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

Navigating antifungal treatment

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
- 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 on page 13.
Click here for Full Prescribing Information for CRESEMBA.

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

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

Trial 1: Invasive aspergillosis

Objective

- A Phase 3, randomized, double-blind, noninferiority trial to evaluate the safety and efficacy of CRESEMBA® (isavuconazonium sulfate) vs voriconazole for primary treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi[1]

Primary endpoint

- All-cause mortality through Day 42[1]

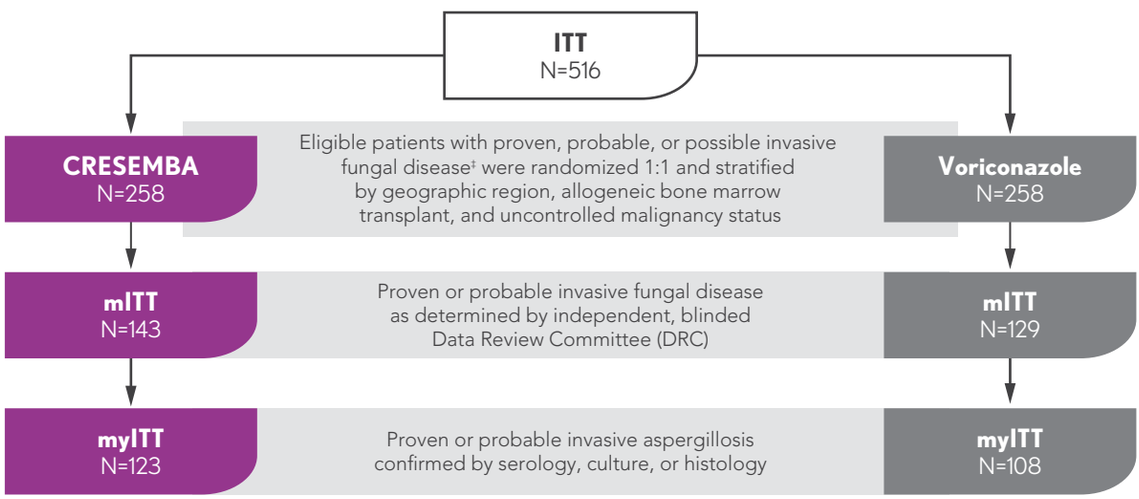
Patient population

- The mean age of patients was 51 years (range 17–87) and the majority were Caucasian (78%), male (60%), with fungal disease involving the lungs (95%)[1]
- Patients with moderate to severe renal impairment (creatinine clearance <50 mL/min, or currently on or likely to require dialysis) were excluded per labeling restrictions associated with the active comparator[2]
- At least 1 *Aspergillus* species was identified in 30% of the subjects[1]
  - *A. fumigatus* and *A. flavus* were the most common pathogens identified
  - Other *Aspergillus* species identified included *A. niger*, *A. sydowii*, *A. terreus*, and *A. westerdijkiae*

Baseline risk factors in intent-to-treat (ITT) population*[1]	CRESEMBA N=258 n (%)	Voriconazole N=258 n (%)
Hematologic malignancy	211 (82)	222 (86)
Allogeneic hematopoietic stem cell transplant (HSCT)	54 (21)	51 (20)
Neutropenia†	163 (63)	175 (68)
Corticosteroid use	48 (19)	39 (15)
T-cell immunosuppressant use	111 (43)	109 (42)

*ITT includes all randomized patients who received at least 1 dose of study drug.
†Neutropenia defined as neutrophil count <500 cells/mm^3.

Disposition of patients and analysis sets[1,2]



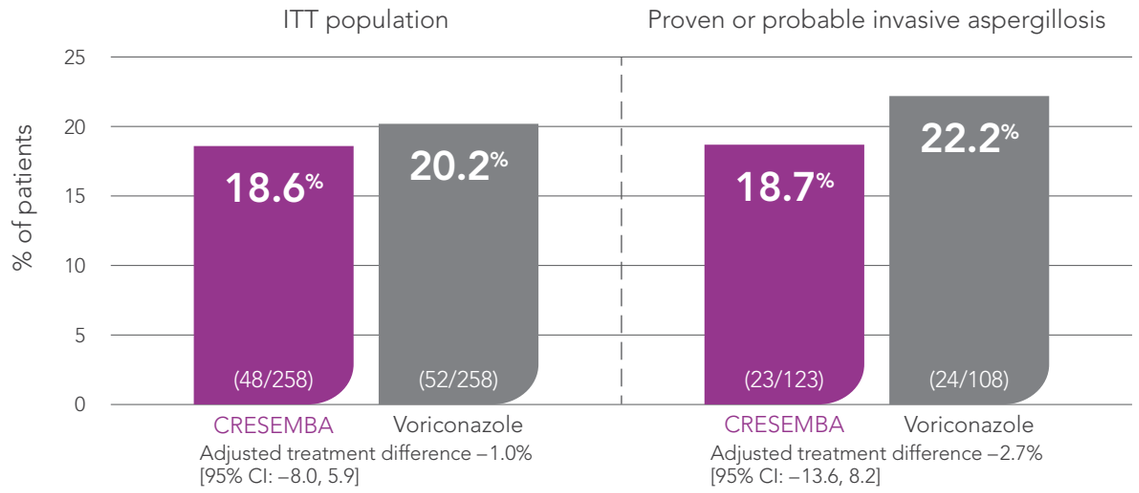
CRESEMBA: LD: IV 372 mg§ q8h for 48 hours; MD: IV or PO 372 mg§ q24h (Day 3 onward)
Voriconazole: LD: IV 6 mg/kg q12h for 24 hours; MD: IV 4 mg/kg q12h or PO 200 mg q12h (Day 2 onward)

‡Based on European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria.
§372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole.
ITT=intent to treat; mITT=modified intent to treat; myITT=mycological intent to treat; LD=loading dose; MD=maintenance dose; IV=intravenous; PO=by mouth.

Proven efficacy in the treatment of invasive aspergillosis

CRESEMBA demonstrated noninferiority to voriconazole in all-cause mortality[1]

All-cause mortality through Day 42[1]



CRESEMBA: LD: IV 372 mg* q8h for 48 hours; MD: IV or PO 372 mg* q24h (Day 3 onward)
Voriconazole: LD: IV 6 mg/kg q12h for 24 hours; MD: IV 4 mg/kg q12h or PO 200 mg q12h (Day 2 onward)

*372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole.

CI=confidence interval.

Phase 3, randomized, double-blind, noninferiority trial designed to evaluate the safety and efficacy of CRESEMBA vs 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 based on European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria. Adjusted treatment difference (CRESEMBA–voriconazole) by Cochran-Mantel-Haenszel method stratified by randomization factors.[1]

- Mean treatment duration was 47 days for both treatment groups, of which 8–9 days were by an IV route of administration[1]

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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Trial 2: Invasive mucormycosis

Objective

- A Phase 3, open-label, noncomparative trial to evaluate the safety and efficacy of CRESEMBA® (isavuconazonium sulfate) in the treatment of invasive aspergillosis in patients with renal impairment or in patients with invasive fungal disease caused by rare molds, yeasts, or dimorphic fungi[1,3]

Key endpoints

- All-cause mortality through Day 42[1]
- Overall response at end of treatment as assessed by the independent Data Review Committee (DRC)[1]

Mucorales patient population

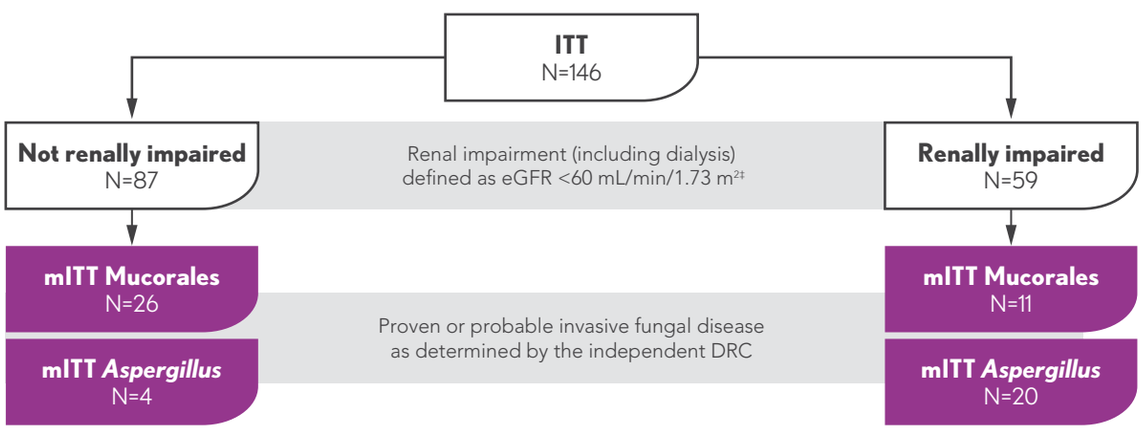
- A total of 37 patients were assessed by the DRC as having proven or probable invasive mucormycosis. These patients comprise the modified intent-to-treat (mITT)-Mucorales population[1]
- The mean age of patients was 49 years (range 22–79) and the majority were Caucasian (68%) and male (81%)[1]
- 59% of patients had pulmonary disease involvement, half of whom also had other organ involvement[1]
  - The most common nonpulmonary disease locations were sinus (43%), eye (19%), central nervous system (16%), and bone (14%)
- *Rhizopus oryzae* and Mucormycetes were the most common pathogens identified[1]
  - Other Mucorales identified included *Lichtheimia corymbifera, Mucor amphibiorum, Mucor circinelloides, Rhizomucor pusillus, Rhizopus azygosporus,* and *Rhizopus microsporus*

Baseline risk factors in Mucorales patients[1]	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 HSCT	4 (19)	4 (36)	5 (100)	13 (35)
Neutropenia*	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)

*Neutropenia defined as neutrophil count <500 cells/mm^3.

Therapy status assessed by DRC: Primary=patients received CRESEMBA as primary treatment; Refractory=patients' underlying infection not adequately treated by prior therapy; Intolerant=patients unable to tolerate prior therapy.

Disposition of patients and analysis sets[1,4]



CRESEMBA: LD: IV or PO 372 mg† q8h for 48 hours; MD: IV or PO 372 mg† q24h (Day 3 onward)

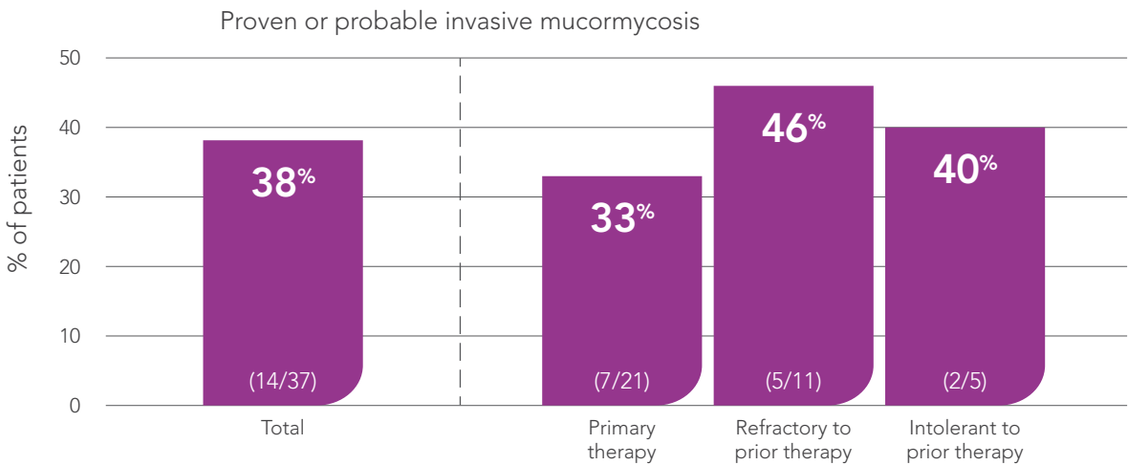
†372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole.
‡By the Modification of Diet in Renal Disease formula.
eGFR=estimated glomerular filtration rate; ITT=intent to treat; IV=intravenous; LD=loading dose; MD=maintenance dose; mITT=modified intent to treat; PO=by mouth.

The first and only FDA-approved azole antifungal to treat invasive mucormycosis[1,4]

CRESEMBA was effective against invasive mucormycosis in an open-label, noncomparative trial[1]

- Results provide evidence that CRESEMBA is effective for the treatment of mucormycosis in light of the natural history of untreated mucormycosis[1]
- The efficacy of CRESEMBA for the treatment of invasive mucormycosis has not been evaluated in concurrent, controlled clinical trials[1]

All-cause mortality through Day 42[1]



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Phase 3, open-label, noncomparative trial designed to evaluate the safety and efficacy of CRESEMBA in the treatment of invasive aspergillosis in patients with renal impairment or in patients with invasive fungal disease caused by rare molds, yeasts, or dimorphic fungi. 37 patients had proven or probable mucormycosis based on EORTC/MSG criteria. The DRC classified patients receiving CRESEMBA (1) as primary therapy, (2) for invasive mold disease refractory to prior antifungal therapy, or (3) due to intolerance of prior antifungal therapy.[1,3]

DRC=Data Review Committee; EORTC/MSG=European Organisation for Research and Treatment of Cancer/Mycoses Study Group; FDA=Food and Drug Administration; IV=intravenous; LD=loading dose; MD=maintenance dose; PO=by mouth.

- Median treatment duration was 102 days for patients classified as primary, 33 days for refractory, and 85 days for intolerant[1]

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.

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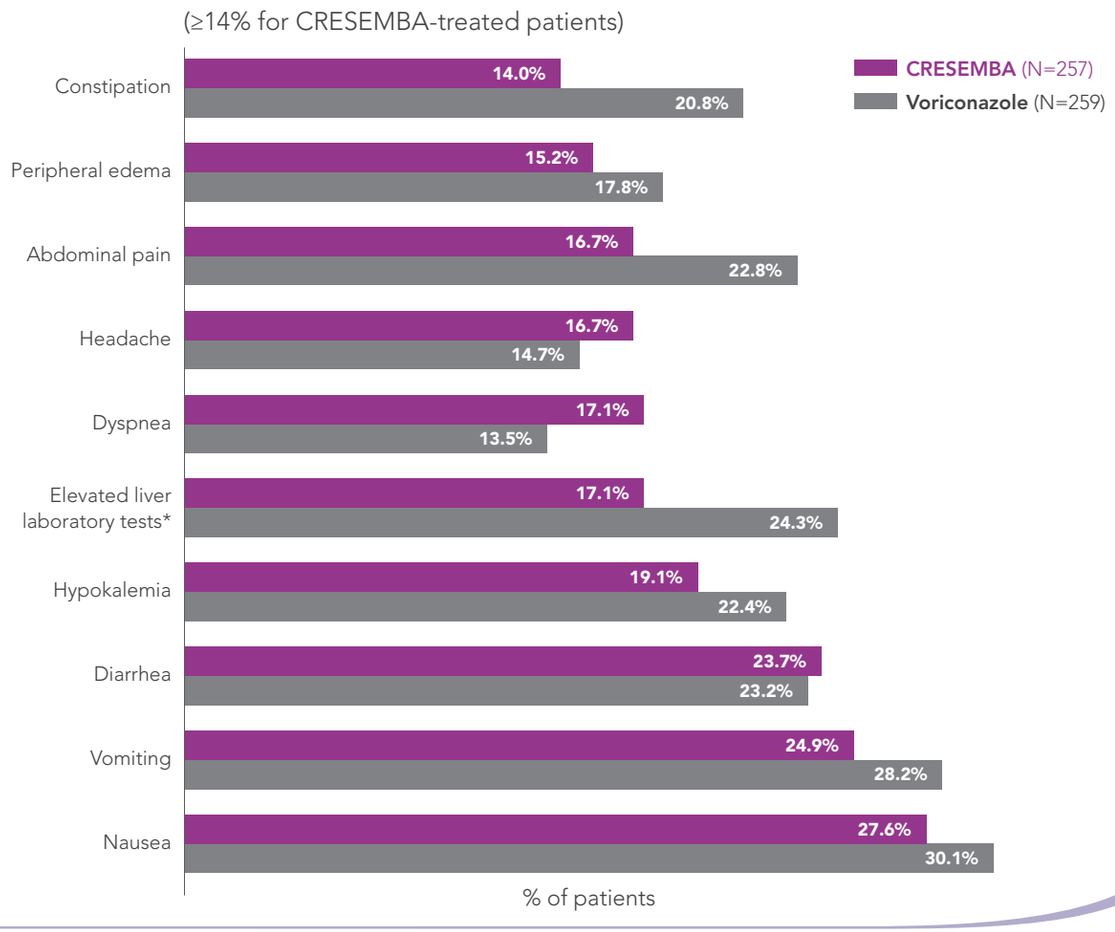
Adverse reactions in clinical trials

Clinical safety in Trials 1 and 2[1]

- The most frequently reported adverse reactions among CRESEMBA® (isavuconazonium sulfate)-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%)[1]
- The frequencies and types of adverse reactions observed in CRESEMBA-treated patients were similar between Trial 1 and Trial 2[1]

Trial 1: Most frequent treatment-emergent adverse reactions[1]



*Liver laboratory elevations included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin, and gamma-glutamyltransferase.

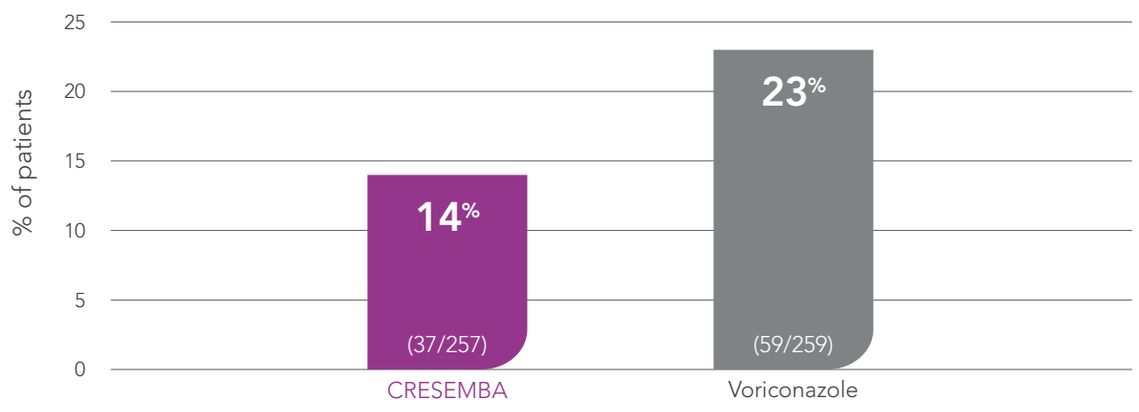
- CRESEMBA has no warning for visual disturbances[1]
- In Trial 1, the observed rates of adverse reactions by system organ classes for CRESEMBA and voriconazole were: skin (33.5% and 42.5%), eye (15.2% and 26.6%), and hepatobiliary disorders (8.9% and 16.2%)[2,4]

Elevated liver transaminases in Trial 1[1]

- ALT or AST >3 times upper limit of normal (ULN) was reported at the end of study treatment in 4.4% of patients who received CRESEMBA
- ALT or AST >10 times ULN developed in 1.2% of patients who received CRESEMBA

Treatment discontinuations due to adverse reactions for CRESEMBA and voriconazole[1]

Trial 1: Permanent discontinuation due to treatment-emergent adverse reactions[1]



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*372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole.

Phase 3, randomized, double-blind, noninferiority trial designed to evaluate the safety and efficacy of CRESEMBA vs 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 based on EORTC/MSG criteria.[1]

- In Trial 2, adverse reactions resulting in permanent discontinuation were reported in 19 (13%) CRESEMBA-treated patients[1]
- In Trials 1 and 2, adverse reactions which most often led to permanent discontinuation of CRESEMBA therapy 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%)[1]

IMPORTANT SAFETY INFORMATION (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.

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Predictable and consistent pharmacokinetic (PK) 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†[5]

†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; 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 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

IMPORTANT SAFETY INFORMATION (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.

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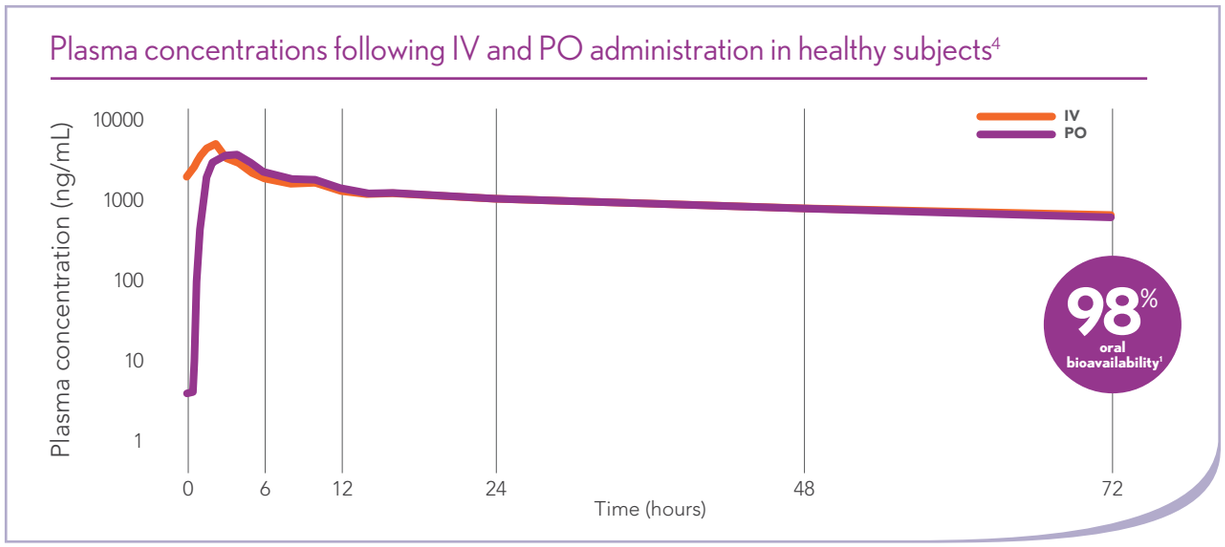
CRESEMBA offers bioequivalent IV and PO formulations[1]



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.[4]

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.

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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[1,6-10]

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[4,6-10]

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

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.

Please see additional Important Safety Information on page 13. Click here for Full Prescribing Information for CRESEMBA.

Start and stay on CRESEMBA® (isavuconazonium sulfate)

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

IV and PO dosing regimen[1]		
	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**
CRESEMBA Capsules 186 mg† of isavuconazonium sulfate per capsule	**2 Capsules** **q8h for 6 doses (48 h)**	**2 Capsules** **Once Daily**

Capsules not actual size.

*372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole.
†186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole.
‡Start maintenance doses 12–24 hours after the last loading dose.
IV=intravenous; PO=by mouth.

CRESEMBA for injection: a water-soluble formulation[1]

- IV formulation does not contain cyclodextrin and requires no dose adjustment for renal impairment[1]
- Can be administered through a peripheral or central venous line[4]
- IV formulation must be administered via an infusion set with an in-line filter (pore size 0.2–1.2 microns)[1]
- 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[1]
- Do not infuse CRESEMBA with other IV medications[1]
- Flush IV lines with 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP, prior to and after infusion of CRESEMBA[1]
- After dilution of the IV formulation, avoid unnecessary vibration or vigorous shaking of the solution. Do not use pneumatic transport system[1]
- 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[1]

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.[1]

CRESEMBA capsules: an option throughout the care continuum[1]

- 98% absolute bioavailability[1]
- Capsules can be taken with or without food[1]
- Swallow whole; do not chew, crush, dissolve, or open the capsules[1]

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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.

Please visit CRESEMBASupportSolutions.com to learn more

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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INDICATIONS AND USAGE

CRESEMBA 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
- 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

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.

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.

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.

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

ADVERSE REACTIONS

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%).

References: 1. CRESEMBA® (isavuconazonium sulfate) [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. *Lancet.* 2016;387:760-769. **3.** Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis.* 2016;16:828-837. **4.** Data on file. Northbrook, IL: Astellas Pharma US, Inc. **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;60:5483-5491. **6.** 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. **7.** Townsend R, Dietz A, Hale C, et al. Pharmacokinetic evaluation of CYP3A4-mediated drug-drug interactions with rifampin, ketoconazole, midazolam, and ethinyl estradiol/norethindrone in healthy adults. *Clin Pharmacol Drug Dev.* 2017;6:44-53. **8.** Yamazaki T, Desai A, Goldwater R, et al. Pharmacokinetic effects of isavuconazole coadministration with cytochrome p450 enzyme substrates buproprion, repaglinide, caffeine, dextromethorphan, and methadone in healthy subjects. *Clin Pharmacol Drug Dev.* 2017;6:54-65. **9.** 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. **10.** Groll AH, Desai A, Han D, et al. Pharmacokinetic assessment of drug-drug interactions of isavuconazole with immunosuppressants cyclosporine, mycophenolic acid, prednisolone, sirolimus, and tacrolimus in healthy adults. *Clin Pharmacol Drug Dev.* 2017;6:76-85. **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;6:86-92. **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, and is not affected by food, or drugs that alter stomach pH. *Int J Clin Pharmacol Ther.* 2016;54:572-580.

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

Navigating antifungal treatment

Proven efficacy in the treatment of invasive aspergillosis*[1]

- CRESEMBA® (isavuconazonium sulfate) demonstrated noninferiority to voriconazole in all-cause mortality through Day 42 (18.6% and 20.2%, respectively, adjusted treatment difference −1.0% [95% CI: −8.0, 5.9])

The first and only FDA-approved azole antifungal to treat invasive mucormycosis†[1,4]

Safety profile[1]

- Treatment-emergent adverse reactions resulting in permanent discontinuation were reported in 37 (14%) CRESEMBA-treated patients and 59 (23%) voriconazole-treated 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%)
- No dose adjustment in patients with renal impairment, including end-stage renal disease
- CRESEMBA has no warning for visual disturbances

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)
- 98% absolute bioavailability following PO administration

Start and stay on CRESEMBA‡[1]

- Once-daily maintenance dosing, regardless of indication or formulation‡
- Loading dose: 372 mg (1 vial or 2 capsules) q8h for 48 hours
- Maintenance dose: 372 mg (1 vial or 2 capsules) once daily

INDICATIONS AND USAGE

CRESEMBA 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
- 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 on page 13. Click here for Full Prescribing Information for CRESEMBA.

*Based on a Phase 3, randomized, double-blind, noninferiority trial vs voriconazole for the primary treatment of invasive fungal disease caused by *Aspergillus* or other filamentous fungi (N=516).[1]

†Based on results from a Phase 3, open-label, noncomparative study of CRESEMBA in a subset of patients with invasive mucormycosis (n=37).[1]

‡372 mg of isavuconazonium sulfate per vial is equivalent to 200 mg of isavuconazole. 186 mg of isavuconazonium sulfate per capsule is equivalent to 100 mg of isavuconazole. Start maintenance doses 12–24 hours after the last loading dose.

AUC=area under the curve; FDA=Food and Drug Administration; PO=by mouth.

astellas

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