NEW

CRESEMBA®
(ISAVUCONAZOLE)

SURVIVAL WITH LESS DRUG RELATED ADVERSE EVENTS

vs voriconazole in Invasive Aspergillosis[1]

CRESEMBA® is indicated in adults for the treatment of:[2]

- 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.[2]

Invasive Aspergillosis and Mucormycosis can be life threatening, difficult to identify and are increasing in incidence[3-6, 9-11]

Mortality with invasive mould infections can vary depending on the underlying condition, but rates are generally very high if not diagnosed and treated[3]

- Invasive Aspergillosis: up to 87%[3,4] in bone marrow transplant patients
- Mucormycosis: up to 88%[5]

Identifying invasive species in a timely manner is often very challenging

- It is estimated only 50% of invasive fungal infections are diagnosed before death[6]
- Diagnostic challenges and a complicated clinical picture often lead to detrimental delays[7,8]
- Discriminating between invasive Aspergillosis and Mucormycosis in a timely fashion can prove to be difficult[8]

Incidence of invasive Aspergillosis and other mould infections has increased in recent years[9-11]

- Estimated annual global cases of invasive Aspergillosis: >300,000[12]
- Estimated annual global cases of invasive Mucormycosis: >10,000[12]

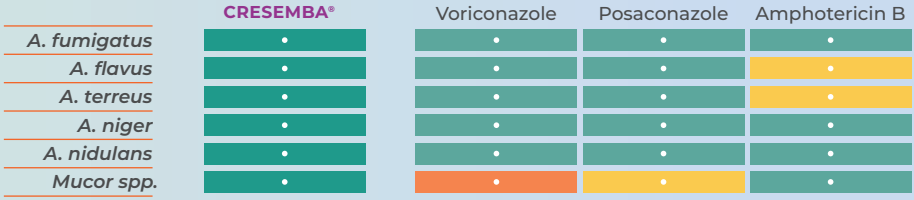
CRESEMBA® is indicated for both invasive Aspergillosis and Mucormycosis[2]

CRESEMBA® is indicated in adults for the treatment of:[2]

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

CRESEMBA® is a new broad spectrum azole with extended anti-mould activity across *Aspergillus* species and Mucorales compared with voriconazole, posaconazole and amphotericin B[18-20]

CRESEMBA® activity *in vitro*[2,18-20]

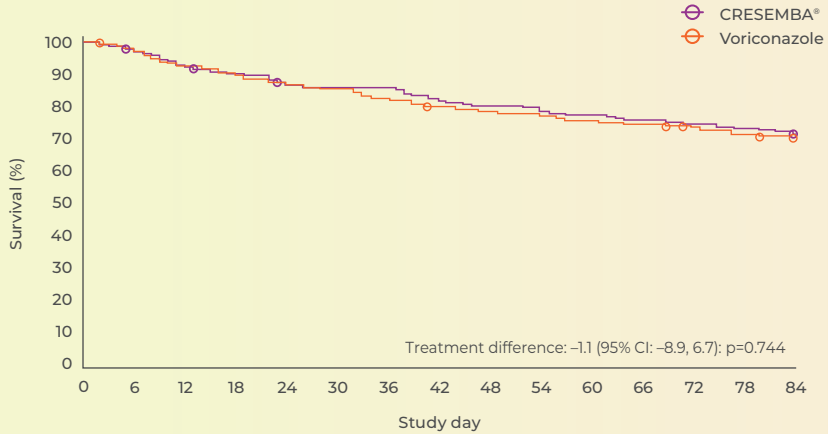


- Activity
- Variable activity
- Little or no activity

CRESEMBA® is as effective as the standard of care in invasive Aspergillosis[1]

In invasive Aspergillosis, CRESEMBA® offers survival rates comparable with the standard of care, voriconazole[1]

- In the SECURE Phase 3 pivotal trial, survival rates were comparable between CRESEMBA® and voriconazole throughout the study[1,a]



Number at risk

CRESEMBA®	258	252	240	232	224	220	220	211	206	204	199	195	192	188	185
Voriconazole	258	253	239	233	225	220	213	206	202	199	194	192	188	182	179

Survival from baseline to day 84 with CRESEMBA® and voriconazole in the SECURE trial (ITT population; results were similar in the mITT population). Patients were censored on the day of their last known survival status (circles). Adapted from Maertens et al[1]

In the SECURE trial, all-cause mortality was comparable with CRESEMBA® and voriconazole in both the ITT and mITT populations[1,a]

- Day 42 (ITT population): 19% vs 20% (adjusted treatment difference: –1.0%; 95% CI: –7.8, 5.7)[1]
- In the SECURE trial, with CRESEMBA® overall response to treatment, as well as clinical, mycological and radiological responses were all comparable with voriconazole[1,a]

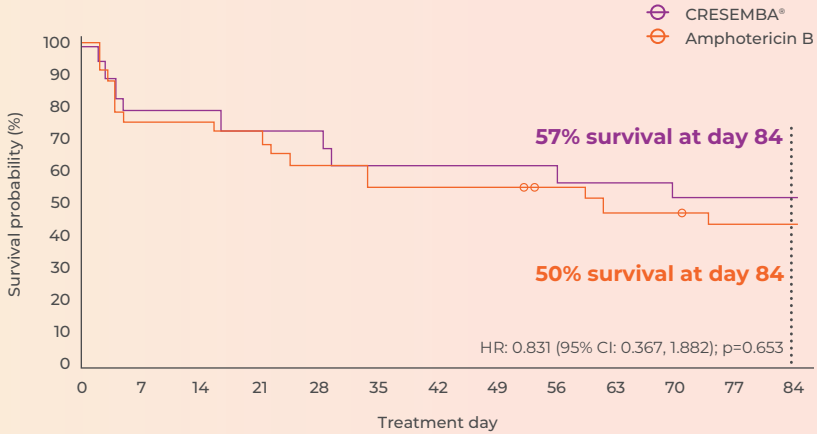
a. The non-inferiority margin was 10% (adjusted treatment differences).

ITT, intention-to-treat; mITT, modified intention-to-treat

CRESEMBA® is effective in Mucormycosis[21]

CRESEMBA® has similar survival rates to amphotericin B in Mucormycosis[21]

- A case-control analysis matching patients who received primary CRESEMBA® in VITAL with controls from the FungiScope Registry treated with amphotericin B showed similar survival rates for both drugs[21]



Number at risk

CRESEMBA®	21	17	17	16	16	14	14	14	14	13	12	12	12
Amphotericin B	33	26	26	25	22	20	20	20	18	16	16	14	14

Survival from baseline to day 84 in patients who received CRESEMBA® as primary treatment in VITAL vs matched controls treated with amphotericin B (FungiScope). Adapted from Marty et al[21]

VITAL was a single-arm, open-label trial of CRESEMBA® in rare invasive mould infections, which included 37 patients with Mucormycosis[21]

In the VITAL trial, CRESEMBA® was associated with an overall response of 11% at day 42 (primary endpoint), rising to 31% (complete and partial response) at the end of treatment[21,a]

a. Overall response was based on individual clinical, mycological, and radiological response assessed by the Data Review Committee[21]

HR, hazard ratio; CI, confidence interval

In invasive Aspergillosis, CRESEMBA® has less drug-related adverse events vs the standard of care[1]

In invasive Aspergillosis, CRESEMBA® combines standard-of-care efficacy with improved tolerability vs voriconazole[1]

- In the SECURE trial, the proportion of invasive Aspergillosis patients with treatment-emergent AEs was similar overall with CRESEMBA® and voriconazole (96% vs 98%)[1]
- Significantly fewer patients reported events considered by investigators to be drug related for Cresemba versus voriconazole (42% vs 60% p<0.001)[1]
- The frequency of AEs and drug-related AEs leading to discontinuation were considerably lower with CRESEMBA® than with voriconazole[1]

Drug-related AEs and treatment discontinuations in the SECURE trial[1]

	CRESEMBA® (n=257)	Voriconazole (n=259)	p value
Drug-related AEs*	42%	60%	<0.001
AEs leading to discontinuation	14%	23%	p value not reported
Drug-related AEs leading to discontinuation	8%	14%	p value not reported

AE, adverse event
*As considered by investigators

AEs typical to voriconazole were less common with CRESEMBA®[1]

- Voriconazole is often associated with neurotoxic, hepatic and visual AEs, which can lead to premature treatment discontinuation[1]
- In invasive Aspergillosis, CRESEMBA® showed significant reductions vs voriconazole in the frequency of skin and subcutaneous tissue disorders[1]

System organ classes with significantly fewer drug-related AEs with CRESEMBA® vs voriconazole[1]

	CRESEMBA® (n=257)	Voriconazole (n=259)	p value
Skin and subcutaneous tissue disorders	33%	42%	0.037
Eye disorders	15%	27%	0.002
Hepatobiliary disorders	9%	16%	0.016

Adapted from Maertens et al[1]

CRESEMBA® has a consistent tolerability profile across clinical trials for invasive Aspergillosis and Mucormycosis[21]

In the VITAL trial, only 16% of patients discontinued CRESEMBA® due to AEs[21]

The AE profile in VITAL was consistent with observations from the SECURE trial[21]

Most common (≥10%) TEAEs reported for CRESEMBA® in VITAL[21]

TEAE	Incidence® (N=37)
Overall	95%
Vomiting	32%
Diarrhoea	27%
Nausea	27%
Pyrexia	27%
Constipation	22%
Decreased appetite	16%
Headache	16%
Oedema, peripheral	16%
Abdominal pain	14%
Dyspnoea	14%
Pneumonia	14%
Back pain	11%
Cough	11%
Hypoglycaemia	11%
Insomnia	11%
Restlessness	11%

Adapted from Marty et al[21]

AE, adverse event; TEAE, treatment-emergent adverse event

CRESEMBA® helps you manage the invasive mould infection while focusing on the underlying condition[7,9,22–28]

CRESEMBA® can be used in patients with renal impairment, without dose adjustments[2,22,23]

- Unlike other mould-active IV azoles, CRESEMBA® does not contain cyclodextrin, eliminating the potential for renal toxicity[2,13,15,24]

Unlike voriconazole, CRESEMBA® does not require dose adjustments in patients with mild or moderate hepatic impairment[2,13]

- CRESEMBA® has not been studied in patients with severe hepatic impairment; use in these patients is not recommended unless the potential benefit is considered to outweigh the risks[2]

While voriconazole and posaconazole prolong the QTc interval, CRESEMBA® shortens it[2,13,14,25]

- CRESEMBA® is contraindicated in patients with familial short QT syndrome; caution should be used when prescribing CRESEMBA® in combination with other medicines that decrease the QTc interval[2,25]

CRESEMBA® has fewer drug-drug interactions than other azoles[2,23]

- CRESEMBA® is contraindicated in coadministration with ketoconazole, high-dose ritonavir, and strong CYP3A4/5 inducers such as rifampicin, rifabutin, carbamazepine, long acting barbiturates, phenytoin and St. John's wort, or with moderate CYP3A4/5 inducers such as efavirenz, nafcillin and etravirine[2]

CRESEMBA® allows for simple and reliable IV and oral dosing[2,25,27,28]

- For both IV and oral administration, the recommended loading dose is 200 mg of CRESEMBA® every 8 hours for 48 hours, followed by a maintenance dose of 200 mg once daily[2]
- TDM is not routinely recommended for CRESEMBA®[29,30]

IV, intravenous; TDM therapeutic drug monitoring

References

1. Maertens JA et al. *Lancet* 2016;**387**(10020):760–769.
2. CRESEMBA Approved Product Information.
3. Lin SJ et al. *Clin Infect Dis* 2001;**32**(3):358–366.
4. Garcia-Vidal C *et al. PLoS One* 2015;**10**(3):e0120370.
5. Guinea J *et al. PLoS One* 2017;**12**(6):e0179136.
6. Dignani MC. F1000Prime Rep 2014;**6**:81.
7. Mercier T and Maertens J. *J Antimicrob Chemother* 2017;**72**(suppl_1):i29–i38.
8. Chamilos G *et al. Clin Infect Dis* 2008;**47**(4):503–509.
9. Donnelley MA *et al. Infect Drug Resist* 2016;**9**:79–86.
10. Lass-Florl C and Cuenca-Estrella M. *J Antimicrob Chemother* 2017;**72**(suppl_1):i5–i11.
11. Limper AH. *Proc Am Thorac Soc* 2010;**7**(3):163–168.
12. Bongomin F *et al. J Fungi (Basel)* 2017;**3**(4).
13. VFEND Approved Product Information.
14. Noxafil Approved Product Information.
15. Sporanox Approved Product Information.
16. Miceli MH and Kauffman CA. *Clin Infect Dis* 2015;**61**(10):1558–1565.
17. Falci DR and Pasqualotto AC. *Infect Drug Resist* 2013;**6**:163-174. Epub 2013/11/05.
18. Arendrup MC *et al. Antimicrob Agents Chemother* 2015;**59**(12):7735–7742.
19. Guinea J *et al. Antimicrob Agents Chemother* 2008;**52**(4):1396–1400.
20. Sabatelli F *et al. Antimicrob Agents Chemother* 2006;**50**(6):2009-2015.
21. Marty FM *et al. Lancet Infect Dis* 2016;**16**(7):828–837.
22. Mullane KM *et al. ECCMID* 2015. Poster presentation (EV0932).
23. Natesan SK and Chandrasekar PH. *Infect Drug Resist* 2016;**9**:291–300.
24. Horn D *et al. J Med Econ* 2016;**19**(7):728–734.
25. Mellinghoff SC *et al. Mycoses* 2018;**61**(4):256-260. Epub 2017/11/28.
26. Perfect JR. *Nat Rev Drug Discov* 2017;**16**(9):603–616.
27. Kaindl T *et al. J Antimicrob Chemother* 2018. doi: 10.1093/jac/dky463. [Epub ahead of print]
28. Schmitt-Hoffmann A *et al. Antimicrob Agents Chemother* 2006;**50**(1):279–285.
29. Andes D *et al. Antimicrob Agents Chemother* 2018;**62**(7).
30. Desai AV *et al. Antimicrob Agents Chemother* 2017;**61**(12).

PBS Information: Cresemba is not listed on the PBS.

BEFORE PRESCRIBING, PLEASE REVIEW FULL PRODUCT INFORMATION AVAILABLE FROM WWW.PFIZER.COM.AU

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

Minimum Product Information

CRESEMBA® (isavuconazole, 200 mg) Powder for Injection
CRESEMBA® (isavuconazole, 100 mg) Capsules Therapeutic indications: Treatment of invasive Aspergillosis and treatment of Mucormycosis in patients for whom amphotericin B is inappropriate. **Contraindications:** Hypersensitivity to the active substance or excipients, co-administration with ketoconazole, high dose ritonavir (>200 mg every 12 hours), strong or moderate CYP3A4/5 inducers, familial short QT syndrome. **Special warnings and precautions for use:** Hypersensitivity, infusion-related reactions, severe cutaneous adverse reactions, cardiovascular (QT shortening), elevated liver transaminases or hepatitis, severe hepatic impairment, concomitant use with other medicinal products (CYP3A4/5 inhibitors, inducers, substrates including immunosuppressants, CYP2B6 substrates, P-gp substrates). See PI for details. **Interactions with other medicines and other forms of interactions:** Co-administration of CYP3A4 and/or CYP3A5 inhibtors may increase the plasma concentrations of isavuconazole. Co-administration of CYP3A4 and/or CYP3A5 inducers may decrease the plasma concentrations of isavuconazole. Co-administration with CYP3A4, CYP3A5, P-gp, BCRP, OCT2 and UGT substrates may result in increased plasma concentrations of these medicines. Co-administration with CYP2B6 substrates may result in decreased plasma concentrations of these medicines. See PI for details. **Adverse effects (undesirable effects):** Common: hypokalaemia, decreased appetite, delirium, headache, somnolence, thrombophlebitis, dyspnoea, acute respiratory failure, vomiting, diarrhoea, nausea, abdominal pain, elevated liver chemistry tests, rash, pruritus, renal failure, chest pain, fatigue, injection site reaction. See PI for details.**Dose and method of administration:** Powder for injection: Loading dose: 1 reconstituted vial (200 mg) intravenously every 8 hours for 6 doses (48 hours). Maintenance Dose: 1 reconstituted vial (200 mg) intravenously once daily. Capsules: Loading dose: 2 capsules (200 mg) orally every 8 hours for 6 doses (48 hours). Maintenance Dose: 2 capsules (200 mg) orally once daily. See PI for details. ® Registered trademark V10519

Pfizer Australia Pty. Ltd. Sydney, Australia.
www.pfizer.com.au Medical Information 1800 675 229
PP-CRB-AUS-0007 Prepared February 2020

Pfizer Anti-Infectives

CRESEMBA: SURVIVAL WITH LESS DRUG-RELATED ADVERSE EVENTS

- CRESEMBA® is as effective as the standard of care in invasive Aspergillosis and is also active against Mucormycosis[1,21]
- CRESEMBA® has fewer drug related adverse events and fewer drug discontinuations than the standard of care in invasive Aspergillosis[1,17]
- CRESEMBA® offers simplicity and flexibility to help you focus on your patient's underlying condition[1,2,7,17,26]

CRESEMBA®
(ISAVUCONAZOLE)