AN HCP GUIDE FOR PRACTICAL USE

CRESEMBA® is indicated in adults for the treatment of:[1]

- Invasive aspergillosis
- Mucormycosis in patients for whom amphotericin B is inappropriate

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

Before prescribing CRESEMBA® please refer to the full Summary of Product Characteristics (SmPC). Please refer to your local authorities concerning reimbursement status.

Medicinal product subject to medical prescription.

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HCP, healthcare professional.

CRESEMBA® (ISAVUCONAZOLE)

Formulations and strengths[1]

IV

200 mg powder for concentrate for solution for infusion

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

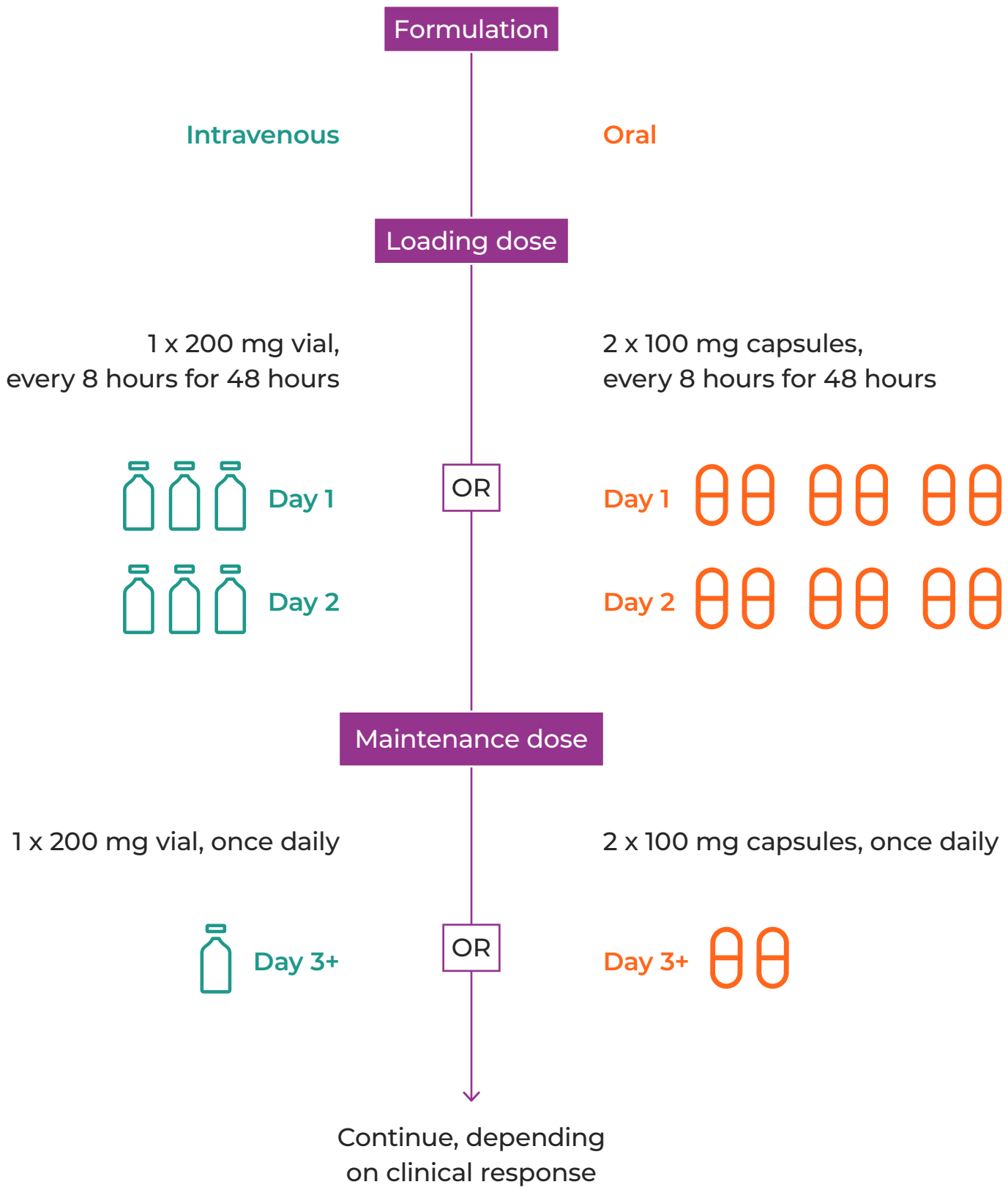
Oral

100 mg hard capsules (as 186.3 mg isavuconazonium sulfate)

- CRESEMBA® must be reconstituted and then further diluted to a concentration corresponding to approximately 0.8 mg/mL isavuconazole before administration by intravenous infusion over a minimum of 1 hour to reduce the risk of infusion-related reactions
- Infusions of CRESEMBA® 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® for injection must only be given as an intravenous infusion
- Switching between intravenous and oral administration is appropriate on the basis of the high oral bioavailability (98%) and when clinically indicated
- For long-term treatment beyond 6 months, carefully consider the benefit-risk balance
- CRESEMBA® capsules should be swallowed whole, with or without food. Do not chew, crush, dissolve or open the capsules.

IV, intraveous.

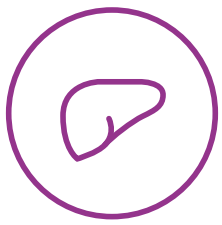
Recommended dose[1]



Dose adjustments[1]

No dose adjustment is necessary for:

- Patients with renal impairment (including patients with end-stage renal disease)



- Patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B). CRESEMBA® 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

- Elderly patients

Contraindications[1]

- Hypersensitivity to the active substance or to any of the excipients listed in the Summary of Product Characteristics
- Coadministration with ketoconazole, high-dose ritonavir (>200 mg every 12 hours), 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
- Patients with familial short QT syndrome

Special warnings and precautions for use[1]

- Hypersensitivity to isavuconazole may result in adverse reactions that include: hypotension, respiratory failure, dyspnoea, drug eruption, pruritus and rash. Prescribe with caution in patients with hypersensitivity to other azole antifungal agents
- Infusion-related reactions including hypotension, dyspnoea, dizziness, paraesthesia, nausea and headache have been reported. The infusion should be stopped if these reactions occur
- 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
- CRESEMBA® is contraindicated in patients with familial short QT syndrome. Caution is warranted when prescribing CRESEMBA® to patients taking medicinal products, such as rufinamide, known to decrease the QT interval
- Elevated liver transaminases have been reported in clinical studies and rarely required discontinuation of CRESEMBA®. Monitoring of hepatic enzymes should be considered, as clinically indicated
- Severe hepatic impairment (Child-Pugh Class C) has not been evaluated in studies with CRESEMBA®. Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. Patients should be carefully monitored for potential drug toxicity

Drug–drug interactions[1]

CYP3A4/5 inhibitors

- Coadministration with ketoconazole is contraindicated
- A two-fold increase in isavuconazole exposure was observed with the strong CYP3A4 inhibitor lopinavir/ritonavir
- A less pronounced effect can be expected with other strong CYP3A4/5 inhibitors
- No dose adjustment is necessary when co-administered with strong CYP3A4/5 inhibitors, however, caution is advised as adverse drug reactions may increase

CYP3A4/5 inducers

- Coadministration with mild CYP3A4/5 inducers such as aprepitant, prednisone and pioglitazone may result in mild to moderate decreases in isavuconazole plasma levels
- Coadministration with mild CYP3A4/5 inducers should be avoided unless the potential benefit is considered to outweigh the risk

CYP3A4/5 substrates, including immunosuppresants

- Isavuconazole can be considered a moderate inhibitor of CYP3A4/5, and systemic exposure to medicinal products metabolised by CYP3A4 may be increased when coadministered with CRESEMBA®
- Concomitant use of CRESEMBA® with CYP3A4 substrates such as the immunosuppressants tacrolimus, sirolimus or ciclosporin may increase systemic exposure to these medicinal products
- Appropriate therapeutic drug monitoring and dose adjustment may be necessary during coadministration

CYP2B6 substrates

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

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®

Fertility, pregnancy and lactation[1]

Pregnancy

- There are no data from the use of CRESEMBA® in pregnant women
- Animal studies have shown reproductive toxicity but 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 childbearing potential who are not using contraception

Breast-feeding

- Available pharmacodynamic/toxicological data in animals have shown excretion of isavuconazole/metabolites in milk
- Breast-feeding should be discontinued during treatment with CRESEMBA®
- A risk to newborns and infants cannot be excluded

Fertility

- There are no data on the effect of CRESEMBA® on human fertility
- Studies in animals did not show impairment of fertility in male or female rats

Adverse reactions[1]

Summary of the safety profile

Most common treatment-related adverse events:

- 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%)
- Rash (1.7%)

Adverse reactions that most often led to permanent discontinuation of CRESEMBA®:

- 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%)
- Vomiting (0.5%)

Effects on ability to drive and use machines

- CRESEMBA® has a moderate potential to influence the ability to drive and use machines
- Patients should avoid driving or operating machinery if they experience symptoms of confusional state, somnolence, syncope and/or dizziness

Overdose

- Symptoms reported more frequently at supratherapeutic doses of CRESEMBA® (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
- In the event of an overdose, initiate supportive treatment. Isavuconazole is not removed by haemodialysis and there is no specific antidote for isavuconazole

References

1. CRESEMBA Summary of Product Characteristics. 2021.

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