LOCAL PRODUCT DOCUMENT
PT. PFIZER INDONESIA

Generic Name: Isavuconazonium sulfate
Trade Name: CRESEMBA
EU SPC Effective Date: July 17, 2025
Supersedes: May 20, 2024

1. Name of the Medicinal Product

1.1 Product name

CRESEMBA

1.2 Strength

200 mg

1.3 Pharmaceutical dosage form

Powder for concentrate for solution for infusion

2. Qualitative and Quantitative Composition

Each vial contains 200 mg isavuconazole (as 372.6 mg isavuconazonium sulfate).

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Powder for concentrate for solution for infusion

Appearance:

White to yellow powder

4. Clinical Particulars

4.1 Therapeutic indication

CRESEMBA is indicated in adults for the treatment of

- invasive aspergillosis
- mucormycosis in patients for whom amphotericin B is inappropriate (see sections 4.4 and 5.1)

Consideration should be given to official guidance on the appropriate use of antifungal agents.

Usage

Specimens for fungal culture and other relevant laboratory studies (including histopathology) to isolate and identify causative organism(s) should be obtained prior to initiating antifungal therapy. Therapy may be instituted before the results of the cultures and other laboratory studies are known depending on national guideline. However, once these results become available, antifungal therapy should be adjusted accordingly.

4.2 Posology and method of administration

Posology

Early targeted therapy (pre-emptive or diagnostic-driven therapy) may be instituted pending confirmation of the disease from specific diagnostic tests. However, once these results become available, antifungal therapy should be adjusted accordingly.

Loading dose

The recommended loading dose is one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours (6 administrations in total).

Maintenance dose

The recommended maintenance dose is one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) once daily, starting 12 to 24 hours after the last loading dose.

Duration of therapy should be determined by the clinical response (see section 5.1).

For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered (see sections 5.1 and 5.3).

Switch to oral isavuconazole

CRESEMBA is also available as hard capsules containing 100 mg isavuconazole.

On the basis of the high oral bioavailability (98%, see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

Elderly

No dose adjustment is necessary for elderly patients; however the clinical experience in elderly patients is limited.

Renal impairment
No dose adjustment is necessary in patients with renal impairment, including patients with end-stage renal disease (see section 5.2).

Hepatic impairment
No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B) (see sections 4.4 and 5.2).

Isavuconazole has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks (see sections 4.4, 4.8 and 5.2).

Paediatric population
The safety and efficacy of CRESEMBA in children aged below 18 years has not yet been established. No data are available.

Method of administration
Intravenous use.

Precautions to be taken before handling or administering the medicinal product.

CRESEMBA must be reconstituted and then further diluted to a concentration corresponding to approximately 0.8 mg/mL isavuconazole prior to administration by intravenous infusion over a minimum of 1 hour to reduce the risk of infusion-related reactions. The infusion must be administered via an infusion set with an in-line filter with a microporous membrane made of polyethersulfone (PES) and with a pore size of 0.2 µm to 1.2 µm. CRESEMBA must only be given as an intravenous infusion.

For detailed instructions on the reconstitution and dilution of CRESEMBA before administration, see section 6.6.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ketoconazole (see section 4.5).

Co-administration with high dose ritonavir (>200 mg every 12 hours) (see section 4.5).

Co-administration with strong CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g., phenobarbital), phenytoin and St. John's wort or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine (see section 4.5).

Patients with familial short QT syndrome (see section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity

Hypersensitivity to isavuconazole may result in adverse reactions that include: anaphylactic reaction, hypotension, respiratory failure, dyspnoea, drug eruption, pruritus, and rash (see section 4.8). In case of anaphylactic reaction, isavuconazole should be discontinued immediately and appropriate medical treatment should be initiated.

Caution should be used in prescribing isavuconazole to patients with hypersensitivity to other azole antifungal agents.

Infusion-related reactions

During intravenous administration of isavuconazole, infusion-related reactions including hypotension, dyspnoea, dizziness, paraesthesia, nausea, and headache were reported (see section 4.8). The infusion should be stopped if these reactions occur.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported during treatment with azole antifungal agents. If a patient develops a severe cutaneous adverse reaction, CRESEMBA should be discontinued.

Cardiovascular

QT shortening

Isavuconazole is contraindicated in patients with familial short QT syndrome (see section 4.3).

In a QT study in healthy human subjects, isavuconazole shortened the QTc interval in a concentration-related manner. For the 200 mg dosing regimen, the least squares mean (LSM) difference from placebo was 13.1 ms at 2 hours post dose [90% CI: 17.1, 9.1 ms]. Increasing the dose to 600 mg resulted in an LSM difference from placebo of 24.6 ms at 2 hours post dose

[90% CI: 28.7, 20.4 ms].

Caution is warranted when prescribing isavuconazole to patients taking other medicinal products known to decrease the QT interval, such as rufinamide.

Elevated liver transaminases

Elevated liver transaminases have been reported in clinical studies (see section 4.8). The elevations in liver transaminases rarely required discontinuation of isavuconazole. Monitoring of hepatic enzymes should be considered, as clinically indicated.

Severe hepatic impairment

Isavuconazole has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. These patients should be carefully monitored for potential drug toxicity (see sections 4.2, 4.8 and 5.2).

Concomitant use with other medicinal products

CYP3A4/5 inhibitors

Ketoconazole is contraindicated (see section 4.3). For the strong CYP3A4 inhibitor lopinavir/ritonavir, a two-fold increase in isavuconazole exposure was observed. For other strong CYP3A4/5 inhibitors, a less pronounced effect can be expected. No dose adjustment of isavuconazole is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see section 4.5).

CYP3A4/5 inducers

Co-administration with mild CYP3A4/5 inducers such as aprepitant, prednisone, and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels; co-administration with mild CYP3A4/5 inducers should be avoided unless the potential benefit is considered to outweigh the risk (see section 4.5).

CYP3A4/5 substrates including immunosuppressants

Isavuconazole can be considered a moderate inhibitor of CYP3A4/5, and systemic exposure to medicinal products metabolised by CYP3A4 may be increased when co-administered with isavuconazole. Concomitant use of isavuconazole with CYP3A4 substrates such as the immunosuppressants tacrolimus, sirolimus or ciclosporin may increase the systemic exposure

to these medicinal products. Appropriate therapeutic drug monitoring and dose adjustment may be necessary during co-administration (see section 4.5).

CYP2B6 substrates
Isavuconazole is an inducer of CYP2B6. Systemic exposure to medicinal products metabolised by CYP2B6 may be decreased when co-administered with isavuconazole. Therefore, caution is advised when CYP2B6 substrates, especially medicinal products with a narrow therapeutic index such as cyclophosphamide, are co-administered with isavuconazole. The use of the CYP2B6 substrate efavirenz with isavuconazole is contraindicated because efavirenz is a moderate inducer of CYP3A4/5 (see section 4.3).

P-gp substrates
Isavuconazole may increase the exposure of medicinal products that are P-gp substrates. Dose adjustment of medicinal products that are P-gp substrates, especially medicinal products with a narrow therapeutic index such as digoxin, colchicine and dabigatran etexilate, may be needed when concomitantly administered with CRESEMBA (see section 4.5).

Limitations of the clinical data
The clinical data for isavuconazole in the treatment of mucormycosis are limited to one prospective non-controlled clinical study in 37 patients with proven or probable mucormycosis who received isavuconazole for primary treatment, or because other antifungal treatments (predominantly amphotericin B) were inappropriate.

For individual Mucorales species, the clinical efficacy data are very limited, often to one or two patients (see section 5.1). Susceptibility data were available in only a small subset of cases. These data indicate that concentrations of isavuconazole required for inhibition *in vitro* are very variable between genera/species within the order of Mucorales, and generally higher than concentrations required to inhibit *Aspergillus* species. It should be noted that there was no dose-finding study in mucormycosis, and patients were administered the same dose of isavuconazole as was used for the treatment of invasive aspergillosis.

4.5 Interaction with other medicinal products and other forms of interactions

Potential of medicinal products to affect the pharmacokinetics of isavuconazole
Isavuconazole is a substrate of CYP3A4 and CYP3A5 (see section 5.2). Co-administration of medicinal products which are inhibitors of CYP3A4 and/or CYP3A5 may increase the plasma concentrations of isavuconazole. Co-administration of medicinal products which are inducers of CYP3A4 and/or CYP3A5 may decrease the plasma concentrations of isavuconazole.

Medicinal products that inhibit CYP3A4/5

Co-administration of isavuconazole with the strong CYP3A4/5 inhibitor ketoconazole is contraindicated, since this medicinal product can significantly increase plasma concentrations of isavuconazole (see sections 4.3 and 4.5).

For the strong CYP3A4 inhibitor lopinavir/ritonavir, a two-fold increase in isavuconazole exposure was observed. For other strong CYP3A4 inhibitors, such as clarithromycin, indinavir and saquinavir, a less pronounced effect can be expected, based on their relative potency. No dose adjustment of isavuconazole is necessary when co-administered with strong CYP3A4/5 inhibitors, however caution is advised as adverse drug reactions may increase (see section 4.4).

No dose adjustment is warranted for moderate to mild CYP3A4/5 inhibitors.

Medicinal products that induce CYP3A4/5

Co-administration of isavuconazole with potent CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long-acting barbiturates (e.g., phenobarbital), phenytoin and St. John's wort, or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine, is contraindicated, since these medicinal products can significantly decrease plasma concentrations of isavuconazole (see section 4.3).

Co-administration with mild CYP3A4/5 inducers such as aprepitant, prednisone and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels; co-administration with mild CYP3A4/5 inducers should be avoided unless the potential benefit is considered to outweigh the risk (see section 4.4).

Co-administration with high-dose ritonavir (>200 mg twice daily) is contraindicated, as at high doses ritonavir may induce CYP3A4/5 and decrease isavuconazole plasma concentrations (see section 4.3).

Potential for isavuconazole to affect exposures of other medicines

Medicinal products metabolised by CYP3A4/5

Isavuconazole is a moderate inhibitor of CYP3A4/5; co-administration of CRESEMBA with medicinal products which are substrates of CYP3A4/5 may result in increased plasma concentrations of these medicinal products.

Medicinal products metabolised by CYP2B6

Isavuconazole is a mild CYP2B6 inducer; co-administration of isavuconazole may result in decreased plasma concentrations of CYP2B6 substrates.

Medicinal products transported by P-gp in the intestine

Isavuconazole is a mild inhibitor of P-glycoprotein (P-gp); co-administration with isavuconazole may result in increased plasma concentrations of P-gp substrates.

Medicinal products transported by BCRP

Isavuconazole is an inhibitor *in vitro* of BCRP, and plasma concentrations of substrates of BCRP may therefore be increased. Caution is advised when isavuconazole is given concomitantly with substrates of BCRP.

Medicinal products renally excreted via transport proteins

Isavuconazole is a mild inhibitor of the organic cation transporter 2 (OCT2). Co-administration of isavuconazole with medicinal products which are substrates of OCT2 may result in increased plasma concentrations of these medicinal products.

Uridine diphosphate-glucuronosyltransferases (UGT) substrates

Isavuconazole is a mild inhibitor of UGT. Co-administration of isavuconazole with medicinal products which are substrates of UGT may result in mildly increased plasma concentrations of these medicinal products.

Interaction table

Interactions between isavuconazole and co-administered medicinal products are listed in Table 1 (increase is indicated as "↑", decrease as "↓"), ordered by therapeutic class. Unless otherwise stated, studies detailed in Table 1 have been performed with the recommended dose of isavuconazole.

Table 1 Interactions

Co-administered medicinal product by therapeutic area	**Effects on drug concentrations/ Geometric Mean Change (%) in AUC, C_{max} (Mode of action)**	**Recommendation concerning co-administration**
Anticonvulsants		
Carbamazepine, phenobarbital and phenytoin (strong CYP3A4/5 inducers)	Isavuconazole concentrations may decrease (CYP3A induction by carbamazepine, phenytoin and long-acting barbiturates such as phenobarbital).	The concomitant administration of isavuconazole and carbamazepine, phenytoin and long-acting barbiturates such as phenobarbital is contraindicated.
Antibacterials		

Rifampicin (strong CYP3A4/5 inducer)	Isavuconazole: AUC_{tau}: ↓ 90% C_{max}: ↓ 75% (CYP3A4/5 induction)	The concomitant administration of isavuconazole and rifampicin is contraindicated.
Rifabutin (strong CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and rifabutin is contraindicated.
Nafcillin (moderate CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and nafcillin is contraindicated.
Clarithromycin (strong CYP3A4/5 inhibitor)	Not studied. Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary; caution is advised as adverse drug reactions may increase.
Antifungals		
Ketoconazole (strong CYP3A4/5 inhibitor)	Isavuconazole: AUC_{tau}: ↑ 422% C_{max}: ↑ 9% (CYP3A4/5 inhibition)	The concomitant administration of isavuconazole and ketoconazole is contraindicated.
Herbal medicines		
St. John's wort (strong CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4 induction)	The concomitant administration of isavuconazole and St. John's wort is contraindicated.
Immunosuppressants		
Ciclosporin, sirolimus, tacrolimus (CYP3A4/5 substrates)	Ciclosporin: AUC_{inf}: ↑ 29% C_{max}: ↑ 6% Sirolimus: AUC_{inf}: ↑ 84% C_{max}: ↑ 65% Tacrolimus: AUC_{inf}: ↑ 125% C_{max}: ↑ 42% (CYP3A4 inhibition)	No isavuconazole dose adjustment necessary. Ciclosporin, sirolimus, tacrolimus: monitoring of plasma levels and appropriate dose adjustment if required.
Mycophenolate mofetil (MMF) (UGT substrate)	Mycophenolic acid (MPA, active metabolite): AUC_{inf}: ↑ 35% C_{max}: ↓ 11% (UGT inhibition)	No isavuconazole dose adjustment necessary. MMF: monitoring for MPA-related toxicities is advised.

Prednisone (CYP3A4 substrate)	Prednisolone (active metabolite): AUC_{inf}: ↑ 8% C_{max}: ↓ 4% (CYP3A4 inhibition) Isavuconazole concentrations may decrease. (CYP3A4/5 induction)	Co-administration should be avoided unless the potential benefit is considered to outweigh the risk.
Opioids		
Short-acting opiates (alfentanil, fentanyl) (CYP3A4/5 substrate)	Not studied. Short-acting opiate concentrations may increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary. Short-acting opiates (alfentanil, fentanyl): careful monitoring for any occurrence of drug toxicity, and dose reduction if required.
Methadone (CYP3A4/5, 2B6 and 2C9 substrate)	S-methadone (inactive opiate isomer) AUC_{inf}: ↓ 35% C_{max}: ↑ 1% 40% reduction in terminal half-life R-methadone (active opiate isomer). AUC_{inf}: ↓ 10% C_{max}: ↑ 4% (CYP2B6 induction)	No isavuconazole dose adjustment necessary. Methadone: no dose adjustment required.
Anti-cancer		
Vinca alkaloids (vincristine, vinblastine) (P-gp substrates)	Not studied. Vinca alkaloid concentrations may increase. (P-gp inhibition)	No isavuconazole dose adjustment necessary. Vinca alkaloids: careful monitoring for any occurrence of drug toxicity, and dose reduction if required.
Cyclophosphamide (CYP2B6, CYP3A4 substrate)	Not studied. Active metabolites of cyclophosphamide may increase or decrease. (CYP2B6 induction, CYP3A4 inhibition)	No isavuconazole dose adjustment necessary. Cyclophosphamide: careful monitoring for any occurrence of lack of efficacy or increased toxicity, and dose adjustment if required.
Methotrexate (BCRP, OAT1, OAT3 substrate)	Methotrexate: AUC_{inf}: ↓ 3% C_{max}: ↓ 11% 7-hydroxymetabolite: AUC_{inf}: ↑ 29% C_{max}: ↑ 15% (Mechanism unknown)	No isavuconazole dose adjustment necessary. Methotrexate: no dose adjustment required.

Other anti-cancer agents (daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan) (BCRP substrates)	Not studied. Daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone, topotecan concentrations may increase. (BCRP inhibition)	No isavuconazole dose adjustment necessary. Daunorubicin, doxorubicin, imatinib, irinotecan, lapatinib, mitoxantrone or topotecan: careful monitoring for any occurrence of drug toxicity, and dose reduction if required.
Antiemetics		
Aprepitant (mild CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may decrease. (CYP3A4/5 induction)	Co-administration should be avoided unless the potential benefit is considered to outweigh the risk.
Antidiabetics		
Metformin (OCT1, OCT2 and MATE1 substrate)	Metformin: AUC_{inf}: ↑ 52% C_{max}: ↑ 23% (OCT2 inhibition)	No isavuconazole dose adjustment necessary. Metformin: dose reduction may be required.
Repaglinide (CYP2C8 and OATP1B1 substrate)	Repaglinide: AUC_{inf}: ↓ 8% C_{max}: ↓ 14%	No isavuconazole dose adjustment necessary. Repaglinide: no dose adjustment required.
Pioglitazone (mild CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may decrease. (CYP3A4/5 induction)	Co-administration should be avoided unless the potential benefit is considered to outweigh the risk.
Anticoagulants		
Dabigatran etexilate (P-gp substrate)	Not studied. Dabigatran etexilate concentrations may increase. (P-gp inhibition)	No isavuconazole dose adjustment necessary. Dabigatran etexilate has a narrow therapeutic index and should be monitored, and dose reduction if required.
Warfarin (CYP2C9 substrate)	S-warfarin AUC_{inf}: ↑ 11% C_{max}: ↓ 12% R-warfarin AUC_{inf}: ↑ 20% C_{max}: ↓ 7%	No isavuconazole dose adjustment necessary. Warfarin: no dose adjustment required.

Antiretroviral agents		
Lopinavir 400 mg / Ritonavir 100 mg (CYP3A4/5 strong inhibitors and substrates)	Lopinavir: AUC_{tau}: ↓ 27% C_{max}: ↓ 23% $C_{min, ss}$: ↓ 16%[a)] Ritonavir: AUC_{tau}: ↓ 31% C_{max}: ↓ 33% (Mechanism unknown) Isavuconazole: AUC_{tau}: ↑ 96% C_{max}: ↑ 74% (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary; caution is advised as adverse drug reactions may increase. Lopinavir/ritonavir: no dose adjustment for lopinavir 400 mg/ritonavir 100 mg every 12 hours required, but careful monitoring for any occurrence of lack of anti-viral efficacy.
Ritonavir (at doses >200 mg every 12 hours) (strong CYP3A4/5 inducer)	Not studied. Ritonavir at high doses may significantly decrease isavuconazole concentrations. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and high doses of ritonavir (>200 mg every 12 hours) is contraindicated.
Efavirenz (CYP3A4/5 moderate inducer and CYP2B6 substrate)	Not studied. Efavirenz concentrations may decrease. (CYP2B6 induction) Isavuconazole drug concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and efavirenz is contraindicated.
Etravirine (moderate CYP3A4/5 inducer)	Not studied. Isavuconazole concentrations may significantly decrease. (CYP3A4/5 induction)	The concomitant administration of isavuconazole and etravirine is contraindicated.
Indinavir (CYP3A4/5 strong inhibitor and substrate)	Indinavir:[b)] AUC_{inf}: ↓ 36% C_{max}: ↓ 52% (Mechanism unknown) Isavuconazole concentrations may increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary; caution is advised as adverse drug reactions may increase. Indinavir: careful monitoring for any occurrence of lack of anti-viral efficacy, and dose increase if required.

Saquinavir (strong CYP3A4 inhibitor)	Not studied. Saquinavir concentrations may decrease (as observed with lopinavir/ritonavir) or increase (CYP3A4 inhibition). Isavuconazole concentrations may increase. (CYP3A4/5 inhibition).	No isavuconazole dose adjustment necessary; caution is advised as adverse drug reactions may increase. Saquinavir: careful monitoring for any occurrence of drug toxicity and /or lack of anti-viral efficacy, and dose adjustment if required.
Other protease inhibitors (e.g., fosamprenavir) (CYP3A4/5 strong or moderate inhibitors and substrates)	Not studied. Protease inhibitor concentrations may decrease (as observed with lopinavir/ritonavir) or increase. (CYP3A4 inhibition) Isavuconazole concentrations may increase. (CYP3A4/5 inhibition).	No isavuconazole dose adjustment necessary. Protease inhibitors: careful monitoring for any occurrence of drug toxicity and /or lack of anti-viral efficacy, and dose adjustment if required.
Other NNRTI (e.g., nevirapine) (CYP3A4/5 and 2B6 inducers and substrates)	Not studied. NNRTI concentrations may decrease (CYP2B6 induction by isavuconazole) or increase. (CYP3A4/5 inhibition)	No isavuconazole dose adjustment necessary. NNRTIs: careful monitoring for any occurrence of drug toxicity and/or lack of anti-viral efficacy, and dose adjustment if required.
Antiacids		
Esomeprazole (CYP2C19 substrate and gastric pH ↑)	Isavuconazole: AUC_{tau}: ↑ 8% C_{max}: ↑ 5%	No isavuconazole dose adjustment necessary. Esomeprazole: no dose adjustment required.
Omeprazole (CYP2C19 substrate and gastric pH ↑)	Omeprazole: AUC_{inf}: ↓ 11% C_{max}: ↓ 23%	No isavuconazole dose adjustment necessary. Omeprazole: no dose adjustment required.
Lipid-lowering agents		
Atorvastatin and other statins (CYP3A4 substrates e.g., simvastatin, lovastatin, rosuvastatin) (CYP3A4/5 and/or BCRP substrates)	Atorvastatin: AUC_{inf}: ↑ 37% C_{max}: ↑ 3% Other statins were not studied. Statins concentrations may increase. (CYP3A4/5 or BCRP inhibition)	No isavuconazole dose adjustment necessary. Based on results with atorvastatin, no statin dose adjustment required. Monitoring of adverse reactions typical of statins is advised.

Antiarrhythmics		
Digoxin (P-gp substrate)	Digoxin: AUC_{inf}: ↑ 25% C_{max}: ↑ 33% (P-gp inhibition)	No isavuconazole dose adjustment necessary. Digoxin: serum digoxin concentrations should be monitored and used for titration of the digoxin dose.
Oral contraceptives		
Ethinyl oestradiol and Norethindrone (CYP3A4/5 substrates)	Ethinyl oestradiol AUC_{inf}: ↑ 8% C_{max}: ↑ 14% Norethindrone AUC_{inf}: ↑ 16% C_{max}: ↑ 6%	No isavuconazole dose adjustment necessary. Ethinyl oestradiol and Norethindrone: no dose adjustment required.
Antitussives		
Dextromethorphan (CYP2D6 substrate)	Dextromethorphan: AUC_{inf}: ↑ 18% C_{max}: ↑ 17% Dextrorphan (active metabolite): AUC_{inf}: ↑ 4% C_{max}: ↓ 2%	No isavuconazole dose adjustment necessary. Dextromethorphan: no dose adjustment required.
Benzodiazepines		
Midazolam (CYP3A4/5 substrate)	Oral midazolam: AUC_{inf}: ↑ 103% C_{max}: ↑ 72% (CYP3A4 inhibition)	No isavuconazole dose adjustment necessary. Midazolam: careful monitoring of clinical signs and symptoms recommended, and dose reduction if required.
Antigout agent		
Colchicine (P-gp substrate)	Not studied. Colchicine concentrations may increase. (P-gp inhibition)	No isavuconazole dose adjustment necessary. Colchicine has a narrow therapeutic index and should be monitored, dose reduction if required.
Natural products		
Caffeine (CYP1A2 substrate)	Caffeine: AUC_{inf}: ↑ 4% C_{max}: ↓ 1%	No isavuconazole dose adjustment necessary. Caffeine: no dose adjustment required.
Smoking cessation aids		
Bupropion (CYP2B6 substrate)	Bupropion: AUC_{inf}: ↓ 42% C_{max}: ↓ 31% (CYP2B6 induction)	No isavuconazole dose adjustment necessary. Bupropion: dose increase if required.

NNRTI, non-nucleoside reverse-transcriptase inhibitor; P-gp, P-glycoprotein.
[a] % decrease of the mean trough level values.
[b] Indinavir was only studied after a single dose of 400 mg isavuconazole.

AUC_{inf} = area under the plasma concentration-time profiles extrapolated to infinity; AUC_{tau} = area under the plasma concentration-time profiles during the 24 h interval at steady state; C_{max} = peak plasma concentration; $C_{min, ss}$ = trough levels at steady state.

4.6 Pregnancy and lactation

Pregnancy

There are no data from the use of CRESEMBA in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

CRESEMBA must not be used during pregnancy except in patients with severe or potentially life-threatening fungal infections, in whom isavuconazole may be used if the anticipated benefits outweigh the possible risks to the foetus.

Women of child-bearing potential

CRESEMBA is not recommended for women of child-bearing potential who are not using contraception.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of isavuconazole/metabolites in milk (see section 5.3).

A risk to newborns and infants cannot be excluded.

Breast-feeding should be discontinued during treatment with CRESEMBA.

Fertility

There are no data on the effect of isavuconazole on human fertility. Studies in animals did not show impairment of fertility in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machine

Isavuconazole has a moderate potential to influence the ability to drive and use machines. Patients should avoid driving or operating machinery if symptoms of confusional state, somnolence, syncope, and/or dizziness are experienced.

4.8 Undesirable effects

Summary of the safety profile

The most common treatment-related adverse reactions were elevated liver chemistry tests (7.9%), nausea (7.4%), vomiting (5.5%), dyspnoea (3.2%), abdominal pain (2.7%), diarrhoea (2.7%), injection site reaction (2.2%), headache (2.0%), hypokalaemia (1.7%) and rash (1.7%).

The adverse reactions which most often led to permanent discontinuation of isavuconazole treatment were confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnoea (0.5%), epilepsy (0.5%), respiratory failure (0.5%) and vomiting (0.5%).

Tabulated list of adverse reactions

Table 2 presents adverse reactions with isavuconazole in the treatment of invasive fungal infections, by System Organ Class and frequency.

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100); not known (frequency cannot be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Summary of adverse reactions by MedDRA System Organ Class and frequency

System Organ Class	**Adverse Drug Reactions**
Blood and lymphatic system disorders	
Uncommon	Neutropenia; Thrombocytopenia^; Pancytopenia; Leukopenia^; Anaemia^
Immune system disorders	
Uncommon	Hypersensitivity^
Not known	Anaphylactic reaction*
Metabolism and nutrition disorders	
Common	Hypokalaemia; Decreased appetite
Uncommon	Hypomagnesaemia; Hypoglycaemia; Hypoalbuminaemia; Malnutrition^; Hyponatraemia
Psychiatric disorders	
Common	Delirium^#
Uncommon	Depression; Insomnia^
Nervous system disorders	
Common	Headache; Somnolence
Uncommon	Convulsion^; Syncope; Dizziness; Paraesthesia^; Encephalopathy; Presyncope; Neuropathy peripheral; Dysgeusia

Ear and labyrinth disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Atrial fibrillation; Tachycardia; Bradycardia^; Palpitations; Atrial flutter; Electrocardiogram QT shortened; Supraventricular tachycardia; Ventricular extrasystoles; Supraventricular extrasystoles
Vascular disorders	
Common	Thrombophlebitis^
Uncommon	Circulatory collapse; Hypotension
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea^; Acute respiratory failure^
Uncommon	Bronchospasm; Tachypnoea; Haemoptysis; Epistaxis
Gastrointestinal disorders	
Common	Vomiting; Diarrhoea; Nausea; Abdominal pain^
Uncommon	Dyspepsia; Constipation; Abdominal distension
Hepatobiliary disorders	
Common	Elevated liver chemistry tests^#
Uncommon	Hepatomegaly
Skin and subcutaneous tissue disorders	
Common	Rash^; Pruritus
Uncommon	Petechiae; Alopecia; Drug eruption; Dermatitis^
Musculoskeletal and connective tissue disorders	
Uncommon	Back pain
Renal and urinary disorders	
Common	Renal failure
General disorders and administration site conditions	
Common	Chest pain^; Fatigue; Injection site reaction^
Uncommon	Oedema peripheral^; Malaise; Asthenia

^ Indicates that grouping of appropriate preferred terms into a single medical concept occurred.
* ADR identified post-marketing.
# See section Description of selected adverse reactions below.

Description of selected adverse reactions

Delirium includes reactions of confusional state.

Elevated liver chemistry tests includes events of alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, liver function test abnormal, and transaminases increased.

Laboratory effects

In a double-blind, randomized, active-controlled clinical study of 516 patients with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi, elevated liver

transaminases (alanine aminotransferase or aspartate aminotransferase) >3 × Upper Limit of Normal (ULN) were reported at the end of study treatment in 4.4% of patients who received isavuconazole. Marked elevations of liver transaminases >10 × ULN developed in 1.2% of patients on isavuconazole.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

PT Pfizer Indonesia
Email: IDN.AEReporting@pfizer.com
Website: www.pfizersafetyreporting.com

4.9 Overdose

Symptoms

Symptoms reported more frequently at supratherapeutic doses of isavuconazole (equivalent to isavuconazole 600 mg/day) evaluated in a QT study than in the therapeutic dose group (equivalent to isavuconazole 200 mg/day dose) included: headache, dizziness, paraesthesia, somnolence, disturbance in attention, dysgeusia, dry mouth, diarrhoea, oral hypoaesthesia, vomiting, hot flush, anxiety, restlessness, palpitations, tachycardia, photophobia and arthralgia.

Management of overdose

Isavuconazole is not removed by haemodialysis. There is no specific antidote for isavuconazole. In the event of an overdose, supportive treatment should be instituted.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole and tetrazole derivative,

ATC code: J02AC05.

Mechanism of action

Isavuconazole is the active moiety formed after oral or intravenous administration of isavuconazonium sulfate (see section 5.2).

Isavuconazole demonstrates a fungicidal effect by blocking the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P450-dependent enzyme lanosterol 14-alpha-demethylase, responsible for the conversion of lanosterol to ergosterol. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane, thus weakening the structure and function of the fungal cell membrane.

Microbiology

In animal models of disseminated and pulmonary aspergillosis, the pharmacodynamic (PD) index important in efficacy is exposure divided by minimum inhibitory concentration (MIC) (AUC/MIC).

No clear correlation between *in vitro* MIC and clinical response for the different species (*Aspergillus* and *Mucorales*) could be established.

Concentrations of isavuconazole required to inhibit *Aspergillus* species and genera/species of the order *Mucorales in vitro* have been very variable. Generally, concentrations of isavuconazole required to inhibit *Mucorales* are higher than those required to inhibit the majority of *Aspergillus* species.

Clinical efficacy has been demonstrated for the following *Aspergillus* species: *Aspergillus fumigatus, A. flavus, A. niger,* and *A. terreus* (see further below).

Mechanism(s) of resistance

Reduced susceptibility to triazole antifungal agents has been associated with mutations in the fungal cyp51A and cyp51B genes coding for the target protein lanosterol 14-alpha-demethylase involved in ergosterol biosynthesis. Fungal strains with reduced in vitro susceptibility to isavuconazole have been reported, and cross-resistance with voriconazole and other triazole antifungal agents cannot be excluded.

EUCAST Breakpoints

Aspergillus species	**Minimal Inhibitory Concentration (MIC) breakpoint (mg/L)**	
	≤S (Susceptible)	**>R (Resistant)**
Aspergillus flavus	1	2
Aspergillus fumigatus	1	2
Aspergillus nidulans	0.25	0.25
Aspergillus terreus	1	1

There are currently insufficient data to set clinical breakpoints for other Aspergillus species.

Clinical efficacy and safety

Treatment of invasive aspergillosis

The safety and efficacy of isavuconazole for the treatment of patients with invasive aspergillosis was evaluated in a double-blind, active-controlled clinical study in 516 patients with invasive fungal disease caused by Aspergillus species or other filamentous fungi. In the intent-to-treat (ITT) population, 258 patients received isavuconazole and 258 patients received voriconazole. Isavuconazole was administered intravenously (equivalent to 200 mg isavuconazole) every 8 hours for the first 48 hours, followed by once-daily intravenous or oral treatment (equivalent to 200 mg isavuconazole). The protocol-defined maximum treatment duration was 84 days. Median treatment duration was 45 days.

The overall response at end-of-treatment (EOT) in the myITT population (patients with proven and probable invasive aspergillosis based on cytology, histology, culture or galactomannan testing) was assessed by an independent blinded Data Review Committee. The myITT population comprised 123 patients receiving isavuconazole and 108 patients receiving voriconazole. The overall response in this population was n = 43 (35%) for isavuconazole and n = 42 (38.9%) for voriconazole. The adjusted treatment difference (voriconazole−isavuconazole) was 4.0 (95% confidence interval: −7.9; 15.9).

The all-cause mortality at Day 42 in this population was 18.7% for isavuconazole and 22.2% for voriconazole. The adjusted treatment difference (isavuconazole−voriconazole) was −2.7% (95% confidence interval: −12.9; 7.5).

Treatment of mucormycosis

In an open-label non-controlled study, 37 patients with proven or probable mucormycosis received isavuconazole at the same dose regimen as that used to treat invasive aspergillosis. Median treatment duration was 84 days for the overall mucormycosis patient population, and

102 days for the 21 patients not previously treated for mucormycosis. For patients with probable or proven mucormycosis as defined by the independent Data Review Committee (DRC), all-cause mortality at Day 84 was 43.2% (16/37) for the overall patient population, 42.9% (9/21) for mucormycosis patients receiving isavuconazole as primary treatment, and 43.8% (7/16) for mucormycosis patients receiving isavuconazole who were refractory to, or intolerant of, prior antifungal therapy (mainly amphotericin B based treatments). The DRC assessed overall success rate at EOT was 11/35 (31.4%), with 5 patients considered completely cured and 6 patients partially cured. A stable response was observed in an additional 10/35 patients (28.6%). In 9 patients with mucormycosis due to *Rhizopus* spp., 4 patients showed a favourable response to isavuconazole. In 5 patients with mucormycosis due to *Rhizomucor* spp., no favourable responses were observed. The clinical experience in other species is very limited (Lichtheimia spp. n=2, Cunninghamella spp. n=1, Actinomucor elegans n=1).

Paediatric population

No data are available for the safety and efficacy of CRESEMBA in children aged below 18 years.

5.2 Pharmacokinetic properties

Isavuconazonium sulfate is a water-soluble prodrug that can be administered as an intravenous infusion or orally as hard capsules. Following administration, isavuconazonium sulfate is rapidly hydrolysed by plasma esterases to the active moiety isavuconazole; plasma concentrations of the prodrug are very low, and detectable only for a short time after intravenous dosing.

Absorption

Following oral administration of CRESEMBA in healthy subjects, the active moiety isavuconazole is absorbed and reaches maximum plasma concentrations (C_{max}) approximately 2–3 hours after single and multiple dosing (see Table 3).

Table 3 Steady state pharmacokinetic parameters of isavuconazole following oral administration of CRESEMBA

Parameter Statistic	**Isavuconazole 200 mg (n = 37)**	**Isavuconazole 600 mg (n = 32)**
C_{max} (ng/mL)		
Mean SD CV %	7499 1893.3 25.2	20028 3584.3 17.9
t_{max} (h)		
Median	3.0	4.0

Parameter Statistic	**Isavuconazole 200 mg (n = 37)**	**Isavuconazole 600 mg (n = 32)**
Range	2.0 – 4.0	2.0 – 4.0
AUC (h•ng/mL)		
Mean SD CV %	121402 35768.8 29.5	352805 72018.5 20.4

As shown in table 4 below, the absolute bioavailability of isavuconazole following oral administration of a single dose of CRESEMBA is 98%. Based on these findings, intravenous and oral dosing can be used interchangeably.

Table 4 Pharmacokinetic comparison for oral and intravenous dose (Mean)

	ISA 400 mg oral	**ISA 400 mg i.v.**
AUC (h•ng/mL)	189462.8	193906.8
CV %	36.5	37.2
Half-life (h)	110	115

Effect of food on absorption
Oral administration of CRESEMBA equivalent to 400 mg isavuconazole with a high-fat meal reduced isavuconazole C_{max} by 9% and increased AUC by 9%. CRESEMBA can be taken with or without food.

Distribution
Isavuconazole is extensively distributed, with a mean steady state volume of distribution (Vss) of approximately 450 L. Isavuconazole is highly bound (>99%) to human plasma proteins, predominantly to albumin.

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

Following single doses of [cyano ^{14}C] isavuconazonium and [pyridinylmethyl ^{14}C] isavuconazonium sulfate in humans, in addition to the active moiety (isavuconazole) and the inactive cleavage product, a number of minor metabolites were identified. Except for the active moiety isavuconazole, no individual metabolite was observed with an AUC >10% of total radio-labelled material.

Elimination

Following oral administration of radio-labelled isavuconazonium sulfate to healthy subjects, a mean of 46.1% of the radioactive dose was recovered in faeces, and 45.5% was recovered in urine.

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

The inactive cleavage product is primarily eliminated by metabolism and subsequent renal excretion of the metabolites.

Linearity/non-linearity

Studies in healthy subjects have demonstrated that the pharmacokinetics of isavuconazole are proportional up to 600 mg per day.

Pharmacokinetics in special populations

Paediatric patients

The pharmacokinetics in paediatric patients (<18 years) have not yet been evaluated. No data are available.

Renal impairment

No clinically relevant changes were observed in the total C_{max} and AUC of isavuconazole in subjects with mild, moderate or severe renal impairment compared to subjects with normal renal function. Of the 403 patients who received isavuconazole in the Phase 3 studies, 79 (20%) of patients had an estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2. No dose adjustment is required in patients with renal impairment, including those patients with end-stage renal disease. Isavuconazole is not readily dialysable (see section 4.2).

Hepatic impairment

After a single 100 mg dose of isavuconazole was administered to 32 patients with mild (Child-Pugh Class A) hepatic insufficiency and 32 patients with moderate (Child-Pugh Class B) hepatic insufficiency (16 intravenous and 16 oral patients per Child-Pugh class), the least square mean systemic exposure (AUC) increased 64% in the Child-Pugh Class A group, and 84% in the Child-Pugh Class B group, relative to 32 age- and weight-matched healthy subjects with normal hepatic function. Mean plasma concentrations (C_{max}) were 2% lower in the Child-Pugh Class A group and 30% lower in the Child-Pugh Class B group. The population pharmacokinetic evaluation of isavuconazole in healthy subjects and patients with mild or moderate hepatic dysfunction demonstrated that the mild and moderate hepatic impairment populations had 40% and 48% lower isavuconazole clearance (CL) values, respectively, than

the healthy population.

No dose adjustment is required in patients with mild to moderate hepatic impairment.

Isavuconazole has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. See sections 4.2 and 4.4.

5.3 Preclinical safety data

In rats and rabbits, isavuconazole at systemic exposures below the therapeutic level were associated with dose-related increases in the incidence of skeletal anomalies (rudimentary supernumerary ribs) in offspring. In rats, a dose-related increase in the incidence of zygomatic arch fusion was also noted in offspring (see section 4.6).

Administration of isavuconazonium sulfate to rats at a dose of 90 mg/kg/day (approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole) during pregnancy through the weaning period showed an increased perinatal mortality of the pups. *In utero* exposure to the active moiety isavuconazole had no effect on the fertility of the surviving pups.

Intravenous administration of 14C-labelled isavuconazonium sulfate to lactating rats resulted in the recovery of radiolabel in the milk.

Isavuconazole did not affect the fertility of male or female rats treated with oral doses up to 90 mg/kg/day (approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole).

Isavuconazole has no discernible mutagenic or genotoxic potential. Isavuconazole was negative in a bacterial reverse mutation assay, was weakly clastogenic at cytotoxic concentrations in the L5178Y tk+/- mouse lymphoma chromosome aberration assay, and showed no biologically relevant or statistically significant increase in the frequency of micronuclei in an in vivo rat micronucleus test.

Isavuconazole has demonstrated carcinogenic potential in 2-year rodent carcinogenicity studies. Liver and thyroid tumours are likely caused by a rodent-specific mechanism that is not relevant for humans. Skin fibromas and fibrosarcomas were seen in male rats. The mechanism underlying this effect is unknown. Endometrial adenomas and carcinomas of the uterus were

seen in female rats, which is likely due to a hormonal disturbance. There is no safety margin for these effects. The relevance for humans of the skin and uterine tumours cannot be excluded.

Isavuconazole inhibited the hERG potassium channel and the L-type calcium channel with an IC50 of 5.82 µM and 6.57 µM respectively (34 and 38 fold the human non-protein bound C_{max} at maximum recommended human dose [MRHD], respectively). The in vivo 39-week repeated-dose toxicology studies in monkeys did not show QTcF prolongation at doses up to 40 mg/kg/day (at approximately 1.0-fold the systemic exposure at the human clinical maintenance dose of 200 mg isavuconazole).

Environmental risk assessment has shown that CRESEMBA may pose a risk for the aquatic environment.

6. Pharmaceutical Particulars

6.1 List of excipients

Mannitol (E421)
Sulfuric acid (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years

Chemical and physical in-use stability after reconstitution and dilution has been demonstrated for 24 hours at 2°C to 8°C, or 6 hours at room temperature.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Storage conditions after reconstitution and dilution are 24 hours at 2°C to 8°C, or 6 hours at room temperature.

6.5 Nature and contents of container

Box, 1 vial @ 200 mg

6.6 Special precautions for disposal and other handling

Reconstitution

One vial of the powder for concentrate for solution for infusion should be reconstituted by addition of 5 mL water for injections to the vial. The vial should be shaken to dissolve the powder completely. The reconstituted solution should be inspected visually for particulate matter and discoloration. Reconstituted concentrate should be clear and free of visible particulate. It must be further diluted prior to administration.

Dilution and administration

After reconstitution, the entire content of the reconstituted concentrate should be removed from the vial and added to an infusion bag containing at least 250 mL of either sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) dextrose solution. The infusion solution contains approximately 0.8 mg isavuconazole per mL. After the reconstituted concentrate is further diluted, the diluted solution may show fine white-to-translucent particulates of isavuconazole, that do not sediment (but will be removed by in-line filtration). The diluted solution should be mixed gently, or the bag should be rolled to minimise the formation of particulates. Unnecessary vibration or vigorous shaking of the solution should be avoided. The solution for infusion must be administered via an infusion set with an in-line filter (pore size 0.2 µm to 1.2 µm) made of polyethersulfone (PES).

Isavuconazole should not be infused into the same line or cannula concomitantly with other intravenous products.

Storage conditions after reconstitution and dilution are 24 hours at 2°C to 8°C, or 6 hours at room temperature.

If possible, the intravenous administration of isavuconazole should be completed within 6 hours after reconstitution and dilution at room temperature. If this is not possible, the infusion solution should be immediately refrigerated after dilution, and infusion should be completed within 24 hours. Further information regarding the storage conditions after reconstitution and dilution of the medicinal product is provided in section 6.3.

An existing intravenous line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) dextrose solution.

This medicinal product is for single use only. Discard partially-used vials.

This medicinal product may pose a risk to the environment (see section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Manufactured by:
Baxter Pharmaceutical Solutions, LLC
Bloomington, Indiana, US

Secondary Packaged and Released by:
Almac Pharma Services Limited,
Craigavon, United Kingdom

Imported by:
PT. Pfizer Indonesia,
Jakarta, Indonesia

8. Marketing Authorization Numbers

Box, 1 vial @ 200 mg; Reg. No.: DKI2057100280A1

HARUS DENGAN RESEP DOKTER

Nama Generik: Isavuconazonium sulfate
Nama Dagang: CRESEMBA
Tanggal Efektif EUSPC: 17 Juli 2025
Menggantikan: 21 Juni 2022
Disetujui oleh BPOM:

Brosur kemasan: Informasi untuk pasien

CRESEMBA 200 mg serbuk untuk konsentrat larutan infus

Isavuconazonium sulfate

Baca semua bagian brosur ini dengan cermat sebelum mulai menggunakan obat ini karena berisi informasi penting bagi Anda.
- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala bentuk efek samping yang tidak tercantum di dalam brosur ini. Lihat bagian 8.

Isi brosur ini:

1. Nama Produk
CRESEMBA

2. Deskripsi Produk
CRESEMBA adalah obat antijamur yang mengandung bahan aktif isavuconazole. Isavukonazol bekerja dengan cara membunuh atau menghentikan pertumbuhan jamur penyebab infeksi.

Pemerian:
Serbuk putih hingga kuning.

3. Apa kandungan obat ini?
CRESEMBA 200 mg tersedia dalam vial kaca sekali pakai sebagai serbuk untuk konsentrat larutan infus.

Daftar zat tambahan:
Mannitol (E421) dan asam sulfat (untuk penyesuaian pH)

4. Kekuatan obat
200 mg

5. Apa kegunaan obat ini?
CRESEMBA digunakan pada orang dewasa untuk mengobati infeksi jamur berikut ini:
- aspergilosis invasif;
- mukormikosis pada pasien yang tidak dapat menjalani pengobatan dengan amfoterisin B.

Penggunaan

Spesimen untuk kultur jamur dan penelitian laboratorium terkait lainnya (termasuk histopatologi) untuk mengisolasi dan mengidentifikasi organisme penyebab diperlukan sebelum memulai terapi anti jamur. Perlu dilakukan kultur spesimen dan penelitian laboratorium untuk mengidentifikasi jamur penyebab infeksi sebelum terapi. Terapi dapat dimulai sebelum hasil kultur/lab diperoleh sesuai dengan pedoman nasional. Akan tetapi, setelah hasil kultur/lab diperoleh, terapi perlu disesuaikan dengan hasil tersebut.

6. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini?
CRESEMBA akan diberikan kepada Anda oleh dokter atau perawat.

Dosis awal untuk dua hari pertama (48 jam)
Dosis yang dianjurkan adalah satu vial setiap 8 jam selama 48 jam pertama (total pemberian adalah 6 kali).

Dosis biasa setelah dua hari pertama
Dosis ini dimulai 12 hingga 24 jam setelah dosis awal yang terakhir. Dosis yang dianjurkan adalah satu vial sekali sehari.

Anda akan menerima dosis ini hingga dokter menyatakan sebaliknya. Durasi pengobatan dengan CRESEMBA dapat mencapai lebih dari 6 bulan jika pertimbangan dokter mengharuskan demikian.

Isi vial akan diberikan dalam bentuk infus intra vena oleh dokter atau perawat.

7. Kapan seharusnya Anda tidak menggunakan obat ini?
Jangan gunakan CRESEMBA:
- jika Anda alergi terhadap isavuconazole atau bahan lainnya dalam obat ini,
- jika Anda mengalami masalah denyut jantung yang disebut ‘sindrom QT pendek turunan’,
- **jika Anda menggunakan obat-obatan mana pun berikut ini:**
  - ketokonazol, digunakan untuk mengobati infeksi jamur,
  - ritonavir dosis tinggi (> 200 mg setiap 12 jam), digunakan untuk mengobati HIV,
  - rifampisin, rifabutin, digunakan untuk mengobati tuberkulosis,
  - karbamazepin, digunakan untuk mengobati epilepsi,
  - obat-obatan barbiturat kerja panjang seperti fenobarbital, digunakan untuk mengobati epilepsi dan gangguan tidur,
  - fenitoin, digunakan untuk mengobati epilepsi,
  - St. John’s wort, obat herbal yang digunakan untuk mengobati depresi,
  - efavirenz, etravirin, digunakan untuk mengobati HIV,
  - nafsilin, digunakan untuk mengobati infeksi bakteri.

8. Efek yang tidak diharapkan

Seperti semua obat-obatan yang ada, obat ini dapat menimbulkan efek samping, meskipun tidak semua orang mengalaminya.

Hentikan penggunaan CRESEMBA dan segera beri tahu dokter Anda jika Anda mengalami efek samping mana pun berikut ini:

- reaksi alergi berat (anafilaksis) seperti mengi mendadak, masalah pernapasan, pembengkakan pada wajah, bibir, mulut atau lidah, gatal-gatal berat, berkeringat, pusing atau pingsan, detak jantung cepat atau dada berdebar terlalu keras.

Segera beri tahu dokter Anda jika Anda mengalami efek samping mana pun berikut ini:

- lepuh yang parah pada kulit, mulut, mata, atau organ kemaluan.

Efek samping lainnya

Beri tahu dokter, apoteker, atau perawat jika Anda mengalami efek samping mana pun berikut ini:

Umum: dapat dialami hingga 1 dalam 10 orang

- kadar kalium darah rendah,
- penurunan nafsu makan,
- halusinasi (delirium),
- sakit kepala,
- mengantuk,
- pembengkakan vena yang dapat menimbulkan bekuan darah,
- sesak napas atau mengalami kesulitan bernapas yang tiba-tiba dan berat,
- rasa mual, muntah, diare, sakit perut,
- perubahan hasil tes darah untuk fungsi hati,
- ruam, gatal,
- gagal ginjal (gejala bisa termasuk pembengkakan pada tungkai kaki),
- nyeri dada, merasa lelah atau mengantuk,
- gangguan di lokasi injeksi.

Tidak umum: dapat dialami hingga 1 dalam 100 orang

- penurunan sel darah putih - dapat meningkatkan risiko infeksi dan demam,
- penurunan sel darah yang disebut ‘trombosit’ - dapat meningkatkan risiko perdarahan atau memar,
- penurunan sel darah merah - dapat membuat Anda merasa lemah atau sesak napas atau menjadikan kulit Anda pucat,
- penurunan sel darah yang berat - dapat membuat Anda merasa lemah, dapat menyebabkan memar atau lebih mudah terkena infeksi,
- pembengkakan bibir, mulut, lidah, atau tenggorokan disertai kesulitan bernapas (hipersensitivitas),
- kadar gula darah rendah,
- kadar magnesium darah rendah,
- kadar protein yang disebut ‘albumin’ dalam darah rendah,
- tidak mendapatkan gizi yang memadai dari pola makan Anda (malnutrisi),
- kadar natrium dalam darah rendah (hiponatremia),
- depresi, susah tidur,
- kejang, pingsan atau merasa ingin pingsan, pening,
- sensasi kesemutan, geli, atau seperti ditusuk jarum pada kulit (parestesia),
- perubahan kondisi mental (ensefalopati),
- perubahan indera pengecap (disgeusia),
- perasaan ‘berputar’ atau merasa pening (vertigo),

- gangguan denyut jantung - mungkin terlalu cepat atau tidak rata, atau terdapat denyut jantung ekstra – kondisi ini dapat dilihat dalam pemeriksaan jantung Anda (elektrokardiogram atau EKG),
- gangguan sirkulasi darah,
- tekanan darah rendah,
- mengi, napas sangat cepat, batuk darah atau dahak berdarah, hidung berdarah,
- gangguan pencernaan,
- konstipasi,
- merasa kembung (distensi abdomen),
- pembesaran hati,
- gangguan kulit, bintik-bintik merah atau ungu pada kulit (petekie), peradangan kulit (dermatitis), kerontokan rambut,
- nyeri punggung,
- pembengkakan ekstremitas,
- merasa lemah, sangat lelah, atau mengantuk atau secara umum merasa kurang sehat (malaise).

Efek samping dengan frekuensi yang belum diketahui:
- anafilaksis (reaksi alergi berat).

Melaporkan efek samping
Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala bentuk efek samping yang tidak tercantum di dalam brosur ini. Untuk melaporkan efek samping, hubungi www.pfizersafetyreporting.com atau email di IDN.AEReporting@pfizer.com.

9. Apa saja obat atau makanan lain yang harus dihindari selama menggunakan obat ini?

Beri tahu dokter atau apoteker Anda jika Anda sedang, belum lama ini, atau akan menggunakan obat lain. Beberapa obat dapat memengaruhi cara kerja CRESEMBA atau CRESEMBA dapat memengaruhi cara kerja obat-obatan lainnya, jika digunakan secara bersamaan.

Khususnya, jangan meminum obat ini dan beri tahu dokter atau apoteker Anda jika Anda sedang meminum obat-obatan mana pun berikut ini:
- ketokonazol, digunakan untuk mengobati infeksi jamur,
- ritonavir dosis tinggi (> 200 mg setiap 12 jam), digunakan untuk mengobati HIV,
- rifampisin, rifabutin, digunakan untuk mengobati tuberkulosis,
- karbamazepin, digunakan untuk mengobati epilepsi,
- obat-obatan barbiturat kerja panjang seperti fenobarbital, digunakan untuk mengobati epilepsi dan gangguan tidur,
- fenitoin, digunakan untuk mengobati epilepsi,
- St. John’s wort, obat herbal yang digunakan untuk mengobati depresi,
- efavirenz, etravirin, digunakan untuk mengobati HIV,
- nafsilin, digunakan untuk mengobati infeksi bakteri.

Kecuali dokter Anda menyatakan lain, jangan meminum obat ini dan beri tahu dokter atau apoteker Anda jika Anda sedang meminum obat-obatan mana pun berikut ini:
- rufinamid atau obat-obatan lainnya yang menurunkan interval QT pada pemeriksaan jantung (EKG),
- aprepitant, digunakan untuk mencegah mual dan muntah yang disebabkan pengobatan kanker,
- prednison, digunakan untuk mengobati reumatoid artritis,
- pioglitazon, digunakan untuk mengobati diabetes,

Beri tahu dokter atau apoteker Anda jika Anda sedang meminum obat-obatan mana pun berikut ini, sebab penyesuaian dosis atau pemantauan mungkin diperlukan untuk memastikan bahwa obat-obatan tersebut masih memberikan efek yang diharapkan:
- siklosporin, takrolimus dan sirolimus, digunakan untuk mencegah penolakan transplantasi,
- siklofosfamid, digunakan untuk mengobati kanker,
- digoksin, digunakan untuk mengobati gagal jantung atau denyut jantung tidak merata,
- kolkisin, digunakan untuk mengobati serangan gout,
- dabigatran eteksilat, digunakan untuk menghentikan bekuan darah setelah bedah penggantian panggul atau lutut,
- klaritromisin, digunakan untuk mengobati infeksi bakteri,
- kombinasi saquinavir, fosamprenavir, indinavir, nevirapin, lopinavir/ritonavir, digunakan untuk mengobati HIV,
- alfentanil, fentanil, digunakan untuk meredakan nyeri yang berat,
- vinkristin, vinblastin, digunakan untuk mengobati kanker,
- mikofenolat mofetil (MMF), digunakan pada pasien transplantasi,
- midazolam, digunakan untuk mengobati insomnia dan stres berat,
- bupropion, digunakan untuk mengobati depresi,
- metformin, digunakan untuk mengobati diabetes.
- daunorubisin, doksorubisin, imatinib, irinotekan, lapatinib, mitoksantron, topotekan, digunakan untuk mengobati berbagai jenis kanker.

10. Apa yang harus dilakukan jika ada dosis terlewat atau berhenti menggunakan Cresemba?

Jika Anda lupa meminum Cresemba
Karena Anda akan menerima obat ini di bawah pengawasan medis yang ketat, kecil kemungkinannya dosis Anda akan terlewat. Namun demikian, beri tahu dokter Anda jika Anda merasa ada dosis yang terlewatkan.

Jika Anda berhenti menggunakan Cresemba
Pengobatan dengan Cresemba hanya akan dilanjutkan selama dokter Anda menginstruksikan demikian. Ini dilakukan untuk memastikan bahwa infeksi jamur sudah mereda.

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

11. Bagaimana cara menyimpan obat ini?

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Umur simpan: 4 tahun.

Jangan menggunakan obat ini setelah tanggal kedaluwarsa yang tertera pada label setelah tulisan EXP. Tanggal kedaluwarsa mengacu pada hari terakhir dari bulan yang tertera.

Simpan di lemari pendingin (2 °C hingga 8 °C).

Jangan membuang obat melalui saluran pembuangan air. Tanyakan kepada apoteker cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

12. Tanda dan Gejala overdosis

Anda mungkin mengalami lebih banyak efek samping seperti:
- sakit kepala, merasa pening, gelisah, atau mengantuk,
- kesemutan, penurunan kemampuan indera peraba atau sensasi di dalam mulut,

- gangguan menyadari berbagai hal, muka kemerahan, kecemasan, nyeri sendi,
- perubahan indera pengecap, mulut kering, diare, muntah,
- denyut jantung yang terasa, denyut jantung lebih cepat, lebih sensitif terhadap cahaya.

13. Apa yang harus dilakukan jika Anda menggunakan dosis melebihi anjuran?

Jika Anda merasa menerima dosis CRESEMBA terlalu banyak, segera beri tahu dokter atau perawat Anda.

14. Apa saja yang perlu diperhatikan saat menggunakan obat ini?

Peringatan dan langkah-langkah pencegahan

Konsultasikan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan CRESEMBA:

- jika Anda mengalami reaksi alergi terhadap obat-obatan antijamur 'azol' lainnya di waktu lalu, seperti ketokonazol, flukonazol, itrakonazol, vorikonazol, atau posakonazol,
- jika Anda menderita penyakit hati berat. Dokter akan memantau kemungkinan efek samping yang Anda alami.

Cermati setiap efek samping

Hentikan penggunaan CRESEMBA dan segera beri tahu dokter Anda jika Anda mengalami efek samping mana pun berikut ini:

- mengi mendadak, kesulitan bernapas, pembengkakan pada wajah, bibir, mulut atau lidah, gatal-gatal berat, berkeringat, pusing atau pingsan, detak jantung cepat atau dada berdebar terlalu keras–ini mungkin merupakan tanda-tanda reaksi alergi berat (anafilaksis).

Gangguan saat menerima dosis CRESEMBA dalam bentuk infus intravena

Segera beri tahu dokter Anda jika Anda mengalami efek samping mana pun berikut ini:

- tekanan darah rendah, merasa sesak napas, mual, pening, sakit kepala, kesemutan, – dokter Anda dapat memutuskan untuk menghentikan infus.

Perubahan fungsi hati Anda

CRESEMBA kadang-kadang dapat memengaruhi fungsi hati Anda. Dokter dapat melakukan tes darah selama Anda menggunakan obat ini.

Gangguan kulit

Segera beri tahu dokter Anda jika Anda mengalami lepuh yang berat pada kulit, mulut, mata, atau organ kemaluan.

Pasien anak-anak dan remaja

CRESEMBA tidak boleh digunakan pada anak-anak atau remaja berusia di bawah 18 tahun karena tidak ada informasi terkait penggunaan dalam kelompok usia ini.

Kehamilan dan menyusui

Jika Anda hamil atau sedang menyusui, menduga bahwa diri Anda sedang hamil, atau berencana untuk hamil, mintalah saran dokter Anda sebelum menggunakan obat ini.

Jangan menggunakan CRESEMBA jika Anda sedang hamil, kecuali jika dokter Anda menganjurkan sebaliknya. Karena tidak diketahui apakah obat ini dapat memengaruhi atau membahayakan janin Anda.

Jangan menyusui jika Anda sedang menggunakan CRESEMBA.

Mengemudi dan menjalankan mesin
CRESEMBA dapat membuat Anda merasa bingung, lelah, atau mengantuk. Obat ini juga dapat membuat Anda jatuh pingsan. Oleh karena itu, anda disarankan untuk tidak mengemudi atau mengoperasikan mesin apabila mengalami hal tersebut.

15. Kapan sebaiknya Anda berkonsultasi dengan dokter?
Pengobatan dengan CRESEMBA akan terus dilanjutkan selama dokter Anda menganjurkan. Tujuannya adalah untuk memastikan bahwa infeksi jamur sudah berakhir.

Jika Anda memiliki pertanyaan lebih lanjut mengenai kegunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

16. Nama produsen/importir/Pemegang Hak Pemasaran

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HARUS DENGAN RESEP DOKTER

Kotak, 1 vial @ 200 mg; Reg. No.: DKI2057100280A1