For first-line treatment of invasive aspergillosis and invasive mucormycosis in adults

Dosing & administration guide

INDICATIONS AND USAGE

CRESEMBA® (isavuconazonium sulfate) is an azole antifungal indicated for patients 18 years of age and older for the treatment of **invasive aspergillosis and invasive mucormycosis**.

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.

IMPORTANT SAFETY INFORMATION

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

Please see additional Important Safety Information throughout brochure. Click here for full Prescribing Information for CRESEMBA.

CRESEMBA®
(isavuconazonium sulfate)
372 mg for injection • 186 mg capsules

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Dosage formulations and strengths[1]

CRESEMBA® (isavuconazonium sulfate) for injection

- CRESEMBA for injection is supplied in a single-dose vial as a sterile lyophilized white to yellow powder
- Each single-dose vial of CRESEMBA for injection contains 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole)
- Store CRESEMBA for injection unreconstituted vials at 2° to 8°C (36° to 46°F) in a refrigerator

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS (CONTINUED)

- 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
- CRESEMBA shortened the QTc interval in a concentration-related manner. CRESEMBA is contraindicated in patients with familial short QT syndrome

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CRESEMBA capsules

Capsules not actual size.

- Each CRESEMBA capsule contains 186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole)
- Capsules are opaque and elongated, and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink
- Available in aluminum blister packs, 7 capsules per sheet with desiccant; 2 sheets per unit
- Store CRESEMBA capsules at 20° to 25°C (68° to 77°F) in the original packaging to protect from moisture
- Excursions are permitted from 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]

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Once-daily maintenance dosing[1]

CRESEMBA® (isavuconazonium sulfate) for injection: a water-soluble formulation

IV dosing regimen		
	Loading Dose	**Maintenance Dose†**
CRESEMBA for Injection 372 mg* of isavuconazonium sulfate per vial	**1 Vial q8h for 6 doses (48 h)**	**1 Vial Once Daily**

*372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole.
†Start maintenance doses 12–24 hours after the last loading dose.
IV=intravenous.

- IV formulation does not contain cyclodextrin and requires no dose adjustment for renal impairment
- Can be administered through a peripheral or central venous line[2]
- IV formulation must be administered via an infusion set with an in-line filter (pore size 0.2–1.2 microns)
- Infuse the IV 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 IV bolus injection
- Do not infuse CRESEMBA with other IV medications
- Flush IV lines with 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP, prior to and after infusion of CRESEMBA
- After dilution of the IV formulation, avoid unnecessary vibration or vigorous shaking of the solution. Do not use a pneumatic transport system
- Infusion-related reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during IV administration of CRESEMBA. Discontinue the infusion if these reactions occur

IMPORTANT SAFETY INFORMATION (CONTINUED)

Hepatic Adverse Drug Reactions (e.g., elevations in ALT, AST, alkaline phosphatase, total bilirubin) have been reported in clinical trials and were generally reversible and did not require discontinuation of CRESEMBA. Cases of 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 tests at the start and during therapy. Monitor patients who develop liver abnormalities during CRESEMBA therapy for severe hepatic injury. Discontinue if clinical signs and symptoms consistent with liver disease develop that may be attributable to CRESEMBA.

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.

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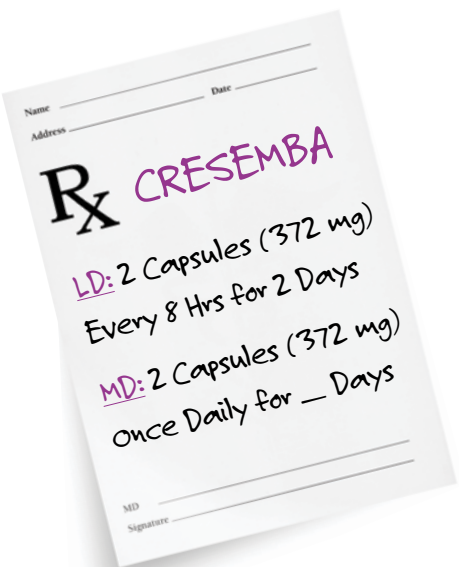
CRESEMBA capsules: an option throughout the care continuum

PO dosing regimen		
	Loading Dose	**Maintenance Dose†**
CRESEMBA Capsules 186 mg* of isavuconazonium sulfate per capsule	**2 Capsules q8h for 6 doses (48 h)**	**2 Capsules Once Daily**

*186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole.
†Start maintenance doses 12–24 hours after the last loading dose.
PO=by mouth.

- 98% absolute bioavailability
- Capsules can be taken with or without food
- Swallow whole; do not chew, crush, dissolve, or open the capsules

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



LD=loading dose; MD=maintenance dose.

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Directions for reconstitution, dilution, and preparation[1]

Reconstitution

Aseptic technique must be strictly observed in all handling since no preservative or bacteriostatic agent is present in CRESEMBA® (isavuconazonium sulfate) 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 particulates
- The reconstituted solution may be stored below 25°C for maximum 1 hour prior to preparation of the patient infusion solution

Compatibility

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

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

IMPORTANT SAFETY INFORMATION (CONTINUED)

Serious Hypersensitivity and Severe Skin Reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA if a patient develops a severe cutaneous adverse reaction. Caution should be used when prescribing CRESEMBA to patients with hypersensitivity to other azoles.

Embryo-Fetal Toxicity: During pregnancy, CRESEMBA may cause fetal harm when administered, and CRESEMBA should only be used if the potential benefit to the patient outweighs the risk to the fetus. Women who become pregnant while receiving CRESEMBA are encouraged to contact their physician.

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.

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Dilution and preparation

- 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 0.2–1.2 microns and apply in-line filter reminder sticker to the infusion bag, which is provided behind vial label. Refer to picture
- Do not use a pneumatic transport system
- The IV administration should be completed within 6 hours of dilution at room temperature. If this is not possible, immediately refrigerate (2° to 8°C/36° to 46°F) the infusion solution after dilution and complete the infusion within 24 hours. Do not freeze the infusion solution

IV=intravenous.

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Predictable and consistent pharmacokinetic profile

Dose-proportional pharmacokinetics[1]

- No significant association between area under the curve (AUC) or drug concentration and efficacy in patients treated for invasive aspergillosis in a controlled trial[1]

Steady state pharmacokinetic parameters of isavuconazole following administration of CRESEMBA capsules[1]

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

*Each capsule contains the equivalent of 100 mg of isavuconazole.
C_{max}=maximum plasma concentration; T_{max}=time to reach C_{max}; SD=standard deviation; CV=coefficient of variation.

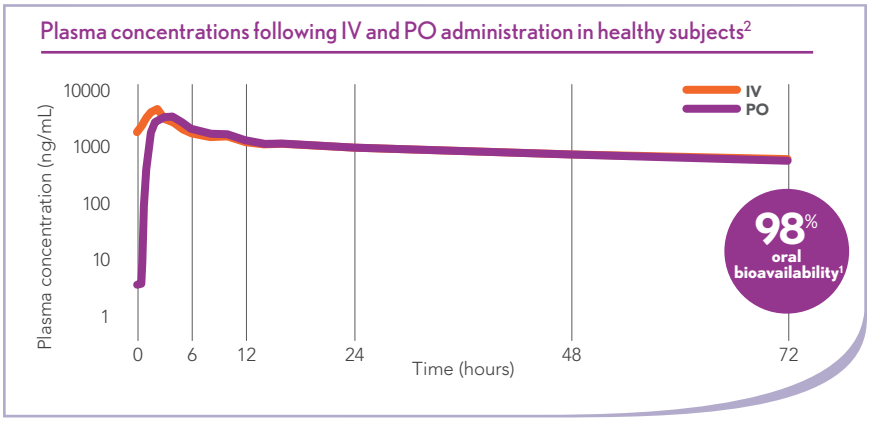
- Dose-proportional pharmacokinetics following PO administration of CRESEMBA® (isavuconazonium sulfate) capsules at doses up to the equivalent of 600 mg/day of isavuconazole (6 capsules)[1]
- Mean plasma half-life was 130 hours based on a population pharmacokinetics analysis of healthy subjects and patients in clinical trials[1]
- No relevant PK differences between healthy subjects and patients with invasive fungal infections[†3]

†Based on a 2-compartment model developed using data from Phase 1 subjects and Phase 3 trial patients administered single and multiple, PO and IV doses of CRESEMBA.[3]
IV=intravenous; PO=by mouth.

No dose adjustments required in specific populations based on[1]:

- Mild, moderate, or severe renal impairment, including end-stage renal disease
  - Of the 403 patients who received CRESEMBA in the Phase 3 trials, 79 (20%) patients had an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2
  - CRESEMBA is not removed by hemodialysis
- Mild to moderate hepatic impairment
  - CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Monitoring for CRESEMBA-related adverse reactions is recommended when treating these patients
- Age or gender

CRESEMBA offers bioequivalent IV and PO formulations[1]



Mean plasma concentrations in healthy subjects (N=14) following a single dose of CRESEMBA equivalent to 400 mg of isavuconazole. CRESEMBA was administered orally or as a 2-hour infusion.[2]
IV=intravenous; PO=by mouth.

Absorption[1]

- CRESEMBA can be taken with or without food
- Reaches maximum plasma concentrations (C_{max}) 2–3 hours after single and multiple PO dosing

Distribution[1]

- Extensively distributed with a mean steady state volume of distribution of approximately 450 L
- Highly protein bound (>99%) predominantly to albumin

Metabolism[1]

- Isavuconazonium sulfate is rapidly hydrolyzed in blood to isavuconazole by esterases
- Isavuconazole is a substrate of cytochrome P450 enzymes 3A4 and 3A5
- In vivo studies indicate that CYP3A4, CYP3A5, and subsequently uridine diphosphate-glucuronosyltransferases (UGT) are involved in the metabolism of isavuconazole

Excretion[1]

- Mean total radioactive dose of radiolabeled CRESEMBA® (isavuconazonium sulfate)*:
  - 46.1% was recovered in the feces
  - 45.5% was recovered in the urine
- Renal excretion of isavuconazole was <1% of the dose administered

*Following PO administration in healthy volunteers.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Drug Particulates: Following dilution, CRESEMBA intravenous formulation may form precipitate from the insoluble isavuconazole. Administer CRESEMBA through an in-line filter.

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Drug-drug interactions

CRESEMBA® (isavuconazonium sulfate) is a sensitive substrate of CYP3A4, a moderate inhibitor of CYP3A4, and a mild inhibitor of P-glycoprotein (P-gp) and organic cation transporter 2 (OCT2).[1]

Contraindicated[1]

Concomitant drug(s)	Effect on CRESEMBA	Comments on concomitant use
Ketoconazole	>5-fold increase in exposure	Contraindicated with all potent CYP3A4 inhibitors
Rifampin	97% decrease in exposure	Contraindicated with all potent CYP3A4 inducers

Use with caution[1,4-8]

Concomitant drug(s)	Drug monitoring/dose adjustment for concomitant drug	Effect on CRESEMBA PK	Effect on concomitant drug PK	
			C_{max}	AUC
Cyclosporine (300 mg)	Monitor drug concentrations and dose adjust as needed	NS	↑ 6%	↑ 29%
Tacrolimus (5 mg)	Monitor drug concentrations and dose adjust as needed	NS	↑ 42%	↑ 125%
Sirolimus (2 mg)	Monitor drug concentrations and dose adjust as needed	NS	↑ 65%	↑ 84%
Mycophenolate mofetil (1 g)	Monitor for MPA-related toxicities	NS	↓ 11%	↑ 35%
Digoxin (0.5 mg)	Monitor and titrate digoxin dose to clinical effect	NS	↑ 33%	↑ 25%
Midazolam (3 mg)	Consider dose reduction	NS	↑ 72%	↑ 103%
Bupropion (100 mg)	Consider dose increase; should not exceed maximum dose	NS	↓ 31%	↓ 42%
Atorvastatin (20 mg)	Monitor for atorvastatin-related AEs	NS	↑ 3%	↑ 37%
Lopinavir (400 mg)	Possible loss of antiviral efficacy	C_{max} ↑ 74% AUC ↑ 96%	↓ 23%	↓ 27%
Ritonavir (100 mg)			↓ 33%	↓ 31%

AEs=adverse events; AUC=area under the curve; C_{max}=maximum plasma concentration; MPA=mycophenolic acid; PK=pharmacokinetics.

No dose adjustment[2,4-10]

Esomeprazole	Omeprazole	Norethindrone	Methadone
Warfarin	Dextromethorphan	Ethinyl estradiol	Prednisone
Caffeine	Repaglinide	Methotrexate	Metformin

IMPORTANT SAFETY INFORMATION (CONTINUED)

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%).

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%).

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CRESEMBA Support Solutions℠

Your resource for access, reimbursement, and patient assistance

CRESEMBA Support Solutions, a component of Astellas Pharma Support Solutions℠, offers access and reimbursement assistance to help patients and healthcare providers overcome challenges to accessing CRESEMBA® (isavuconazonium sulfate).

Access services

- Benefits verification
- Prior authorization assistance
- Patient assistance options

QUICK START+® program

- CRESEMBA QUICK START+ program provides a one-time, 7-day supply of CRESEMBA at no cost to adult patients who experience an insurance delay in prescription fulfillment. To be eligible for CRESEMBA QUICK START+, patients must be new to CRESEMBA therapy, must have experienced an insurance-related access delay, and must have been prescribed CRESEMBA for an FDA-approved indication

Patient assistance

- The CRESEMBA Patient Savings Program is for eligible adult patients who have commercial insurance. Eligible adult patients can expect to pay as little as $25 per prescription, up to a maximum savings of $4,000 annually*
- Astellas Patient Assistance Program provides CRESEMBA at no cost to uninsured patients who qualify†

*In order to participate in the CRESEMBA Patient Savings Program ("Program"), a patient must have commercial prescription insurance for CRESEMBA. This Program is not valid for patients whose prescription claims are reimbursed, in whole or in part, by any state or federal government program, including, but not limited to Medicaid, Medicare, Medigap, Department of Defense (DoD), Veterans Affairs (VA), TRICARE, Puerto Rico Government Insurance, or any state patient or pharmaceutical assistance program. This offer is not valid for cash-paying patients. This Program is void where prohibited by law. Certain rules and restrictions apply. Astellas reserves the right to revoke, rescind, or amend this offer without notice.

†Subject to eligibility. Void where prohibited by law.

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To learn more about CRESEMBA Support Solutions, please call or visit our website.

1-800-477-6472
Mon–Fri, 9 AM to 8 PM ET

CRESEMBASupportSolutions.com

References: 1. CRESEMBA® (isavuconazonium sulfate) [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Data on file. Northbrook, IL: Astellas Pharma US, Inc. **3.** Desai A, Kovanda L, Kowalski D, Lu Q, Townsend R, Bonate PL. Population pharmacokinetics of isavuconazole from phase 1 and phase 3 (SECURE) trials in adults and target attainment in patients with invasive infections due to *Aspergillus* and other filamentous fungi. *Antimicrob Agents Chemother.* 2016;60:5483-5491. **4.** Groll AH, Desai A, Han D, et al. Pharmacokinetic assessment of drug-drug interactions of isavuconazole with the immunosuppressants cyclosporine, mycophenolic acid, prednisolone, sirolimus, and tacrolimus in healthy adults. *Clin Pharmacol Drug Dev.* 2017;6:76-85. **5.** Yamazaki T, Desai A, Goldwater R, et al. Pharmacokinetic interactions between isavuconazole and the drug transporter substrates atorvastatin, digoxin, metformin, and methotrexate in healthy subjects. *Clin Pharmacol Drug Dev.* 2017;6:66-75. **6.** Townsend R, Dietz A, Hale C, et al. Pharmacokinetic evaluation of CYP3A4-mediated drug-drug interactions of isavuconazole with rifampin, ketoconazole, midazolam, and ethinyl estradiol/norethindrone in healthy adults. *Clin Pharmacol Drug Dev.* 2017;6:44-53. **7.** Yamazaki T, Desai A, Goldwater R, et al. Pharmacokinetic effects of isavuconazole coadministration with the cytochrome P450 enzyme substrates bupropion, repaglinide, caffeine, dextromethorphan, and methadone in healthy subjects. *Clin Pharmacol Drug Dev.* 2017;6:54-65. **8.** Yamazaki T, Desai A, Han D, et al. Pharmacokinetic interaction between isavuconazole and a fixed-dose combination of lopinavir 400 mg/ritonavir 100 mg in healthy subjects. *Clin Pharmacol Drug Dev.* 2017;6:93-101. **9.** Desai A, Yamazaki T, Dietz AJ, et al. Pharmacokinetic and pharmacodynamic evaluation of the drug-drug interaction between isavuconazole and warfarin in healthy subjects. *Clin Pharmacol Drug Dev.* 2017;6:86-92. **10.** Schmitt-Hoffmann A, Desai A, Kowalski D, Pearlman H, Yamazaki T, Townsend R. Isavuconazole absorption following oral administration in healthy subjects is comparable to intravenous dosing, and is not affected by food, or drugs that alter stomach pH. *Int J Clin Pharmacol Ther.* 2016;54:572-580.

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Start and stay on CRESEMBA

Once-daily maintenance dosing, regardless of indication or formulation[1]

- Loading dose: 1 vial or 2 capsules (372 mg) q8h for 48 hours
- Maintenance dose: 1 vial or 2 capsules (372 mg) once daily

CRESEMBA offers bioequivalent IV and PO formulations[1]

- Switching between formulations is acceptable as bioequivalence has been demonstrated. Loading dose is not required when switching between formulations

Predictable and consistent pharmacokinetic profile[1]

- No significant association between AUC or drug concentration and efficacy in patients treated for invasive aspergillosis in a controlled trial
- Dose-proportional pharmacokinetics following PO administration of CRESEMBA capsules at doses up to the equivalent of 600 mg/day of isavuconazole (6 capsules)
- Extensively distributed with a mean steady state volume of distribution of approximately 450 L

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