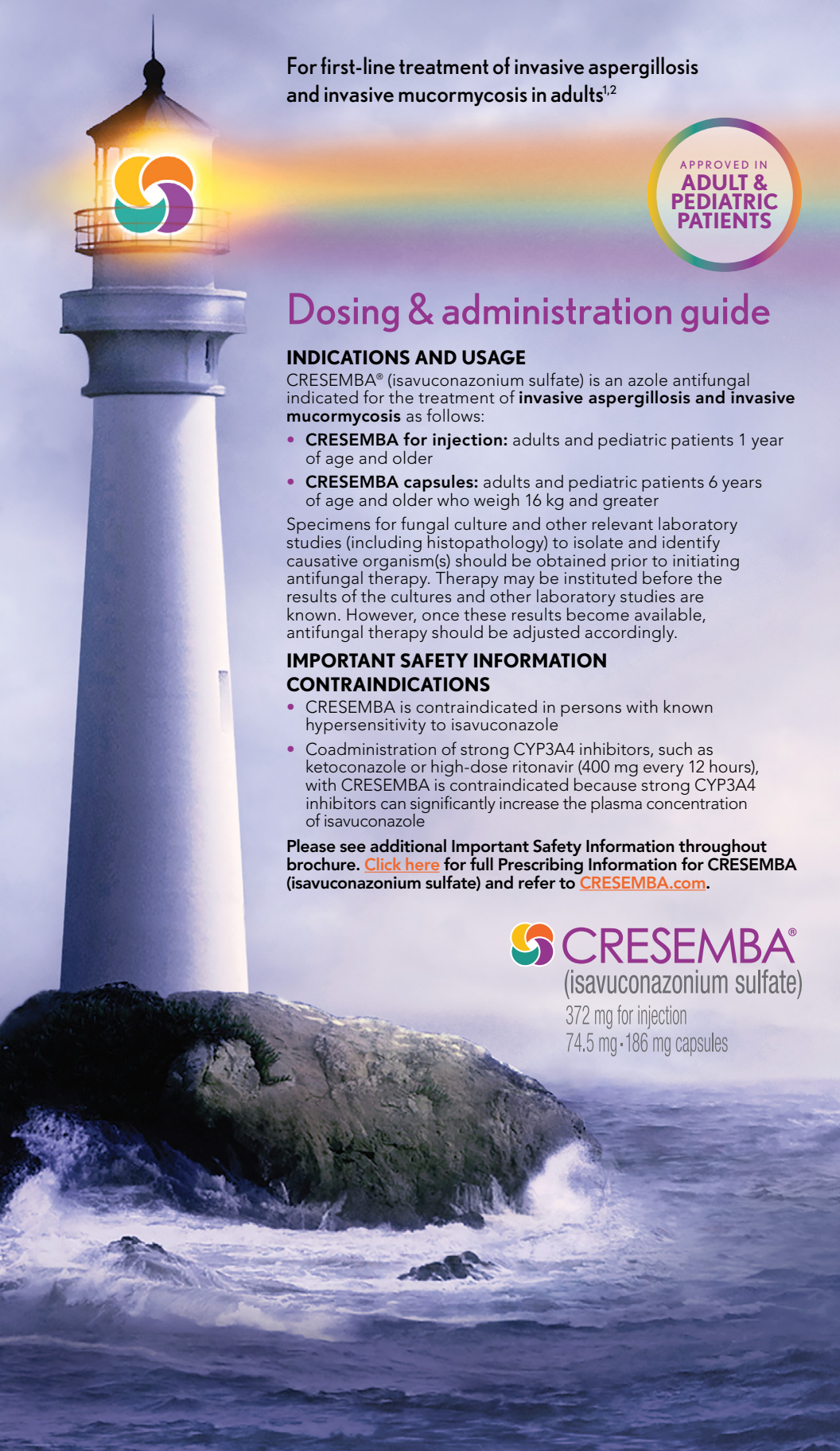


For first-line treatment of invasive aspergillosis and invasive mucormycosis in adults[1,2]

APPROVED IN **ADULT & PEDIATRIC PATIENTS**

Dosing & administration guide

INDICATIONS AND USAGE

CRESEMBA® (isavuconazonium sulfate) is an azole antifungal indicated for the treatment of **invasive aspergillosis and invasive mucormycosis** as follows:

- **CRESEMBA for injection:** adults and pediatric patients 1 year of age and older
- **CRESEMBA capsules:** adults and pediatric patients 6 years of age and older who weigh 16 kg and greater

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 (isavuconazonium sulfate) and refer to CRESEMBA.com.

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

For first-line treatment of invasive aspergillosis and invasive mucormycosis in adults[1,2]

Dosage formulations and strengths[3]

CRESEMBA® (isavuconazonium sulfate) for injection

Vial not actual size.

- 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°C to 8°C (36°F to 46°F) in a refrigerator

CRESEMBA capsules

Capsules not actual size.

- Each CRESEMBA capsule contains 186 mg of isavuconazonium sulfate (equivalent to 100 mg of isavuconazole) or 74.5 mg of isavuconazonium sulfate (equivalent to 40 mg of isavuconazole)
- 186 mg capsules are opaque and elongated, and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with "766" in black ink
- 74.5 mg 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
- 186 mg capsules are available in aluminum blister packs, 7 capsules per sheet with desiccant; 2 sheets per unit
- 74.5 mg capsules are available in aluminum blister packs, 5 capsules per sheet with desiccant; 7 sheets per unit
- 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]

IMPORTANT SAFETY INFORMATION (CONTINUED)

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

Please see additional Important Safety Information throughout brochure. Click here for full Prescribing Information for CRESEMBA (isavuconazonium sulfate) and refer to CRESEMBA.com.

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

For first-line treatment of invasive aspergillosis and invasive mucormycosis in adults[1,2]

Once-daily maintenance dosing[3]

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

Injection dosing regimen in adults

	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.

- CRESEMBA for injection is intended for use in patients who are 1 year of age and older[3]
- Injection formulation does not contain cyclodextrin and requires no dose adjustment for renal impairment[3]
- Intravenous (IV) administration can be through a peripheral or central venous line[4]
- Injection formulation for IV use must be administered via an infusion set with an in-line filter (pore size 0.2–1.2 micron)[3]
  - Infuse the injection 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[3]
  - Do not infuse CRESEMBA with other IV medications[3]
  - Flush IV lines with 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP, prior to and after infusion of CRESEMBA[3]
  - After dilution of the IV formulation, avoid unnecessary vibration or vigorous shaking of the solution. Do not use a pneumatic transport system[3]
  - 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[3]
- CRESEMBA injection formulation can be administered via nasogastric (NG) tube[3]
  - CRESEMBA for injection administered via NG tube is intended for use by patients who are ≥6 years of age and weighing ≥16 kg[3]
  - Flush NG tube with three rinses of 5 mL of water for injection, USP, after NG tube administration of CRESEMBA[3]

IMPORTANT SAFETY INFORMATION (CONTINUED)
WARNINGS AND PRECAUTIONS

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.

Please see additional Important Safety Information throughout brochure. Click here for full Prescribing Information for CRESEMBA (isavuconazonium sulfate) and refer to CRESEMBA.com.

CRESEMBA capsules: an option throughout the care continuum[3]

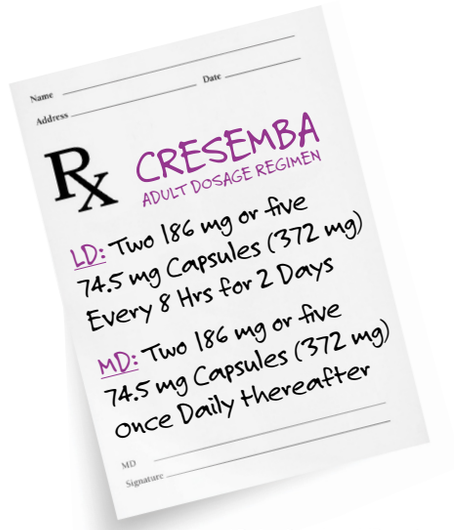
PO dosing regimen in adults

	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**
CRESEMBA capsules 74.5 mg† of isavuconazonium sulfate per capsule	**5 capsules q8h for 6 doses (48 h)**	**5 capsules once daily**

*186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole.
†74.5 mg of isavuconazonium sulfate is equivalent to 40 mg of isavuconazole.
‡Start maintenance doses 12–24 hours after the last loading dose.
PO=by mouth.

- CRESEMBA capsules are intended for use in patients who are ≥6 years of age and weighing ≥16 kg[3]
- 98% absolute bioavailability[3]
- Capsules can be taken with or without food[3]
- Swallow whole; do not chew, crush, dissolve, or open the capsules[3]

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.

For first-line treatment of invasive aspergillosis and invasive mucormycosis in adults[1,2]

Directions for reconstitution, dilution, and preparation[3]

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. The resultant solution will be 74.4 mg/mL of isavuconazonium sulfate
- 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 between 5°C to 25°C (41°F to 77°F) for a maximum of 1 hour prior to preparation of the patient infusion solution
- For nasogastric (NG) tube administration, the reconstituted solution should be administered within 1 hour of reconstitution
- Discard any unused portion of the reconstituted solution

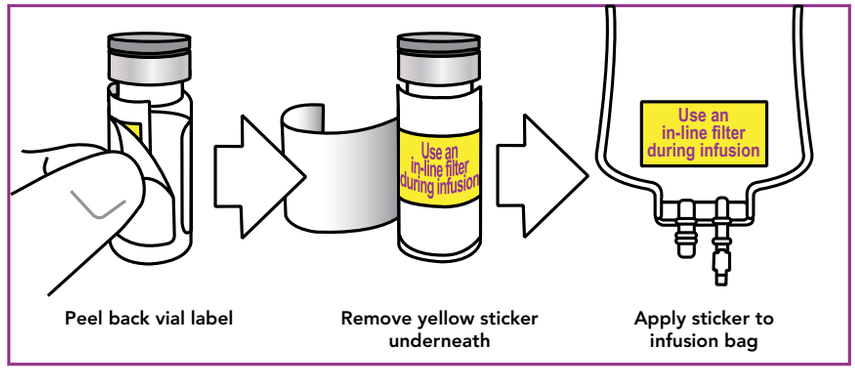
Compatibility

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

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

Dilution and preparation instructions for IV administration

- Based on the adult or pediatric dosage regimen (see pages 14–15 for pediatric dosing information), remove the appropriate volume of the reconstituted solution (74.4 mg/mL of isavuconazonium sulfate) from the vial and add it to an infusion bag containing 250 mL of compatible diluent. A smaller volume infusion bag of compatible diluent may be used as long as the final concentration does not exceed approximately 1.5 mg isavuconazonium sulfate per mL
- 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 micron and apply in-line filter reminder sticker to the infusion bag, which is provided behind vial label. Refer to picture below
- 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°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



Preparation instructions for the nasogastric (NG) tube administration

- Utilizing aseptic technique, reconstitute one vial of CRESEMBA for injection (equivalent to 200 mg isavuconazole) with 5 mL of water for injection, USP
- Based on the adult or pediatric (6 years to less than 18 years of age) regimen (see pages 14–15 for pediatric dosing information), withdraw the appropriate volume of the reconstituted solution from 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 NG tube to deliver the dose. After administering the dose, administer three 5 mL rinses to the NG tube with water
- Administer the reconstituted solution via the nasogastric tube within 1 hour of reconstitution. Discard any unused portion of the reconstituted solution
- **Do not** administer CRESEMBA capsules through a nasogastric tube

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

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.

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.

Please see additional Important Safety Information throughout brochure. Click here for full Prescribing Information for CRESEMBA (isavuconazonium sulfate) and refer to CRESEMBA.com.

For first-line treatment of invasive aspergillosis and invasive mucormycosis in adults[1,2]

Predictable and consistent pharmacokinetic (PK) profile in adult patients

Dose-proportional pharmacokinetics[3]

- No significant association between area under the curve (AUC) or drug concentration and efficacy in patients treated for invasive aspergillosis in a controlled trial[3]

Steady-state pharmacokinetic parameters of isavuconazole following administration of CRESEMBA 186 mg capsules[3]

Parameter	CRESEMBA 2 capsules* (n=37)	CRESEMBA 6 capsules* (n=32)
C_{max} (mg/L)		
Mean	7.5	20.0
SD	1.9	3.6
CV %	25.2	17.9
t_{max} (h)		
Median	3.0	4.0
Range	2.0–4.0	2.0–4.0
AUC (mg•h/L)		
Mean	121.4	352.8
SD	35.8	72.0
CV %	29.5	20.4

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

- 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)[3]
- Mean plasma half-life was 130 hours based on a population pharmacokinetics analysis of healthy subjects and patients in clinical trials[3]
- 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 3.3 (0.6) mg/L and 112.2 (30.3) mg·hr/L, respectively, and 3.3 (0.6) mg/L and 118.0 (33.1) mg·hr/L, respectively[3]
- No relevant PK differences between healthy subjects and patients with invasive fungal infections[15]

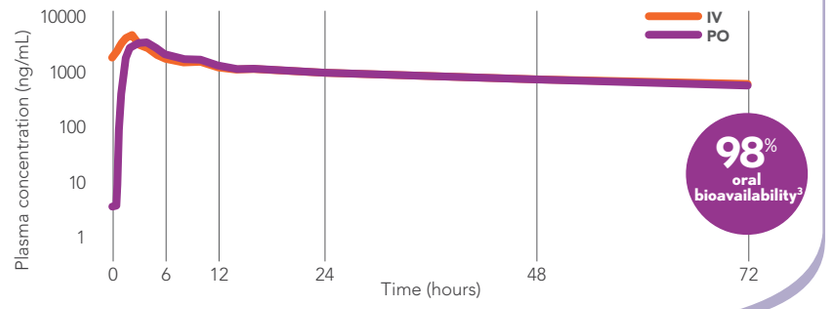
†Based on a 2-compartment model developed using data from Phase 1 subjects and Phase 3 trial patients administered single and multiple, PO and IV doses of CRESEMBA.[5]
IV=intravenous; PK=Pharmacokinetic; PO=by mouth.

IMPORTANT SAFETY INFORMATION (CONTINUED)
WARNINGS AND PRECAUTIONS (CONTINUED)

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.

CRESEMBA offers bioequivalent IV and PO formulations[3]

Plasma concentrations following IV and PO administration in healthy subjects[4]



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.[4]
IV=intravenous; PO=by mouth.

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.

No dose adjustments required in specific populations based on[3]:

- 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 (GFR) <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
- Gender

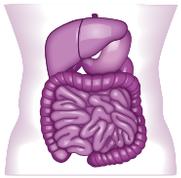
IMPORTANT SAFETY INFORMATION (CONTINUED)
WARNINGS AND PRECAUTIONS (CONTINUED)

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.

Please see additional Important Safety Information throughout brochure. Click here for full Prescribing Information for CRESEMBA (isavuconazonium sulfate) and refer to CRESEMBA.com.

For first-line treatment of invasive aspergillosis and invasive mucormycosis in adults[1,2]

Predictable and consistent pharmacokinetic (PK) profile in adult patients



Absorption[3]

- CRESEMBA can be taken with or without food
- Reaches maximum plasma concentrations (C_{max}) 2–3 hours after single and multiple PO dosing
- NG tube administration provides exposure similar to the oral capsule

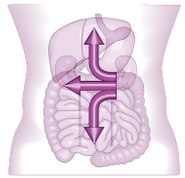
Comparison of plasma pharmacokinetics of isavuconazole following single oral dose administration of 2 capsules of 186 mg (equivalent to 200 mg isavuconazole) and single intravenous solution dose administration of 372 mg (equivalent to 200 mg isavuconazole) via nasogastric (NG) tube[3]*

	CRESEMBA IV Solution via NG Tube		CRESEMBA Oral Capsules†		NG Tube/ Oral Capsule
Parameter	**N**	**Mean (%CV)**	**N**	**Mean (%CV)**	**GMR (90% CI)**
C_{max} (mg/L)	13	2.3 (23.6)	13	2.2 (26.7)	105.34 (89–124)
AUC_{0-72hr} (mg·h/L)	13	34.9 (22.1)	13	35.8 (24.6)	97.81 (93–103)
$AUC_{0-\infty}$ (mg·h/L)	12	98.1 (44.5)	12	100.1 (46.8)	99.27 (93–106)

*In healthy subjects under fasted conditions.

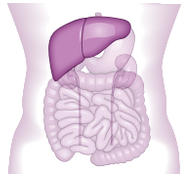
†Each capsule contains the equivalent of 100 mg of isavuconazole.

CI=confidence interval; C_{max}=maximum plasma concentration; CV=coefficient of variation; GMR=geometric least-squares mean ratio.



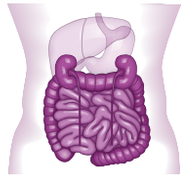
Distribution[3]

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



Metabolism[3]

- 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[3]

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

*Following PO administration in healthy volunteers.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

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

Please see additional Important Safety Information throughout brochure. Click here for full Prescribing Information for CRESEMBA (isavuconazonium sulfate) and refer to CRESEMBA.com.

For first-line treatment of invasive aspergillosis and invasive mucormycosis in adults[1,2]

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).[3]

Contraindicated[3]

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

- Vincristine–avoid concomitant use with CRESEMBA in pediatric and adult patients. CRESEMBA is predicted to have a less than 2-fold increase in vincristine exposure in pediatric and adult patients, which may increase the risk of vincristine-related adverse reactions[3]

Use with caution[3,6-10]

Concomitant drug(s)	Drug monitoring/dose adjustment for concomitant drug	Effect on CRESEMBA PK		Effect on concomitant drug PK	
		C_{max}	AUC	C_{max}	AUC
Cyclosporine (300 mg)	Monitor drug concentrations and dose adjust as needed	↑ 30%	↑ 3%	↑ 6%	↑ 29%
Tacrolimus (5 mg)	Monitor drug concentrations and dose adjust as needed	↑ 26%	↑ 12%	↑ 42%	↑ 125%
Sirolimus (2 mg)	Monitor drug concentrations and dose adjust as needed	↑ 4%	↑ 11%	↑ 65%	↑ 84%
Mycophenolate mofetil (1000 mg)	Monitor for mycophenolic acid–related toxicities	↑ 4%	NS	↓ 11%	↑ 35%
Digoxin (0.5 mg)	Monitor and titrate digoxin dose to clinical effect	NS	NS	↑ 33%	↑ 25%
Midazolam (3 mg)	Consider dose reduction	NS	NS	↑ 72%	↑ 103%
Bupropion (100 mg)	Consider dose increase; should not exceed maximum dose	NS	NS	↓ 31%	↓ 42%
Atorvastatin (20 mg)	Monitor for atorvastatin-related adverse events	NS	NS	↑ 3%	↑ 37%
Lopinavir (400 mg)	Possible loss of antiviral efficacy	↑ 74%	↑ 96%	↓ 23%	↓ 27%
Ritonavir (100 mg)				↓ 33%	↓ 31%

AUC=area under the curve; C_{max}=maximum plasma concentration; NS=not significant; PK=pharmacokinetics.

No dose adjustment[6-9,11,12]

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

IMPORTANT SAFETY INFORMATION (CONTINUED)

ADVERSE REACTIONS

In adult patients, 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%).

In adult patients, 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®
(isavuconazonium sulfate)
372 mg for injection
74.5 mg • 186 mg capsules

CRESEMBA in the pediatric population

Approved in pediatric patients

- The safety and effectiveness of **CRESEMBA for injection** for the treatment of invasive aspergillosis and invasive mucormycosis have been established in pediatric patients **≥1 year of age**, and the safety and effectiveness of **CRESEMBA capsules** have been established in pediatric patients **≥6 years of age and weighing ≥16 kg**[3]
- Use of CRESEMBA in this age group for the treatment of invasive aspergillosis and for the treatment of invasive mucormycosis is supported by evidence from trials in adult patients, and additional pharmacokinetic and safety data in pediatric patients 1 year of age and older[3]

Similar safety profile to adult population

- The clinical safety of CRESEMBA was assessed in 77 pediatric patients who received at least one dose of intravenous or oral CRESEMBA in two uncontrolled studies[3]
- The duration of treatment ranged from 1 to 181 days with a median duration of treatment of 15 days[3]
- In general, adverse reactions in pediatric patients (including serious and those leading to permanent discontinuation) were similar to adverse reactions reported in adults[3]

Predictable pharmacokinetics

Derived steady-state isavuconazole AUC (mg•h/L) values by age group[3]

Dosage	15 mg/kg*	10 mg/kg†	10 mg/kg or Maximum Dose of 372 mg‡	
Age Group	1 to <3 years (n=5)	3 to <6 years (n=10)	6 to <12 years (n=29)	12 to <18 years (n=29)
Mean	80.2	103.3	97.3	104.2
Median	64.3	110.3	87.7	97.7
Minimum–Maximum	53.7–155	51.5–159.1	37.8–153.8	35.5–215.6

*Estimated AUC_{ss} values of 15 mg/kg that were derived from existing values of pediatric patients that received 10 mg/kg of CRESEMBA for injection administered intravenously.
†CRESEMBA for injection administered intravenously.
‡CRESEMBA for injection administered intravenously or CRESEMBA capsules administered orally.

- The pharmacokinetics of isavuconazole were evaluated in two clinical studies (N = 73) in pediatric patients 1 to <18 years of age which included 28 patients with at least possible invasive aspergillosis or possible invasive mucormycosis[3]

IMPORTANT SAFETY INFORMATION (CONTINUED)
ADVERSE REACTIONS (CONTINUED)

In pediatric patients, the most frequently reported adverse reactions were diarrhea (26%), abdominal pain (23%), vomiting (21%), elevated liver chemistry tests (18%), rash (14%), nausea (13%), pruritus (13%), and headache (12%).

In general, adverse reactions in pediatric patients (including serious adverse reactions and adverse reactions leading to permanent discontinuation of CRESEMBA) were similar to those reported in adults.

Please see additional Important Safety Information throughout brochure. Click here for full Prescribing Information for CRESEMBA (isavuconazonium sulfate) and refer to CRESEMBA.com.

Dosage regimen for pediatric patients

Weight- and age-based dosing with once-daily maintenance[3]

Approximate size of vial and capsules.

Injection and PO dosing regimen in pediatric patients[3]

Dosage Form	Age	Body Weight (kg)	Loading Dose	Maintenance Dose‡
CRESEMBA for injection 372 mg* of isavuconazonium sulfate per vial	1 to <3 years of age	<18 kg	15 mg/kg q8h for 6 doses	15 mg/kg once daily
	3 to <18 years of age	<37 kg	10 mg/kg q8h for 6 doses	10 mg/kg once daily
		≥37 kg	1 vial q8h for 6 doses	1 vial once daily
CRESEMBA capsules 74.5 mg† of isavuconazonium sulfate per capsule	6 to <18 years of age	16 kg to <18 kg	2 capsules q8h for 6 doses	2 capsules once daily
		18 kg to <25 kg	3 capsules q8h for 6 doses	3 capsules once daily
		25 kg to <32 kg	4 capsules q8h for 6 doses	4 capsules once daily
		≥32 kg	5 capsules§ q8h for 6 doses	5 capsules§ once daily

*372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole.
†74.5 mg of isavuconazonium sulfate is equivalent to 40 mg of isavuconazole.
‡Start maintenance doses 12–24 hours after the last loading dose.
§Five 74.5 mg CRESEMBA capsules are equivalent to two 186 mg CRESEMBA capsules.

Special considerations

- The maximum of any individual loading or daily maintenance dose to be administered to any pediatric patient is 372 mg of CRESEMBA[3]
- Capsules can be taken with or without food[3]
- Swallow whole; do not chew, crush, dissolve, or open the capsules[3]
- CRESEMBA for injection via nasogastric tube administration is intended for use by patients ≥6 years of age and weighing ≥16 kg[3]
- Do **not** administer CRESEMBA capsules through a nasogastric tube[3]

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 support to help patients overcome challenges to accessing CRESEMBA® (isavuconazonium sulfate) capsules. CRESEMBA Support Solutions provides information regarding patient healthcare coverage options and financial assistance options that may be available to help patients with financial needs.

Access support

- Benefits verification
- Prior authorization assistance
- Patient assistance options

QUICK START+® program

- The CRESEMBA QUICK START+® Program provides a one-time, 7-day supply of CRESEMBA capsules at no cost to eligible new patients who experience an insurance-related delay*

Patient assistance options

- The CRESEMBA Patient Savings Program is for eligible patients who have commercial prescription insurance. Patients can expect to pay as little as $25 per prescription, up to a maximum savings of $4,000 annually†
- The Astellas Patient Assistance Program provides CRESEMBA capsules at no cost to patients who meet the program eligibility requirements‡

*To be eligible for CRESEMBA QUICK START+, patients must have prescription drug insurance, 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.

†By enrolling in the CRESEMBA Patient Savings Program ("Program"), the patient or the patient's legal representative (e.g., parent or legal guardian) acting on behalf of the patient, attests that the patient currently meets the eligibility criteria and will comply with the following terms and conditions: **The 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, or any state patient or pharmaceutical assistance program.** Offer is not valid for cash paying patients. Offer is not health insurance and is void where prohibited by law. Certain rules and restrictions, including a copay assistance limit of $4,000 per calendar year, apply. Astellas reserves the right to revoke, rescind, or amend this offer without notice. For full terms and conditions, visit ActivateTheCard.com/CRESEMBA.

‡Subject to eligibility. Void where prohibited by law.

Please see additional Important Safety Information throughout brochure. Click here for full Prescribing Information for CRESEMBA (isavuconazonium sulfate) and refer to CRESEMBA.com.

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. Cornely OA, Alastruey-Izquiredo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis 2019;19(12):e405-21. **2.** Patterson TF, Thompson GR III, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63(4):1-60. **3.** CRESEMBA [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **4.** Astellas. CRESEMBA. Data on File. **5.** 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(9):5483-91. **6.** 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(1):76-85. **7.** 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(1):66-75. **8.** 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(1):44-53. **9.** 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(1):54-65. **10.** 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(1):93-101. **11.** 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(1):86-92. **12.** 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. Int J Clin Pharmacol Ther 2016;54(8):572-80.

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

For first-line treatment of invasive aspergillosis and invasive mucormycosis in adults[1,2]

APPROVED IN **ADULT & PEDIATRIC PATIENTS**

Start and stay on CRESEMBA

Once-daily maintenance dosing, regardless of indication or formulation[3]

- Adult loading dose: 1 vial, two 186 mg capsules or five 74.5 mg capsules (372 mg) q8h for 48 hours
- Adult maintenance dose: 1 vial, two 186 mg capsules or five 74.5 mg capsules (372 mg) once daily

CRESEMBA offers bioequivalent IV and PO formulations[3]

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

Predictable and consistent pharmacokinetic profile in adults[3]

- 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

Approved in pediatric patients[3]

- Similar safety and pharmacokinetic profile established in pediatric patients
- Variable, weight- and age-based dosing with 74.5 mg capsules
- A CRESEMBA 74.5 mg capsule is smaller than a dime[4]

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
- 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

Please see additional Important Safety Information throughout brochure. Click here for full Prescribing Information for CRESEMBA (isavuconazonium sulfate) and refer to CRESEMBA.com.

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