 1.12.14. The anticipated drug substance

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Ramesh Gopalaswamy

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Date: 11/14/2022 09:25:09AM
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David Lewis

Digitally signed by David Lewis
Date: 11/14/2022 09:44:42AM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

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/s/

RAMESH N GOPALASWAMY
11/14/2022 10:40:04 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207500Orig1s013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Pharmaceutical Quality/Office of New Drug Products/Division of Biopharmaceutics **BIOPHARMACEUTICS REVIEW**			
Application No.:	NDA 207500-SUPPL-13, SDN# 694	**Primary Reviewer:** Payal Agarwal, Ph. D	
Submission Date:	July 28th, 2022		
Division:	Division of Biopharmaceutics	**Biopharmaceutics Lead/SPQA:** Elsbeth Chikhale, Ph. D	
Applicant:	Astellas Pharma US, Inc.	**Biopharmaceutics Branch Chief:** Angelica Dorantes, Ph. D	
Trade Name:	CRESEMBA® (isavuconazonium sulfate) Capsules	**Date Assigned:**	August 26th, 2022
Established Name:		**Date of Review:**	November 7th, 2022
Indication:	(b) (4)	**Type of Submission:** Prior Approval Supplement, CMC (New 74.5 mg Capsule Formulation and associated labeling changes to Prescribing Information)	
Formulation/ strengths	IR Capsules containing 186.3 mg of isavuconazonium sulfate corresponding to 100 mg of isavuconazole		
Route of Administration	Oral		
Type of Review:	Biopharmaceutics assessment		
Recommendation	**Adequate**		

SUMMARY:

Background:

Astellas Pharma US, Inc.'s, is seeking approval for a new capsule strength for Cresemba® (isavuconazonium sulfate), containing 74.5 mg isavuconazonium sulfate corresponding to 40 mg isavuconazole. Cresemba® hard capsules containing 186.3 mg isavuconazonium sulfate corresponding to 100 mg isavuconazole was approved on March 6, 2015, under NDA 207500.

This supplement (for Cresemba Capsules) is submitted along with an additional supplement NDA 207501/S-011 (for Cresemba IV) as these two products share the same prescribing information (PI). The new capsule formulation containing 74.5 mg isavuconazonium sulfate is proportionally similar to the currently approved formulation containing 186.3 mg isavuconazonium sulfate (Table 1). (b) (4)

(b) (4)

Table 1. Composition of Isavuconazonium Sulfate Hard Capsules

Components	Reference Quality Standard	Function	Quantity (mg/capsule)	
			100 mg isavuconazole	40 mg isavuconazole
Isavuconazonium sulfate	In house	Drug substance	186.3 (corresponding to 100 isavuconazole)	74.52 (corresponding to 40 isavuconazole)
Magnesium citrate	USP	(b) (4)		
Microcrystalline cellulose	NF			
Talc	USP			
Colloidal silicon dioxide	NF			
Stearic acid	NF			
Total filling weight (mg)			(b) (4)	
				(b) (4)
Total capsule weight (mg)			**695.9**	**281.76**

USP: United States Pharmacopeia, NF: National Formulary

Submission:

On July 28th, 2022, the Applicant submitted the NDA 207500-Supplement-13, as a CMC Prior Approval Supplement, to add a new dose strength 74.5 mg of isavuconazonium sulfate Capsule for the drug product.

Review:

The Applicant submitted dissolution profiles (Fig. 1) comparing the lots of isavuconazonium sulfate capsules 74.5 mg and 186.3 mg both of which were used in the BE Study (AK1820-102). In this dissolution comparison, dissolution test method and acceptance criterion (Table 2), which was previously approved for the 186.3 mg strength in NDA 207500, was used. The same dissolution method and acceptance criterion is also proposed for the new 74.5 mg strength capsules. The Applicant has referenced the justification for the proposed dissolution method and acceptance criterion for the new 74.5 mg strength from the original NDA 207500 (Module 3.2.P.5.6).

Table 2. Dissolution Method and Acceptance Criteria proposed by the Applicant

Strength	Apparatus	Rotation Speed (rpm)	Dissolution Medium/Volume	Acceptance criterion
74.5 mg	USP Type 2 (Paddle)	75	pH 6.0 diluted McIlaine buffer with 0.5% SLS / 900 mL	Q = (b) (4)% in 75 min

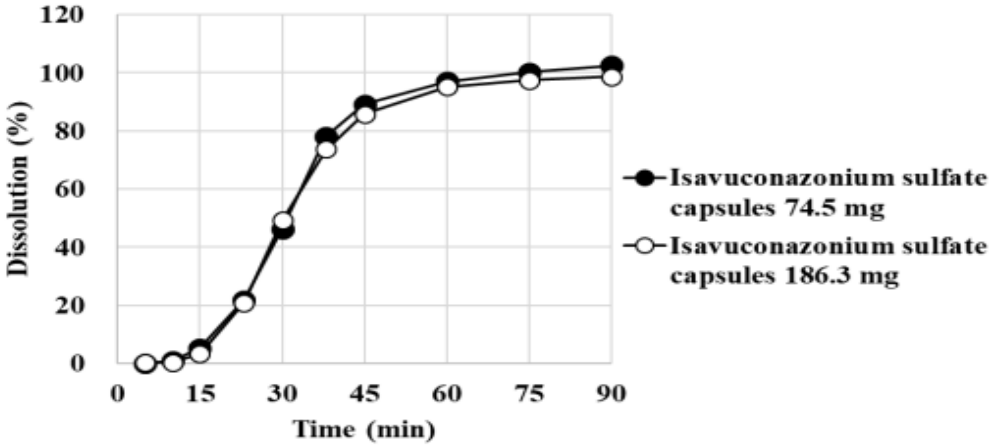

Fig. 1. Comparison of Dissolution Profiles Between Isavuconazonium Sulfate Capsules 74.5 mg and Isavuconazonium Sulfate Capsules 186.3 mg.
Dissolution Conditions: Apparatus 2, 75 rpm, 900 mL diluted McIlvaine buffer pH 6 with 0.5% sodium lauryl sulfate, 1 capsule/vessel, n=12

The Applicant's proposed dissolution method is acceptable for the new strength 74.5 mg; however, based on the provided dissolution data in Supplement-13 and in previous annual reports, the proposed acceptance criterion (Q = (b)(4)% in 75 min) was found too permissive. Therefore, the following dissolution acceptance criterion was recommended for both the already approved 186.3 mg and the proposed 74.5 mg Isavuconazonium Sulfate Capsules: Q=(b)(4)% at 60 minutes. FDA recommended the Applicant to update the drug product specifications and stability protocol accordingly through an Information Request sent on October 13th, 2022.

On October 20th, 2022, in response to the above Request for Information, the Applicant proposes to retain the current (Q = (b)(4)% in 75 min) dissolution acceptance criteria for both the approved 186.3 mg Isavuconazonium Sulfate Capsule and the proposed 74.5 mg Isavuconazonium Sulfate Capsule. The Applicant explains that two out of nine batches would proceed to stage 2 testing and the commercial batch of 186.3 mg capsules (Lot No. 089900118), and the clinical trial material batch of 74.5 mg capsules (Lot No. 091500218) used in the bioequivalence study (AK1820-102) would not meet the specification recommended by the Agency of Q=(b)(4)% at 60 minutes at stage 1 (Table 3). This justification is based on the safe space concept for a clinically relevant dissolution specification.

In addition, due to the availability of dissolution data at 60 minutes for a limited number of batches only, the Applicant has proposed to begin collecting dissolution data at the 60-minute time point for both strengths until data for at least 10 new batches of each strength are available. The Applicant will then submit the results to the Agency with a proposal to either retain the current specification or propose a reduction of the specification for each strength.

Table 3. Dissolution Data at 60 and 75 min of Commercial Isavuconazonium Sulfate Capsules 186.3 mg

Batch	Manufacturing date	%Dissolution Mean (Min – Max)	
		60 min	75 min
08740014 [1]	Jan 2014	95.6 (b) (4)	97.7 (b) (4)
08740024 [1]	Jan 2014	91.3 (b) (4)	94.4 (b) (4)
08740034 [1]	Feb 2014	94.7 (b) (4)	96.7 (b) (4)
08740015	May 2015	97.7 (b) (4)	99.3
08740025	May 2015	96.9 (b) (4)	98.3
087400420 [4]	Jan 2020	100.6 (b) (4)	102.2 (b) (4)
087401422	May 2022	104.4	103.3
087401522	May 2022	101.1	103.6
087401722	May 2022	104.1	100.9

[1] PV batch
[2] Would not pass Q (b) (4)% at 60 minutes at Stage 1
[3] Met the criteria of Q (b) (4)% at 75 minutes at Stage 2
[4] This batch (packaged product batch No. W057780) is used for 2020 annual stability

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 207500 Suppl-13 for Cresemba® (isavuconazonium sulfate) Capsules is recommended for **APPROVAL**.

Biopharmaceutics Assessment:

Isavuconazonium sulfate (BAL8557) is a water-soluble prodrug triazole that was approved for the treatment of adults with severe, (b) (4) (invasive aspergillosis and mucormycosis). It can be administered parenterally as intravenous infusion and orally as hard gelatin capsules.

The prodrug (isavuconazonium sulfate, BAL8557) is considered as a BCS Class-1 compound. The drug substance is highly soluble (>1.0 g/mL) in aqueous media across the pH range of 1-7. The active moiety (isavuconazole, BAL4815) is highly permeable; the mean absolute bioavailability of isavuconazole after a single oral dose of isavuconazonium sulfate hard capsules (equivalent to 400 mg isavuconazole) was found to be approximately 98%, demonstrating complete absorption; with no food effect (NDA 207500, Module 2.7.1) and no gastric pH effect (NDA 207500, Module 2.7.2).

(b) (4)

The Applicant evaluated the *in vivo* performance of isavuconazonium sulfate capsules 74.5 mg in a bioequivalence study (AK1820-102). In this study, bioequivalence between isavuconazonium sulfate capsules 74.5 mg and isavuconazonium sulfate capsules 186.3 mg at a dose of 200 mg as isavuconazole is claimed by the Applicant [Module 2.7.1.2.2]. The bioequivalence was demonstrated for isavuconazonium size 3 oral capsule containing dose strength 74.5 mg (proposed formulation) and the isavuconazonium size 0

oral capsule containing dose strength 186.3 mg (approved formulation) as per the Office of Clinical Pharmacology review (dated 11/4/2022).

The dissolution method shown in Table 2 above and the dissolution acceptance criterion which are already approved for isavuconazonium sulfate capsules 186.3 mg (NDA 207500) are also proposed for the new 74.5 mg strength isavuconazonium sulfate capsules.

The FDA's Guidance for Industry, 2018, titled "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dissolution-testing-and-acceptance-criteria-immediate-release-solid-oral-dosage-form-drug-products] establishes standard dissolution methodology and acceptance criteria to facilitate development and evaluation for drug products that meet the conditions outlined. As per the guidance, the possibility of using the dissolution method (in 500 mL of 0.1 N HCl using USP Apparatus 1 at 100 rpm or USP Apparatus 2 at 50 rpm) should in general be recommended for quality control of the proposed drug product, which contains a highly soluble drug substance. However, the Applicant has provided adequate justification for the selection of the proposed dissolution method and acceptance criterion in Module 3.2.P.5.6 of the original NDA submission under Justification of Specifications. Based on the dissolution method development, the most appropriate dissolution condition for this drug product is using USP Apparatus Type 2, at 75 rpm, in diluted McIlvaine buffer pH 6.0 with 0.5% SLS as the dissolution media. The Applicant was able to demonstrate the discriminating ability of the proposed dissolution method against disintegration of the capsule shell, which is the rate limiting step in the dissolution of isavuconazonium sulfate capsules.

The Applicant's proposed dissolution acceptance criterion is was found too permissive as demonstrated by the submitted dissolution profile (Fig 1). No additional dissolution test data is provided for 74.5 mg capsules. The Applicant accepted the FDA's recommended dissolution acceptance criterion of Q = (b) (4)% at 75 minutes in an amendment of the original NDA (Seq. 0017 dated 12/18/2014) based on the provided data by the Applicant during that time. However, based on all the annual reports submitted from 2014-2022 (Appendix I), dissolution data obtained for batch release and during stability studies for a registration batch (2048-11501 A) demonstrates that a dissolution acceptance criterion of Q = (b) (4) % at 60 min would be more appropriate. It should be noted that the setting of the dissolution acceptance criteria is based on mean values and therefore, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing. The dissolution data shows that the registration batch (2048-11501 A) used for stability study would pass the acceptance criterion of Q= (b) (4)% at 60 minutes. Therefore, FDA

recommended revising the dissolution acceptance criterion and update the drug product specifications and stability protocol accordingly through an information request. In response to the Information Request the Applicant proposes to retain the current dissolution acceptance criteria for both the approved 186.3 mg Isavuconazonium Sulfate Capsule and the proposed 74.5 mg capsules at this time. This justification is based on the safe space concept for a clinically relevant dissolution specification. Since the bioequivalence between the two capsule strengths has been established, the Applicant considers the change in acceptance criterion can raise the risk of batch failure. The Applicant has therefore proposed to begin collecting dissolution data at the 60-minute time point for both strengths until data for at least 10 new batches of each strength are available and submit it to the Agency for further review. The Applicant's justification and approach to collect more dissolution data on 10 additional batches of each strength is acceptable.

Packaging/ Handling Change

CRESEMBA® (isavuconazonium sulfate) 186 mg capsules were supplied as a 14-count carton (contains 2 individual aluminum blister packs of 7 capsules per sheet with desiccant) and 56-count carton (contains four 14-count cartons). In Supplement 13, the Applicant is removing the 56-count carton (contains four 14-count cartons). In addition, the 14-count carton containing 2 individual aluminum blister packs of 7 capsules per sheet will be child resistant.

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA# -SDN	207500 (SDN694), 207501 (SDN613)
Submission Date	07/28/2022
Drug Product	Cresemba® (isavuconazonium sulfate)
OCP Reviewer	Anthony Nicasio, PharmD
OCP Team Leader	Dakshina Chilukuri, PhD
OCP Division	DIDP
OND Division	DAI
Applicant	Astellas Pharma US INC
Formulation	Oral capsules and lyophilized powder for injection
Indication(s)	Treatment of invasive aspergillosis and invasive mucormycosis (b) (4)
Dosage	372 mg/day (equivalent to 200 mg/day isavuconazole) after a loading dose of 372 mg every 8 hours

1. Background

The Applicant submitted a prior approval supplement with a proposed update to prescribing information and a final study report of an *in vivo* bioequivalence phase 1 study in healthy subjects. In the phase 1 study, bioequivalence was assessed with a single dose of a new (size 3) oral capsule containing a dose strength of isavuconazonium sulfate 74.5 mg (equivalent to 40 mg of isavuconazole) and the approved size 0 oral capsule product containing a dose strength of isavuconazonium sulfate 186.3 mg (equivalent to 100 mg of isavuconazole) for oral administration. In this review, the Clinical Pharmacology review team has provided recommendations to both the *in vivo* bioequivalence study and the proposed changes to the label in this submission.

2. Summary of Clinical Pharmacology Information

The Applicant has provided results of an *in vivo* bioequivalence study (study # AK1820-102) entitled- "*Bioequivalence Study of Capsules Containing Different Strengths of AK1820*." Each healthy adult Japanese male was randomized to one of two treatment sequences per a randomization schedule prepared prior to the start of the crossover study. A washout period of at least 35 days was observed between the two periods. Subjects received a single dose of test formulation- a size 3 oral capsule containing isavuconazonium sulfate 74.5 mg (A) followed by a washout period then the standard formulation of size 0 oral capsule containing isavuconazonium sulfate 186.3 mg (B) or B followed by A. The dose orally administered to subjects were five capsules of test formulation (total dose of 372.5 mg) or two capsules of standard formulation (total dose of 372.6 mg) under fasted conditions. Serial blood samples were collected for isavuconazole pre-dose on Day 1 and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 24, 48, 72, 96, 168, 264, 408, 600, and 840 hours post-dose. Plasma samples of isavuconazole were analyzed using a validated HPLC with MS/MS method. The bioanalytical method validation report and sample analysis report for the quantitation of isavuconazole was found to be acceptable.

Plasma pharmacokinetics were evaluated in 68 subjects that received the standard formulation and 69 subjects that received the test formulation. Four subjects in total were rejected from the bioequivalence analysis set; three subjects were rejected due to only receiving one formulation of isavuconazonium and one subject exhibited carry-over effects (pre-dose non-zero baseline concentration is >5% of the C_{max}). Thus, bioequivalence was evaluated in 66 subjects (Group A- 33 subjects and Group B- 33 subjects) (**Figure 1**).

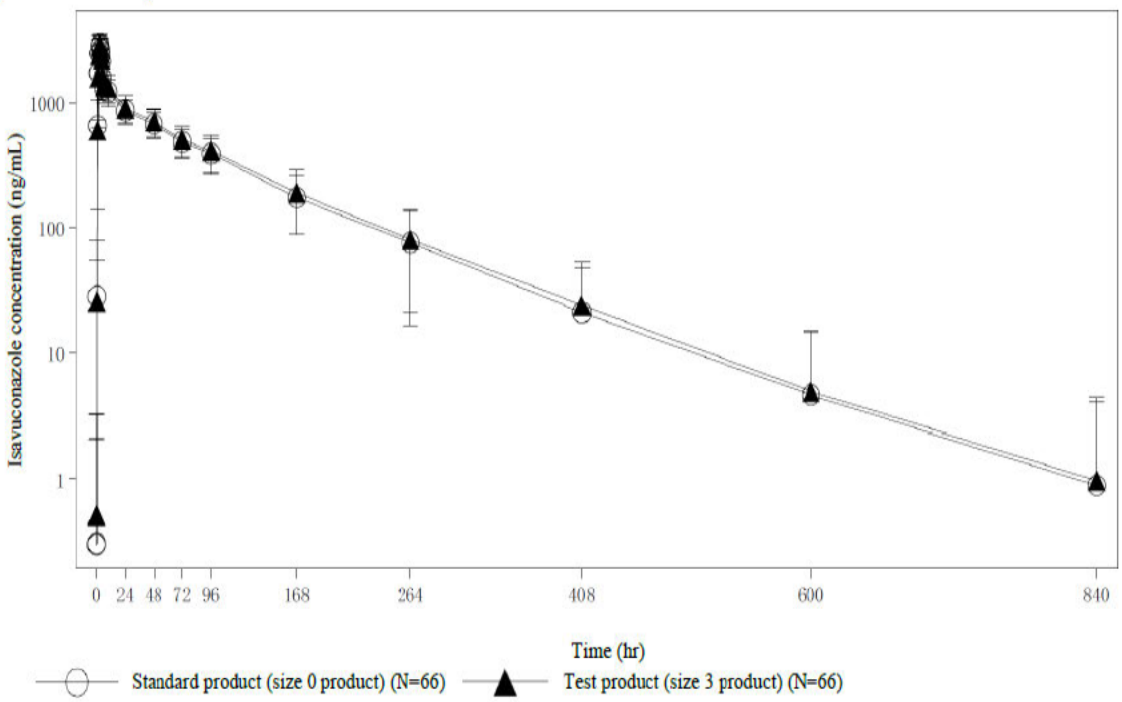
The 90% confidence intervals on the geometric mean test-to-reference ratios for $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and C_{max} were all contained within the 90% CI range of 80.00-125.00% for complete case subjects (**Table 1)**. Therefore, the test formulation has demonstrated to be bioequivalent to the reference formulation.

Table 1: Geometric Least Square Means and 90% Confidence Intervals for Isavuconazole

Statistical Assessement of Bioequivalence of Isavuconazonium Sulfate Size 3 Oral Capsule Containing Dose Strength 74.5 mg (Test Formulation) vs. Isavuconazonium Sulfate Size 0 Oral Capsules Containing Dose Strength 186.3 mg (Reference Formulation) Pharmacokinetic Analysis						
Fasted Bioequivalence Study (Study No. AK1820-102)						
Parameter	Test Formulation		Reference Formulation		Geo. LS Mean Ratio (%)	90% CI of Ratio
	Geo. LS Mean	N	Geo. LS Mean	N		
$AUC_{0\text{-last}}$ (ng*hr/mL)	113,736	66	108,648	66	104.68	101.55 – 107.91
AUC_{∞} (ng*hr/mL)	117,473	66	111,705	66	105.16	102.21 – 108.20
C_{max} (ng/mL)	3,224	66	3,228	66	99.86	95.74 – 104.17

CI: confidence interval; Geo. LS: geometric least-squares.
Source: Clinical Study Report AK1820-102, ADAM dataset (adpc xpt)

Figure 1: Semi-Log Scale Plot of Mean Plasma Concentration of Isavuconazole Oral Reference Formulation (size 0 product) and Test Formulation (size 3 product) Capsules vs. Time



Source: Clinical Study Report, Figure 11.4.2

3. Recommendations

In Study # AK1820-102, bioequivalence was demonstrated for isavuconazonium size 3 oral capsule containing dose strength 74.5 mg (proposed formulation) and the isavuconazonium size 0 oral capsule containing dose strength 186.3 mg (approved formulation). The clinical pharmacology information provided by the Applicant is found to be acceptable for the approval of this prior approval supplement.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207500Orig1s013

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 3, 2022
To:	Alison Rodgers Regulatory Project Manager **Division of Anti-Infectives (DAI)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL, NHDP-BC Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Application Type and Number/ Supplement Number/ Drug Name (established name)/ Dosage Form and Route:	NDA 207500/S-013 CRESEMBA (isavuconazonium sulfate) capsules, for oral use NDA 207501/S-011 CRESEMBA (isavuconazonium sulfate) for injection, for intravenous use
Applicant:	Astellas Pharma US, Inc.

1 INTRODUCTION

On July 28, 2022, Astellas Pharma US, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) - Chemistry, Manufacturing and Control for New Drug Application (NDA) 207500/S-013 CRESEMBA (isavuconazonium sulfate) capsules, for oral use, and NDA 207501/S-011 CRESEMBA (isavuconazonium sulfate) for injection, for intravenous use. The purpose of this PAS is to propose a new capsule formulation. CRESEMBA (isavuconazonium sulfate) is currently indicated for use in the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infectives (DAI) on September 21, 2022 and August 22, 2022, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for CRESEMBA (isavuconazonium sulfate) capsules, for oral use, and for injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft CRESEMBA (isavuconazonium sulfate) PPI received on July 28, 2022, and received by DMPP on October 27, 2022.
- Draft CRESEMBA (isavuconazonium sulfate) PPI received on July 28, 2022, and received by OPDP on October 27, 2022.
- Draft CRESEMBA (isavuconazonium sulfate) Prescribing Information (PI) received on July 28, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on October 27, 2022.
- Draft CRESEMBA (isavuconazonium sulfate) Prescribing Information (PI) received on July 28, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on October 27, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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NYEDRA W BOOKER
11/03/2022 10:07:23 AM

LASHAWN M GRIFFITHS
11/03/2022 10:35:55 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Memorandum:	October 24, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDAs 207500/S-013 and 207501/S-011
Product Name and Strength:	Cresemba (isavuconazonium sulfate) Capsules, 186 mg and 74.5 mg (proposed) Cresemba (isavuconazonium sulfate) for Injection, 372 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Astellas Pharma US, Inc. (Astellas)
FDA Received Date:	July 28, 2022
TTT ID #:	2022-908
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF REVIEW

Astellas submitted a Chemistry, Manufacturing, and Controls (CMC) Prior Approval Supplement (PAS) on July 28, 2022, proposing a new 74.5 mg capsule formulation, as well as updates to their prescribing information for Cresemba.[a,b] Subsequently, the Division of Anti-Infectives (DAI) requested that we review the proposed prescribing information (PI), container label, and carton labeling for Cresemba (Appendix A) to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 DISCUSSION AND CONCLUSION

Astellas proposes to introduce a 74.5 mg strength capsule of Cresemba to achieve the same recommended loading and maintenance dosage (i.e., 372 mg orally every 8 hours for 6 doses, followed by 372 mg once daily) as the currently marketed Cresemba capsule, 186 mg. The new lower strength capsule would result in more capsules needed to achieve the same single dose (five capsules *versus* two capsules). (b) (4)

[a] Cover Letter: Prior Approval Supplement: Chemistry Manufacturing and Control (New 74.5 mg Capsule Formulation and Proposed Updates to Prescribing Information for Cresemba (NDA 207500/S-013). Northbrook (IL): Astellas Pharma US, Inc.; 2022 JUL 28. Available at: \\CDSESUB1\EVSPROD\nda207500\0123\m1\us\12-cover-letters\cover-letter.pdf.

[b] Cover Letter: Prior Approval Supplement: Chemistry Manufacturing and Control (New 74.5 mg Capsule Formulation and Proposed Updates to Prescribing Information for Cresemba (NDA 207501/S-011). Northbrook (IL): Astellas Pharma US, Inc.; 2022 JUL 28. Available at: \\CDSESUB1\EVSPROD\nda207501\0122\m1\us\12-cover-letters\cover-letter.pdf.

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Thus, we ask that the Division takes the identified medication error concerns into consideration in determining the acceptability of introducing the new lower strength 74.5 mg capsule at this time. If the Division determines the new lower strength capsule is acceptable to be introduced at this time, the proposed PI, container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Astellas Pharma US, Inc.

4 RECOMMEDATIONS FOR DIVISION OF ANTI-INFECTIVES (DAI)

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 *Dosage and Administration*			
1.	As currently presented in subsection 2.2 *Dosage Regimen*, Table 1 *Dosage Regimen for CRESMBA*, the difference in capsule strengths (i.e., 186 mg and 74.5 mg) may be missed/overlooked when determining the appropriate dosing (i.e., loading dose and maintenance dose).	The difference in capsule strengths (i.e., 186 mg and 74.5 mg) in Table 1 *Dosage Regimen for CRESMBA* could be missed/ overlooked resulting in wrong dose medication errors.	To increase prominence regarding the difference in capsule strengths (i.e., 186 mg and 74.5 mg) we recommend including the capsule strengths (i.e., 186 mg and 74.5 mg) in bold font next to the text "CRESEMBA Capsules" for the appropriate rows in the first column of Table 1. For example (proposed revisions appear in red font within the screen shot below), **Table 1. Dosage Regimen for CRESEMBA** **CRESEMBA for Injection** 372 mg[2] of isavuconazonium sulfate per vial **CRESEMBA Capsules, 186 mg** 186 mg[3] of isavuconazonium sulfate per capsule **CRESEMBA Capsules, 74.5 mg** 74.5 mg[4] of isavuconazonium sulfate per capsule Additionally, to provide further clarity regarding the additional

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			proposed strength (i.e., 74.5 mg) and its corresponding dosage (i.e., loading dose and maintenance dose) of the oral formulation (i.e., capsules), we recommend within the second and third columns (i.e., "Loading Dose" and "Maintenance Dose", respectively) revising the text "2 capsules" to "Two 186 mg capsules" (b) (4) (b) (4)
Full Prescribing Information – Section 16 *How Supplied/Storage and Handling*			
1.	(b) (4)		To provide clarity and reduce the risk of deteriorated product medication errors, we recommend inclusion of the appropriate cross-references and nasogastric handling within the post-reconstitution and dilution storage and handling text of subsection 16.2. For example, "Following reconstitution of the lyophile

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)		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 [*see Dosage and Administration (2.3)*]. 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°C to 8°C (36°F to 46°F) prior to use [*see Dosage and Administration (2.4)*]. For nasogastric tube use, the reconstituted solution should be used within 1 hour of reconstitution [*see Dosage and Administration (2.5)*]."

5 RECOMMENDATIONS FOR ASTELLAS PHARMA US, INC.

Table 3. Identified Issues and Recommendations for Astellas Pharma US, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	(b) (4)	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if

Table 3. Identified Issues and Recommendations for Astellas Pharma US, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.
Carton Labeling			
1.	(b) (4)	The lot number statement is required on the carton labeling per 21 CFR 201.10(i)(1) and the product expiration date is also required on the carton labeling per 21 CFR 201.17. Additionally, clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the intended location of the lot number statement and expiration date on the carton labeling. When determining this placement, please ensure that there are no other numbers located in close proximity to the lot number or expiration date that can be mistaken as the lot number or expiration date. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use for the expiration date. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the

Table 3. Identified Issues and Recommendations for Astellas Pharma US, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a forward slash be used to separate the portions of the expiration date.
2.	(b) (4)	The Drug Supply Chain Security Act (DSCSA) requires manufacturers and re-packagers, respectively, to affix or imprint a product identifier to the smallest saleable unit (usually the carton) of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (July 2021).[e] Additionally, if the product identifier requirements apply to your product, we recommend you ensure there

[e] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 3. Identified Issues and Recommendations for Astellas Pharma US, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		a human-readable form and machine-readable (2D data matrix barcode) format.	is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Cresemba that Astellas Pharma US, Inc. submitted on July 28, 2022.

Table 4. Relevant Product Information for Cresemba		
Application	NDA 207500	NDA 207501
Initial Approval Date	March 6, 2015	
Active Ingredient	isavuconazonium sulfate	
Indication	For patients 18 years of age and older for the treatment of: • invasive aspergillosis • invasive mucormycosis	
Route of Administration	oral	intravenous nasogastric tube
Dosage Form	capsules	for injection
Strength	Proposed: 74.5 mg (equivalent to 40 mg of isavuconazole) 186 mg (equivalent to 100 mg of isavuconazole)	372 mg/vial (equivalent to 200 mg isavuconazole)
Dose and Frequency	Loading Dose: Proposed: Five 74.5 mg capsules orally every 8 hours for 6 doses (48 hours). Two 186 mg capsules (372 mg) orally every 8 hours for 6 doses (48 hours). Maintenance Dose (start maintenance doses 12 to 24 hours after the last loading dose): Proposed: Five 74.5 mg capsules (372 mg) orally once daily. Two 186 mg capsules (372 mg) orally once daily.	Loading Dose: 1 reconstituted vial (372 mg) intravenously every 8 hours for 6 doses (48 hours). Maintenance Dose (start maintenance doses 12 to 24 hours after the last loading dose): 1 reconstituted vial (372 mg) intravenously once daily.
How Supplied	Proposed: 74.5 mg: 35-count carton (contains seven individual aluminum child-resistant blister packs of 5 capsules per sheet with desiccant).	(b) (4)

	186 mg: 14-count carton (contains two individual aluminum child-resistant blister packs of 7 capsules per sheet with desiccant).	
Storage	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°C to 8°C (36°F to 46°F) in a refrigerator. CRESEMBA is a single-dose vial of unpreserved sterile lyophile.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 7, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, "Cresemba, "NDA 207500," and "NDA 207501." Our search identified thirteen previous reviews[f,g,h,i,j,k,l,m,n,o,p,q,r], and we considered our previous recommendations to see if they are applicable for this current review. We confirmed that our previous recommendations were implemented or are not applicable to this current review.

[f] Myers, D. Label and Labeling Review Memo for Cresemba (NDAs 207500/S-011 and 207201 (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 DEC 10. RCM No.: 2021-1729-2.
[g] Myers, D. Label and Labeling Review Memo for Cresemba (NDAs 207500/S-011 and 207201 (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 NOV 22. RCM No.: 2021-1729-1.
[h] Myers, D. Label and Labeling Review Memo for Cresemba (NDAs 207500/S-011 and 207201 (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 30. RCM No.: 2021-1729.
[i] Myers, D. Label and Labeling Review for Cresemba (NDAs 207500/S-008 and 207201 (b) (4) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 29. RCM No.: 2021-486.
[j] Shepard, J. Label and Labeling Review for Cresemba (NDAs 207500/S-002 and 207501/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 16. RCM No.: 2015-1744.
[k] Shepard, J. Postmarket Medication Error Memorandum for Cresemba (NDAs 207500 and 207501). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 26. RCM No.: 2015-2049.
[l] Sheppard J. Label and Labeling Memo for Cresemba (NDAs 207500 and 207501). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAY 27. RCM No.: 2014-1389-03 and 2014-1393-03.
[m] Sheppard J. Label and Labeling Memo for Cresemba (NDAs 207500 and 207501). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAR 18. RCM No.: 2014-1389-02 and 2014-1393-02.
[n] Sheppard J. Label and Labeling Memo for Cresemba (NDAs 207500 and 207501). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAR 04. RCM No.: 2014-1389-01 and 2014-1393-01.
[o] Sheppard J. Proprietary Name Memo for Cresemba (NDAs 207500 and 207501). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAR 01. RCM No.: 2015-44830 and 2015-44831.
[p] Sheppard J. Label and Labeling Review for Cresemba (NDAs 207500 and 207501). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JAN 21. RCM No.: 2014-1389 and 2014-1393.
[q] Winiarski A. Proprietary Name Memo for Cresemba (NDAs 207500 and 207501). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 AUG 22. RCM No.: 2014-25973 and 2014-25974.
[r] Winiarski A. Proprietary Name Review for Cresemba (INDs 072593 and 119307). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 APR 30. RCM No.: 2013-16658 and 2013-16659.

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

D.1 Methods

On September 22, 2022, we searched FAERS using the criteria in the table below and identified 113 cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the Cresemba capsule formulation *and* issues swallowing the capsules, as well as wrong formulation errors. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[s] We excluded 93 cases because they; did not involve the capsule formulation (i.e., involved Cresemba for Injection or formulation was not reported) (n=30), described inappropriate schedule of drug administration (n=37), wrong technique (e.g., "patient who had trouble opening the blister pack and has to use a tool" and insufficient information to determine the root cause (n=4), incorrect product storage (n=6), use for an unapproved indication (n=3), incorrect dose administration (n=4), wrong quantity dispensed error (n=3), poor quality drug product administered (n=2), drug prescribing error (n=2), and product quality packaging quantity issue (n=2).

Table 5. Criteria Used to Search FAERS

Initial FDA Receive Dates:	open
Product Name:	Cresemba
Drug Role:	Primary Suspect
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

D.2 Results

Our search identified 113 cases, of which 8 cases described medication errors relevant to difficulty swallowing Cresemba capsules for this review including: 4 cases describe patient difficulty/trouble in specifically swallowing the Cresemba capsules (one of these three cases specifically notes "trouble swallowing the medication because it was too large"), 3 cases describe patients who cannot swallow or experienced issues with swallowing; "cannot swallow" (n=1), "cannot swallow food or take whole pills/difficulty swallowing" (n=1), and "experienced issue of swallowing and to whom nurses were opening the capsule and administering" (n=1); however it is unclear if these cases are due to an inability to swallow anything or possibly difficulty swallowing this specific size capsule, and 1 case describes a pediatric patient that "did not like to swallow Cresemba capsules."

[s] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

Additionally, 9 cases described Cresemba capsule administration via a "tube" (e.g., unspecified feeding tube, nasogastric (NG) feeding tube, gastrostomy (G) tube, etc.); thus, resulting in wrong technique in drug usage process medication errors (i.e., FAERS case numbers; 13427097, 13956223, 14392305, 14626447, 16784854, 17550968, 17551025, 17551026, and 20601001); thus, resulting in wrong technique medication errors in drug usage process. We note that the current prescribing information[t] provides preparation instructions for administration of the Cresemba for injection formulation via the nasogastric tube. However, there are no labeled instructions for administering the capsule formulation via a tube (e.g., nasogastric). Instead, the prescribing information, patient information, and carton labeling state, "*Swallow CRESEMBA capsules whole. Do not chew, crush, dissolve, or open the capsules.*"

Furthermore, we note 4 cases described off-label use of Cresemba in pediatric patients, which is an inappropriate age for this product (i.e., indicated for patients 18 years of age and older) (FAERS case FAERS case # 12460250 involves a 2 year old patient, FAERS case # 14626485 involves a 16 year-old patient, # 16095578[u] pediatric patient – age not reported, and FAERS case # 19032696 involves a 4 year old patient).

See subsection D.3 *List of FAERS Case Numbers* for additional case details.

D.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case #	Manufacturer Control #	Initial FDA Received Date	Narrative	Assessment
11496532	US-ASTELLAS-2015US021592	9/11/2015	Information was received on 19-Jun-2015. This is a spontaneous case reported by a pharmacist referring to a patient (unspecified age and gender) who cannot swallow and was administered Cresemba (isavuconazonium sulfate) by opening the capsule (wrong technique in drug usage process). No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided.	Wrong technique in drug usage process Example of patient who cannot swallow and was administered Cresemba (isavuconazonium sulfate) by

[t] Cresemba [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. FEB 2022 [Cited 2022 SEP 28]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207500s011,207501s009lbl.pdf.

[u] Individual FAERS cases may describe multiple concerns. For example, FAERS case # 16095578 describes both possible difficulty swallowing the Cresemba capsules and off-label use of Cresemba in pediatric patients.

			The patient received isavuconazonium sulfate for an unknown indication according to the following dosage regimen(s): (start date not provided) - (stop date not provided): unknown route, formulation, unknown frequency. On an unspecified date the patient could not swallow and was administered isavuconazonium sulfate by opening the capsule (wrong technique in drug usage process). No lab test information was provided. Action taken with isavuconazole treatment was unknown. The outcome of patient who cannot swallow and was administered isavuconazonium sulfate by opening the capsule (wrong technique in drug usage process) was not reported. The pharmacist assessed the following events with respect to isavuconazonium sulfate: - Patient who cannot swallow and was administered Cresemba by opening the capsule (seriousness: Not reported; causality: Not Assessed) - Patient who cannot swallow and was administered Cresemba by opening the capsule (wrong technique in drug usage process) (seriousness: Not reported; causality: Not Assessed) No further information was available. On 10/Jul/2015, this case was found to be a duplicate of 2015US021647. All case information has been added to this case and 2015US021647 will be deleted from the database. Primary reporter was changed to pharmacist from nurse. Follow-up information received on 04-Aug-2015, which indicated that no further information was available.	opening the capsule.
12376509	US-ASTELLAS-2016US018905	5/17/2016	Information was received on 11-May-2016. This is a spontaneous case reported by a pharmacist referring to a male patient of an unspecified age who experienced difficulty in swallowing Cresemba (isavuconazonium sulfate) capsules and administered them by opening the capsules. (wrong technique in drug usage process). No other suspect medications were reported. Current condition included graft versus host disease; and procedure included status post transplant.	Wrong technique in drug usage process Example of patient who experienced difficulty in swallowing Cresemba (isavuconazonium sulfate)

			No concomitant medication information was provided. The patient received isavuconazonium sulfate for an unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): Oral route, dose and frequency unknown. On an unspecified date, the patient developed difficulty in swallowing the capsules of isavuconazonium sulfate and was admitted to the hospital on an unspecified date. The patient has been administered isavuconazonium sulfate by opening while at home. No lab test information was provided. The action taken with isavuconazonium sulfate treatment in response to primary event was unknown. The outcome of difficulty swallowing and isavuconazonium sulfate capsules administered by opening was not reported. The pharmacist assessed the following events with respect to isavuconazonium sulfate: - Difficulty swallowing (seriousness: Hospitalization; causality: Not Assessed) - Cresemba capsules administered by opening (seriousness: Not reported; causality: Not Assessed)	capsules and administered them by opening the capsules.
12460213	US-ASTELLAS-2016US021706	6/13/2016	Information was received on 03-Jun-2016 and 06-Jun-2016. This is a spontaneous case reported by a pharmacist referring to a female patient of an unspecified age who experienced trouble swallowing the medication during and opening Cresemba (isavuconazonium sulfate) and putting it in applesauce (wrong technique in drug usage process) during the treatment. No other suspect medications were reported. Current condition included anatomical issues of swallow before isavuconazonium sulfate; and historical condition included invasive aspergillosis. No concomitant medication information was provided. The patient received isavuconazonium sulfate for 6-8 weeks for an unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): oral, unknown dose (regular dose) and frequency. On an unspecified date, the patient had trouble swallowing the medication because it was large. The patient had been opening the trouble	Wrong technique in drug usage process Example of patient who experienced trouble swallowing the medication because it was too large. Subsequently, the capsules we opened and put in applesauce for administration.

			swallowing the medication and putting it in apple sauce. No lab test information was provided. The action taken with isavuconazonium sulfate treatment in response to trouble swallowing the medication was unknown. The outcome of opening isavuconazonium sulfate and putting it in applesauce was not reported and for trouble swallowing the medication was reported as not recovered/not resolved (ongoing). The pharmacist assessed the following events with respect to isavuconazonium sulfate: - Trouble swallowing the medication (seriousness: Not Reported; causality: Not Assessed) - Opening Cresemba and putting it in applesauce (seriousness: Not Reported; causality: Not Assessed) Follow up information received from pharmacist on 01-Jul-2016. Patient's gender, medical history, event (swallowing the medication) outcome, isavuconazonium sulfate route and case description were updated. No further information is available.	
12727964	US-ASTELLAS-2016US032370	9/9/2016	Information was received on 19-Aug-2016. This is a spontaneous case reported by a pharmacist referring to a 66 years-old female patient who experienced issue of swallowing and to whom nurses were opening the capsule and administering (wrong technique in product usage process) during Cresemba (isavuconazonium sulfate) treatment. No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): Unknown dose, route and frequency. On an unspecified date the patient had issue of swallowing. The pharmacist was unaware of what occurred that created this change since the patient had only been on his service for one day. The pharmacist reported that the nurses had been opening the capsule and administering against the recommendations.	Wrong technique in drug usage process Example of patient who experienced issue of swallowing and to whom nurses were opening the capsule and administering.

			No lab test information was provided. Action taken with isavuconazole treatment was unknown. The outcome of issue of swallowing and opening the capsule and administering was not reported. (b) (4) has been assigned to this case. The pharmacist assessed the following events with respect to isavuconazonium sulfate: - Issue of swallowing (seriousness: Not reported; causality: Not Assessed) - Opening the capsule and administering (seriousness: Not reported; causality: Not Assessed) Follow up information received on 23-Aug-2016. Product quality complaint (trackwise number) details updated.	
12727981	US-ASTELLAS-2016US029367	9/9/2016	Information was received on 28-Jul-2016. This is a spontaneous case reported by a male patient of unspecified age to whom Cresemba (isavuconazonium sulfate) makes little nauseous, who had bitter and awful taste, scaly skin on his ankles, opens isavuconazonium sulfate capsules and would sprinkle it on food and swallow (wrong technique in drug usage process) during isavuconazonium sulfate for a thrush infection treatment (off label use). No other suspect medications were reported. Current condition included throat cancer, cannot swallow food or take whole pills/ difficulty swallowing, tongue cancer, and thrush infection; allergy included different type of unspecified antibiotic; and procedure included throat dilated. No concomitant medication information was provided. The patient received isavuconazonium sulfate for thrush infection according to the following dosage regimens: 26-Jul-2016 (on the day of this report, it was his third day of treatment) - (stop date not provided): Unknown route, 2 DF, thrice daily. The patient was then to take 2 capsules once daily for 12 days. The patient was taking isavuconazonium sulfate for thrush infection. This was his third time to take it and he reported that it always worked fast for him. On an unspecified date isavuconazonium sulfate made him a little nauseous and he reported that it had bitter and awful taste. Due to swallowing difficulty he would open the isavuconazonium sulfate capsule and would	Wrong technique in drug usage process Example of patient who cannot swallow food or take whole pills/difficulty swallowing and who would open the isavuconazonium sulfate capsule and would sprinkle it on food and swallow.

			sprinkle it on food and swallow. He did not crush the beads in isavuconazonium sulfate capsules. On an unspecified date he had scaly skin on his ankles. No lab test information was provided. Action taken with isavuconazonium sulfate treatment in response to the event isavuconazonium sulfate makes little nauseous was unknown. The outcome of isavuconazonium sulfate makes little nauseous, bitter and awful taste, scaly skin on his ankles, opens isavuconazonium sulfate capsules and will sprinkle it on food and swallows and isavuconazonium sulfate for a thrush infection was not reported. The patient assessed the following events with respect to isavuconazonium sulfate: - Cresemba makes little nauseous (seriousness: Not reported; causality: Probable) - Bitter and awful taste (seriousness: Not reported; causality: Not Assessed) - Scaly skin on his ankles (seriousness: Not reported; causality: Not Assessed) - Opens Cresemba capsules and will sprinkle it on food and swallows (seriousness: Not reported; causality: Not Assessed) - Cresemba for a thrush infection (seriousness: Not reported; causality: Not Assessed)	
14626431	US-ASTELLAS-2017US054620	3/12/2018	Information was received on 14-Dec-2017. This is a spontaneous case reported by a pharmacist referring to a patient of an unspecified age and gender who cannot take Cresemba (isavuconazonium sulfate) capsules orally and now requires a nasogastric tube (wrong technique in product usage process) during Cresemba (isavuconazonium sulfate) treatment. No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): Unknown route, dose and frequency. On an unspecified date the patient was not able to take isavuconazonium sulfate capsules orally and now requires a nasogastric tube.	Example of patient who was not able to take isavuconazonium sulfate capsules orally and now requires a nasogastric tube.

			No lab test information was provided. Action taken with isavuconazonium sulfate in response to the event was unknown. The outcome of cannot take isavuconazonium sulfate capsules orally was not reported. The pharmacist assessed the following events with respect to isavuconazonium sulfate: - Cannot take Cresemba capsules orally (seriousness: Not reported; causality: Not Assessed) - Cresemba capsules now requires a nasogastric tube (seriousness: Not reported; causality: Not Assessed)	
16095578*	US-ASTELLAS-2018US046190	3/20/2019	Information was received on 24-Oct-2018. This is a spontaneous case reported by a pharmacist referring to a Pediatric patient of unknown age that did not like to swallow cresemba capsules (Product administered to patient of inappropriate age) during Cresemba (isavuconazonium sulfate) treatment. No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for an unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): Oral, unknown dose and frequency. The patient received isavuconazonium sulfate for an unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): intravenous, unknown dose and frequency. On an unspecified date, patient was given oral isavuconazonium sulfate for a loading dose but did not like it and was switched to the IV formulation of isavuconazonium sulfate. No lab test information was provided. Action taken with isavuconazonium sulfate treatment was not applicable. The Pharmacist assessed the following event with respect to isavuconazonium sulfate: - Pediatric patient that did not like to swallow cresemba capsules (seriousness: Not reported; causality: Not Assessed) No additional information was available.	Off-label use of Cresemba in pediatric patients Example of a pediatric patient of unknown age receiving Cresemba capsules. Also, example of a pediatric patient that did not like to swallow Cresemba capsules; however, unclear if this is due to difficulty swallowing this size capsule.

			Revision to information entered in the database in a prior case version: Upon review on 28-Nov-2018, the following was revised: Preferred Term coding for event of 'pediatric patient that did not like to swallow Cresemba capsules' was updated.	
17550969	US-ASTELLAS-2020US002440	3/17/2020	Information was received on 17-Jan-2020. This is a spontaneous case reported by a consumer referring to a 90 year-old male patient who experienced difficulty swallowing the Cresemba (isavuconazonium sulfate) capsules and opening the capsules during administration (wrong technique in drug usage process). No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for fungal infection according to the following dosage regimen: 10-Jan-2020 (also reported as a week ago) - (ongoing): Oral 372 mg, once daily. On an unknown date in Jan-2020 (reported as since initiation), the patient had difficulty swallowing the isavuconazonium sulfate capsules and started opening the capsules during administration. Action taken with isavuconazonium sulfate treatment in response to events was no change. The outcome of difficulty swallowing the Cresemba capsules was not reported. The consumer assessed the following events with respect to isavuconazonium sulfate: - Difficulty swallowing the Cresemba capsules (seriousness: Not Reported; causality: Not Assessed) - Opening the capsules during administration (seriousness: Not Reported; causality: Not Assessed) No additional information was available.	Wrong technique in drug usage process Example of patient who experienced difficulty swallowing the isavuconazonium sulfate capsules and started opening the capsules during administration.
13427097	US-ASTELLAS-2017US013605	4/11/2017	Information was received on 04-Apr-2017. This is a spontaneous case reported by a pharmacist referring to a male patient of unspecified age who was aspirating during Cresemba (isavuconazonium sulfate) treatment administered via the feeding tube (wrong technique in product usage process). No other suspect medications were reported. No medical history was provided.	Cresemba capsule formulation being administered via tubes; thus resulting in wrong formulation and wrong technique in

			No concomitant medication information was provided. The patient received isavuconazonium sulfate for an unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): intravenous route, unknown dose and frequency and 17-Mar-2017 - (stop date not provided): Unknown route, 372 mg, once daily. The patient had been receiving isavuconazonium sulfate via IV administration, but was switched to isavuconazonium sulfate capsules. Since, the patient had been aspirating, the capsules had been administered via the feeding tube since 17-Mar-2017. No lab test information was provided. Action taken with isavuconazonium sulfate treatment in response to event aspirating was unknown. The outcome of aspirating was not reported. The pharmacist assessed the following events with respect to isavuconazonium sulfate treatment: - Aspirating (seriousness: Not Reported; causality: Not Assessed) - Cresemba administered via the feeding tube (seriousness: Not Reported; causality: Not Assessed)	drug usage process Example of capsule formulation being administered via a feeding tube.
13956223	US-ASTELLAS-2017US023677	9/11/2017	Information was received on 13-Jun-2017. This is a spontaneous case reported by other health professional referring to a patient of unknown gender and age who opened Cresemba (isavuconazonium sulfate) capsules and administered via J-tube (wrong technique in product usage process) during treatment. No other suspect medications were reported. Procedure included J-tube insertion. No concomitant medication information was provided. The patient received isavuconazonium sulfate for unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): Unknown route, dose and frequency. On an unspecified date, the isavuconazonium sulfate capsules were opened and administered via J-tube to the patient. No lab test information was provided.	Cresemba capsule formulation being administered via tubes; thus resulting in wrong formulation and wrong technique in drug usage process Example of Cresemba capsules being administered via J-tube.

			Action taken with isavuconazonium sulfate treatment in response to event was unknown The other health professional assessed the following event with respect to isavuconazonium sulfate: - Opened Cresemba capsules and administered via J-tube (seriousness: Not Reported; causality: Not Assessed)	
14392305	US-ASTELLAS-2018US001624	1/16/2018	Information was received on 08-Jan-2018. This is a spontaneous case reported by a physician via case manager referring to 72 years-old male patient who received Cresemba (isavuconazonium sulfate) by g-tube (wrong technique in product usage process) and later by patient's wife that patient died during isavuconazonium sulfate treatment. No other suspect medications were reported. Current condition included comatose. No concomitant medication information was provided. The patient received isavuconazonium sulfate for aspergillosis according to the following dosage regimen: On an unspecified date in 2017 - (stop date not provided): Oral 372 mg, once daily. The patient was in comatose prior to isavuconazonium sulfate which did not improve or worsen after the treatment. It was reported that, the patient was receiving isavuconazonium sulfate by g-tube. On (b) (6) patient died due to unknown reason. Death certificate was not provided. It was unknown if autopsy was performed. No lab test information was provided. Action taken with isavuconazonium sulfate treatment in response to the event deceased was not applicable. The physician assessed the following event with respect to isavuconazonium sulfate: - Receiving Cresemba by g-tube (seriousness: Not reported; causality: Not Assessed) The patient's wife assessed the following event with respect to isavuconazonium sulfate: - Deceased (seriousness: Death; causality: Not Assessed) No additional information was available. Follow up information received on 12-Jan-2018 from physician via case manager. New event (Receiving Cresemba by g-tube) was added.	Cresemba capsule formulation being administered via tubes; thus resulting in wrong formulation and wrong technique in drug usage process Example of patient who received Cresemba capsules being administered by g-tube.

			Follow up information received on 14-Feb-2018 from physician via case manager. Event (comatose) was deleted and added under medical history. Follow up information received from patient's wife on 20-Mar-2018. New event (deceased), death details added and isavuconazonium sulfate dose updated and event (taking one 186 milligram capsules once daily) was deleted.	
14626447	US-ASTELLAS-2018US002246	3/12/2018	Information was received on 10-Jan-2018. This is a spontaneous case reported by other health professional referring to a 70 years-old male patient who was given Cresemba (isavuconazonium sulfate) capsules by opening and giving it via the feeding tube (wrong technique in product usage process). No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for unknown indication according to the following dosage regimen: (start date not provided) - (ongoing): Unknown dose, route and frequency. It was reported that the patient was on the feeding tube and the caregiver had been opening the isavuconazonium sulfate capsules and giving it via the feeding tube. No lab test information was provided. Action taken with isavuconazole treatment was no change. The other health professional assessed the following event with respect to isavuconazonium sulfate: - Opening the Cresemba capsules and giving it via the feeding tube (wrong technique in product usage process) (seriousness: Not reported; causality: Not Assessed)	Cresemba capsule formulation being administered via tubes; thus resulting in wrong formulation and wrong technique in drug usage process Example of a patient with a feeding tube and the caregiver had been opening the Cresemba capsules and giving it via the feeding tube.
16784854	US-ASTELLAS-2019US033019	9/9/2019	Information was received on 12-Aug-2019. This is a spontaneous case reported by a pharmacist referring to a 72 years-old male patient who experienced acute hypercapnic and hypoxic respiratory failure, capsule was opened and administered via nasogastric feeding tube (incorrect route of product administration and wrong technique in product usage process) during Cresemba (isavuconazonium sulfate) treatment. No other suspect medications were reported.	Cresemba capsule formulation being administered via tubes; thus resulting in wrong formulation and wrong technique in

			Current conditions included respiratory failure, rheumatoid arthritis, multiple myeloma, clostridium difficlle diarrhea and EKG QTc 551msec; and historical drugs included leflunomide and prednisolone. Concomitant medications included amiodarone, azithromycin, ceftriaxone, cyanocobalamin, fentanyl, filgrastim, furosemide, hydrocortisone, ipratropium, melatonin, methylprednisolone, metoprolol, metronidazole, micafungin, ascorbic acid, calcium pantothenate, ergocalciferol, nicotinamide, pyridoxine hydrochloride, retinol, riboflavin, thiamine hydrochloride, norepinephrine, pantoprazole, prednisolone, propofol, and rosuvastatin. Additional concomitant medications exist - please refer to the case for details. The patient received isavuconazonium sulfate for aspergillus fumigatus PNA (pneumonia) according to the following dosage regimens (b) (6) Nasogastric route, 372 mg, every 8 hours and (b) (6): Oral 372 mg, once daily. On (b) (6) the patient was intubated and was receiving isavuconazonium sulfate via nasogastric feeding tube. The reporter confirmed that patient had received one (372mg) dose. The isavuconazonium sulfate capsule was opened and administered via the patient's feeding tube. He received the loading dose intravenously. The patient had multiple molds growing and was in a bad way. The reporter inquired if we had any additional data to support isavuconazonium sulfate being administered via nasogastric feeding tube. On an unspecified date in (b) (6) the patient didn't effect the peak/trough levels. On (b) (6) the patient developed recurrence of acute hypercapnic and hypoxic respiratory failure. On (b) (6) the patient died due to acute hypercapnic and hypoxic respiratory failure. It was unknown if an autopsy was performed. Lab data included: (b) (6): BAL and Bronch wash: Cultures grew Aspergillus fumigatus, Aspergillus niger (b) (6): Cytology: Cytology shows rare septated fungal hyphae consistent with Aspergillus (b) (6): EKG:QTc 551 msec Action taken isavuconazonium sulfate was not applicable.	drug usage process Example of Cresemba capsule being opened and administered via nasogastric feeding tube.

			The outcome of acute hypercapnic and hypoxic respiratory failure (respiratory failure) was reported as fatal. The pharmacist assessed the following events with respect to isavuconazonium sulfate: - Acute hypercapnic and hypoxic respiratory failure (seriousness: Serious (Death); causality: Not Assessed) - Capsule was opened and administered via nasogastric feeding tube (Incorrect route of product administration) (seriousness: Not Reported; causality: Not Assessed) - Capsule was opened and administered via nasogastric feeding tube (Wrong technique in product usage process) (seriousness: Not Reported; causality: Not Assessed) Follow-up information was received on 04-Sep-2019 from pharmacist: Added event patient expired. Updated medical history, isavuconazonium sulfate therapy details, death details, and narrative description. Follow-up information was received from pharmacist on 07-Dec-2019. Event of death was updated to acute hypercapnic and hypoxic respiratory failure and medical history, concomitant medication, isavuconazonium sulfate dosage regimen, death date and lab data was updated.	
17550968	US-ASTELLAS-2019US009649	3/17/2020	Information was received on 08-Mar-2019. This is a spontaneous case reported by a pharmacist referring to a 36 years-old male patient for whom the nurse staff opened the capsules of Cresemba (isavuconazonium sulfate) and flushed the content in the G-tube (wrong technique in product usage process). No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for an unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): Unknown route, 372 mg, once daily. It was reported that the nursing staff opened the capsules and flushed the content in the G-tube for the patient which was a wrong technique in product usage. The physician escalated to the	Cresemba capsule formulation being administered via tubes; thus resulting in wrong formulation and wrong technique in drug usage process Example of a nurse who opened the capsules of Cresemba and flushed the content in the G-tube.

			pharmacist to inquire for information on the alternative method for administration. No lab test information was provided. Action take with isavuconazonium sulfate treatment in response to the event was unknown. The pharmacist assessed the following event with respect to isavuconazonium sulfate: - Opened the capsules and flushed the content in the G-tube (seriousness: Not Reported; causality: Not Assessed).	
17551025	US-ASTELLAS-2019US040079	3/17/2020	Information was received on 07-Oct-2019. This is a spontaneous case reported by other health professional (pharmacy student) referring to a male patient of an unknown age who was opening Cresemba (isavuconazonium sulfate) capsules and administering via G-tube (wrong technique in drug usage process) during treatment. No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for an unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): Unknown route, dose and frequency. Since an unspecified date, the patient had been receiving isavuconazonium sulfate capsules through a G-tube while in another facility. Reporter stated that, the patient was opening isavuconazonium sulfate capsules and administering via G-tube prior to the patient being admitted upon transfer to his facility which was assessed as wrong technique in drug usage process. No lab test information was provided. Action taken with isavuconazonium sulfate treatment in response to the event was unknown. The pharmacy student assessed the following event with respect to isavuconazonium sulfate: - Opening CRESEMBA capsules and administering via G-tube (seriousness: Not Reported; causality: Not Assessed)	Cresemba capsule formulation being administered via tubes; thus resulting in wrong formulation and wrong technique in drug usage process Example of a patient who was opening Cresemba capsules and administering via G-tube.
17551026	US-ASTELLAS-2019US050344	3/17/2020	Information was received on 16-Dec-2019. This is a spontaneous case reported by a pharmacist referring to an adult female patient who received Cresemba (isavuconazonium sulfate) capsules for prophylaxis post-transplant (product use in	Cresemba capsule formulation being administered

			unapproved indication) and capsules were being opened and administered to the patient via gastric tube (incorrect route of product administration and wrong technique in product usage process) during treatment. No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for prophylaxis post-transplant according to the following dosage regimen (b) (6) (started (b) (6) days ago) - (ongoing): unknown route, dose and frequency. It was reported that, in (b) (6) isavuconazonium sulfate capsules were used for prophylaxis post-transplant which was product use in unapproved indication. The pharmacist reported that the isavuconazonium sulfate capsules were being opened and administered to the patient via gastric tube which was incorrect route of product administration and wrong technique in product usage process. The pharmacist also stated that her institute had not opened any isavuconazonium sulfate capsules to date also mentioned that she did not have any specific details from the previous institution. No lab test information was provided. Action taken with isavuconazole treatment in response to the events was not applicable, however it was ongoing at the time of report. The pharmacist assessed the following events with respect to isavuconazonium sulfate: - Cresemba capsules used for prophylaxis post-transplant (product use in unapproved indication) (seriousness: Not Reported; causality: Not Assessed) - Capsules were being opened and administered to the patient via gastric tube (incorrect route of product administration) (seriousness: Not Reported; causality: Not Assessed) - Capsules were being opened and administered to the patient via gastric tube (wrong technique in product usage process) (seriousness: Not Reported; causality: Not Assessed)	via tubes; thus resulting in wrong formulation and wrong technique in drug usage process Example of a patient receiving Cresemba capsules that were being opened and administered to the patient via gastric tube.
20601001	US-ASTELLAS-2021US041758	3/16/2022	Information was received on 28-Oct-2021. This is a spontaneous case reported by a Pharmacist referring to a 39 years-old female patient who received Cresemba (isavuconazonium sulfate)	Cresemba capsule formulation being

			capsules through a feeding tube for diagnosis of elevated galactomannan/received isavuconazonium sulfate intravenously and then changed the capsules administered (Incorrect route of product administration) during isavuconazonium sulfate treatment. No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for elevated galactomannan according to the following dosage regimen: (start date not provided) - (stop date not provided): intravenous, unknown dose and frequency. The patient was received isavuconazonium sulfate capsules through a feeding tube for diagnosis of elevated galactomannan. The pharmacist reported that the patient received isavuconazonium sulfate intravenously and then changed the capsules administered through a feeding tube. No lab test information was provided. Action taken with the isavuconazonium sulfate treatment was unknown. The Pharmacist assessed the following event with respect to isavuconazonium sulfate: - Cresemba capsules through a feeding tube for diagnosis of elevated galactomannan/received Cresemba intravenously and then changed the capsules administered (Incorrect route of product administration) (seriousness: Not Reported; causality: Not Assessed).	administered via tubes; thus resulting in wrong formulation and wrong technique in drug usage process Example of patient receiving Cresemba capsules through a feeding tube.
12460250	US-ASTELLAS-2016US013605	6/13/2016	Information was received on 07-Apr-2016. This is a spontaneous case reported by a pharmacist referring to a 2 years-old female patient who was receiving Cresemba (isavuconazonium sulfate) (drug administered to patient of inappropriate age) during isavuconazonium sulfate treatment. No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for an unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): Unknown route, dose and frequency.	Off-label use of Cresemba in pediatric patients Example of a 2 years-old female patient who was receiving Cresemba (isavuconazonium sulfate).

			On an unspecified date the 2 year old patient was using isavuconazonium sulfate. Pharmacist reported that patient was doing well and they were monitoring her levels. No lab test information was provided. Action taken with isavuconazonium sulfate treatment was unknown. The outcome of using isavuconazonium sulfate in a 2 year old patient was not reported. The pharmacist assessed the following event with respect to isavuconazole: - Using cresemba in a 2 year old patient (seriousness: Not reported; causality: Not Assessed)	
14626485	US-ASTELLAS-2018US010245	3/12/2018	Information was received on 26-Feb-2018. This is a spontaneous case reported by a pharmacist referring to a 16 years-old female patient who was receiving Cresemba (isavuconazonium sulfate) treatment (off label use and drug administered to patient of inappropriate age). No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazonium sulfate for an unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): unknown dose, route and frequency. The 16 year old female patient was receiving isavuconazonium sulfate and did not report any adverse reactions. No lab test information was provided. Action taken with isavuconazonium sulfate treatment in response to the event was not applicable. The pharmacist assessed the following events with respect to isavuconazonium sulfate: - 16 year old female patient is receiving Cresemba (off label use) (seriousness: Not reported; causality: Not Assessed) - 16 year old female patient is receiving Cresemba (drug administered to patient of inappropriate age) (seriousness: Not reported; causality: Not Assessed)	Off-label use of Cresemba in pediatric patients Example of a 16 year old female patient is receiving Cresemba
19032696	US-ASTELLAS-	3/19/2021	Information was received on 25-Mar-2020. This is a spontaneous case reported by an other healthcare professional referring to a 4 years-old	Off-label use of Cresemba in

	2020US01 1352		patient of unspecified gender who had been receiving intravenous (IV) Cresemba (isavuconazole sulfate) (product use issue) treatment. No other suspect medications were reported. No medical history was provided. No concomitant medication information was provided. The patient received isavuconazole sulfate for an unknown indication according to the following dosage regimen: (start date not provided) - (stop date not provided): intravenously, unknown dose and frequency. On an unspecified date, 4 year old pediatric patient had been receiving intravenous isavuconazole sulfate in the hospital for an unknown indication (no further details are know by the caller). The hospital would like to send the patient home and would like the caller's home infusion pharmacy to manage the patient's isavuconazole sulfate. Reporter was not aware of any specific adverse event. Further stated, the patient should be getting their first home dose today (26-Mar-2020). No lab test information was provided. Action taken with isavuconazole sulfate treatment was not applicable. The other healthcare professional assessed the following event with respect to isavuconazole: - 4 year old pediatric patient has been receiving IV Cresemba (seriousness: Not Reported; causality: Not Assessed) Follow up information was received on 26-Mar-2020: Updated narrative. On 08-Apr-2020, upon internal review, event (4 year old pediatric patient has been receiving IV Cresemba) coding updated.	pediatric patients Example of a 4 years-old patient is receiving Cresemba.

* Individual FAERS cases may describe multiple concerns. For example, FAERS case # 16095578 describes both possible difficulty swallowing the Cresemba capsules and off-label use of Cresemba in pediatric patients.

D.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of

Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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/s/

DEBORAH E MYERS
10/24/2022 04:30:29 PM

VALERIE S VAUGHAN
10/24/2022 04:32:41 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207500Orig1s013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 3, 2022

To: Alison Rodgers, Regulatory Project Manager
Division of Anti-Infectives (DAI)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for CRESEMBA (isavuconazonium sulfate) capsules, for oral use; CRESEMBA (isavuconazonium sulfate) for injection, for intravenous use

NDA: 207500/S-013; 207501/S-011

Background:

In response to DAI's consult request dated August 22, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for supplement S-013 and S-011 for CRESEMBA. This supplement is to propose a new capsule formulation.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on October 27, 2022, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on November 3, 2022.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on November 1, 2022 (in response to DMEPA's comments) and emailed to OPDP on November 2, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov .

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/s/

WENDY R LUBARSKY
11/03/2022 03:01:53 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 2, 2022
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDAs 207500/S-013 and 207501/S-011
Product Name and Strength:	Cresemba (isavuconazonium sulfate) Capsules, 186 mg and 74.5 mg (proposed) Cresemba (isavuconazonium sulfate) for Injection, 372 mg/vial
Applicant/Sponsor Name:	Astellas Pharma US, Inc. (Astellas)
TTT ID #:	2022-908-1
DMEPA 1 Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 1, 2022 for Cresemba. The Division of Anti-Infectives (DAI) requested that we review the revised container label and carton labeling for Cresemba (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Myers, D. Label and Labeling Review for Cresemba (NDAs 207500/S-013 and 207501/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 24. RCM No.: 2022-908.

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DEBORAH E MYERS
11/02/2022 04:00:23 PM

VALERIE S VAUGHAN
11/02/2022 04:52:33 PM

NDA 207500/S-013
NDA 207501/S-011

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Astellas Pharma US Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

We have received your supplemental new drug applications (sNDAs) dated July 28, 2022, received July 28, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for Cresemba (isavuconazonum sulfate) capsules, 186 mg (NDA 207500\S-013) and Cresemba (isavuconazonium sulfate) for injection, 372 mg (NDA 207501\S-011).

These supplemental applications provide for information in support of a new capsule strength (74.5 mg isavuconazonium sulfate) and includes the final study report and associated datasets for a phase 1 bioequivalence study.

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on September 26, 2022, in accordance with 21 CFR 314.101(a).

If the applications are filed, the user fee goal date will be November 28, 2022.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.[1] Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

If you have questions, call Alison Rodgers, Regulatory Project Manager, at 301-796-0797.

Sincerely,

{See appended electronic signature page}

Gregory DiBernardo
Chief, Regulatory Project Management Staff
Anti-Infectives Group 2
Division of Regulatory Operations
for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

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/s/

GREGORY F DIBERNARDO
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