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.

Please consult local SmPCs for correct prescription and usage of our products (European Medicines Agency | https://www.ema.europa.eu/en).

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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)

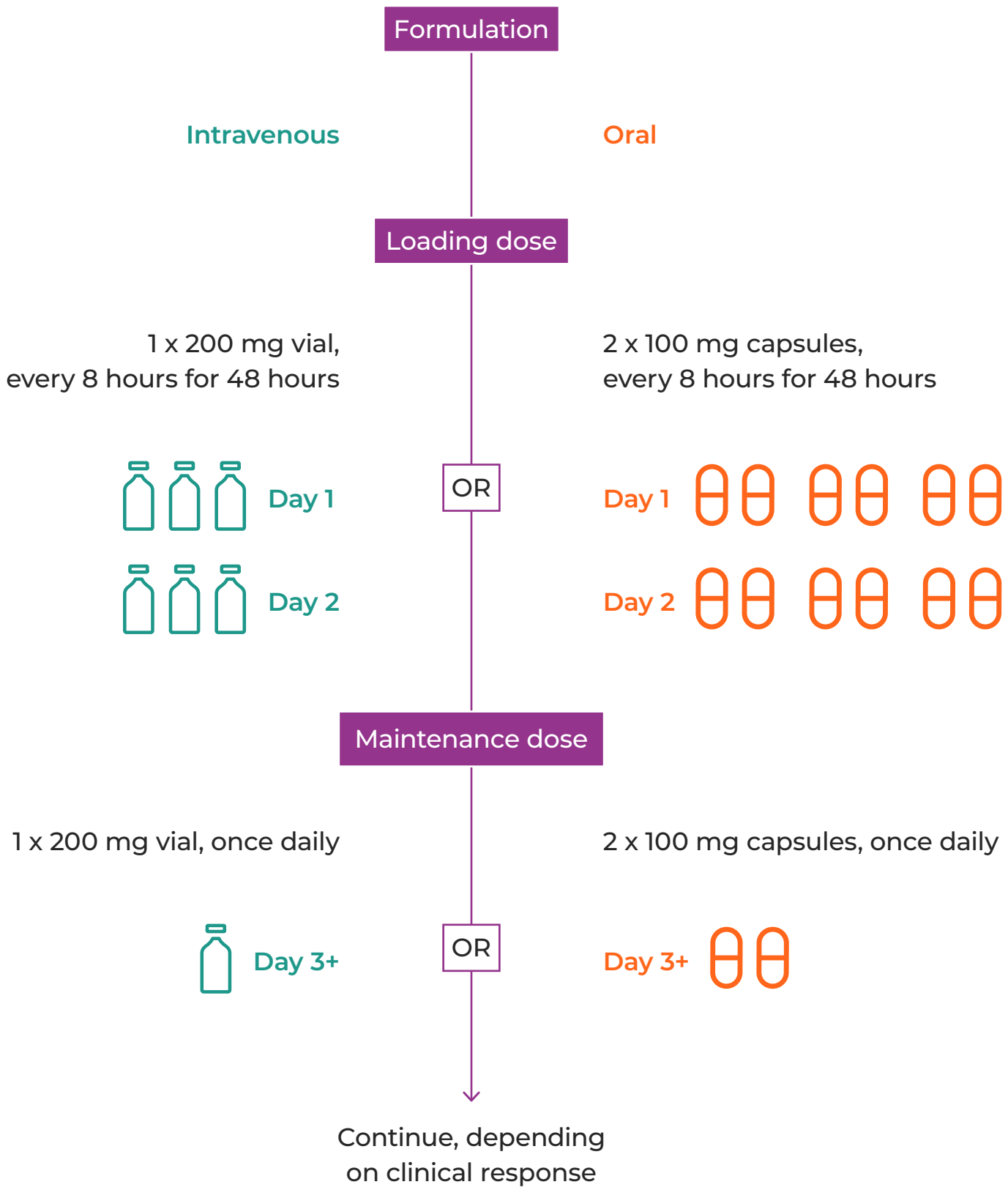
Oral

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.

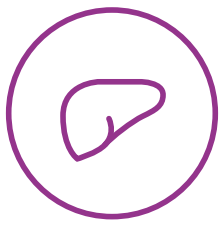
Recommended dose[1]



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. Hepatitis has been reported with azole antifungal agents, including isavuconazole
- 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

Fachkurzinformation

CRESEMBA 100 mg Hartkapseln
CRESEMBA 200 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung

Qualitative und quantitative Zusammensetzung: Hartkapseln: Jede Kapsel enthält 100 mg Isavuconazol (als 186,3 mg Isavuconazoniumsulfat). Pulver für ein Konzentrat zur Herstellung einer Infusionslösung: Jede Durchstechflasche enthält 200 mg Isavuconazol (als 372,6 mg Isavuconazoniumsulfat). **Liste der sonstigen Bestandteile:** Hartkapseln: Kapselinhalt: Magnesiumcitrat, Mikrokristalline Cellulose, Talkum, Hochdisperses Siliciumdioxid, Stearinsäure. Kapselhülle: Hypromellose, Wasser, Eisen(III)-oxid (E172) (nur Kapselkörper), Titandioxid (E171), Gellan Gummi, Kaliumacetat, Natriumedetat, Natriumdodecylsulfat. Drucktinte: Schellack, Propylenglycol, Kaliumhydroxid, Eisen(II, III)-oxid (E172). Pulver für ein Konzentrat zur Herstellung einer Infusionslösung: Mannitol, Schwefelsäure (zur pH-Anpassung). **Anwendungsgebiete:** CRESEMBA wird angewendet zur Behandlung von Erwachsenen mit: - invasiver Aspergillose, - Mukormykose bei Patienten, bei denen eine Behandlung mit Amphotericin B nicht angemessen ist (siehe Abschnitte 4.4 und 5.1 der Fachinformation). Offizielle Leitlinien über die angemessene Anwendung von Antimykotika sind zu berücksichtigen. **Gegenanzeigen:** Überempfindlichkeit gegen den Wirkstoff oder einen der in Abschnitt 6.1 der Fachinformation genannten sonstigen Bestandteile. Gleichzeitige Anwendung mit Ketoconazol (siehe Abschnitt 4.5 der Fachinformation). Gleichzeitige Anwendung mit hoch-dosiertem Ritonavir (> 200 mg alle 12 Stunden; siehe Abschnitt 4.5 der Fachinformation). Gleichzeitige Anwendung mit starken CYP3A4/5-Induktoren, wie z. B. Rifampicin, Rifabutin, Carbamazepin, lang wirkenden Barbituraten (z. B. Phenobarbital), Phenytoin und Johanniskraut, sowie mit mäßig starken CYP3A4/5-Induktoren wie z. B. Efavirenz, Nafcillin und Etravirin (siehe Abschnitt 4.5 der Fachinformation). Patienten mit familiärem Short-QT-Syndrom (siehe Abschnitt 4.4 der Fachinformation). **Pharmakotherapeutische Gruppe:** Antimykotika zur systemischen Anwendung, Triazol-Derivate, ATC-Code: J02AC05. **Inhaber der Zulassung:** Basilea Pharmaceutica Deutschland GmbH, Marie-Curie-Straße 8, 79539 Lörrach, Deutschland. **Stand der Information:** Oktober 2021. **Rezeptpflicht/Apothekenpflicht:** Rezept- und apothekenpflichtig, wiederholte Abgabe verboten. **Angaben zu besonderen Warnhinweisen und Vorsichtsmaßnahmen für die Anwendung, Wechselwirkungen mit anderen Arzneimitteln und sonstigen Wechselwirkungen, Fertilität, Schwangerschaft und Stillzeit und Nebenwirkungen entnehmen Sie bitte der veröffentlichten Fachinformation.**

References

1. CRESEMBA Summary of Product Characteristics. Updated 07 December 2021. Available at: ema.europe.eu. Last accessed 12 May 2022.

For healthcare professionals only.

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