COVID-19[a] AND INVASIVE ASPERGILLOSIS: UNDERSTANDING AN EMERGING ASSOCIATION

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.

a. CRESEMBA® is not indicated for the treatment of COVID-19.

Prescribing information and adverse event reporting can be found at the end of this booklet.

PP-CRB-NLD-0009. February 2021.

CRESEMBA®
(ISAVUCONAZOLE)

Invasive aspergillosis and COVID-19

Invasive aspergillosis is a serious opportunistic infection associated with extremely high mortality.[2] It typically affects individuals who are severely immunocompromised and/or have well-established risk factors:[3–7]

- **Underlying conditions and/or comorbidities,** including neutropenia, malignancies, transplantation, HIV and influenza
- **Certain medications** such as chemotherapy, TNF inhibitors and immunosuppressants
- **Environmental or nosocomial factors**

In addition, the COVID-19 pandemic has revealed an emerging predisposing factor that healthcare professionals must consider: COVID-19 associated pulmonary aspergillosis – abbreviated to CAPA – is increasingly recognised as a threat to COVID-19 patients admitted to intensive care, or who develop ARDS.[8–10]

In these patients, respiratory and ICU healthcare professionals may need to raise the index of suspicion to identify an invasive fungal infection and manage it early.

Some key facts[8]

35

As of 10 June 2020, there were **35 cases of COVID-19 associated pulmonary aspergillosis** published from eight countries

Development of **COVID-19 associated pulmonary aspergillosis is rapid** after ICU admission (median: 6 days)

Prevalence of COVID-19 associated pulmonary aspergillosis is **likely underestimated** due to difficulties in diagnosis

ARDS, acute respiratory distress syndrome; CAPA, COVID-19 associated pulmonary aspergillosis; COVID, coronavirus disease; HIV, human immunodeficiency virus; ICU, intensive care unit; TNF, tumour necrosis factor.

COVID-19 patients who develop ARDS may be at risk for invasive aspergillosis

Increasing evidence suggests that COVID-19 patients with severe ARDS are at risk for invasive pulmonary aspergillosis.[8]

Up to **40%** of hospitalised patients with COVID-19 develop ARDS[8]

The estimated rate of COVID-19 associated pulmonary aspergillosis in patients with ARDS is **19.4–35%**[8]

Aspergillosis in these patients is associated with high mortality rates and may prolong the acute phase of COVID-19[8]

However, monitoring and diagnosis are difficult due to the non-typical presentation of non-neutropenic patients, including those with COVID-19.[8]

> *Physicians face the dilemma of taking the hazard of aerosolization of SARS-CoV-2, risking transmission, versus the endeavor of facilitating the optimal diagnosis and treatment to the patients entrusted to their care.*
>
> **Arastehfar A, *et al. J Fungi.* 2020.[8]**

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

When to suspect COVID-19 associated pulmonary aspergillosis

COVID-19 associated pulmonary aspergillosis is a recently reported phenomenon, and as such data are currently limited.

Clinical associations are difficult to ascertain due to small population numbers, and contributory factors identified in some studies have been found to be non-significant in others.[8,9,11,12]

However, potential risk factors predisposing COVID-19 patients to develop secondary pulmonary aspergillosis have been identified.

Severe lung damage during the course of COVID-19[8,13]

Molecular epithelial damage in COVID-19 may provide an opportunity for *Aspergillus* species to invade tissues in a way that is at least partially distinct from other respiratory viruses.

Use of corticosteroids[8]

In those with ARDS, systemic corticosteroids are used to alleviate immune responses, but may at the same time increase vulnerability for developing secondary infections.

Widespread use of broad-spectrum antibiotics in the ICU[8]

The administration of antibiotics allows fungi to thrive in the human gut microbiome, which may predispose the host to invasive fungal infections once the immune system becomes impaired.

Presence of comorbidities, particularly those causing structural lung damage[8]

Hypertension and diabetes are thought to increase the risk of infection. Structural lung damage caused by COPD or asthma may particularly predispose patients to developing invasive pulmonary aspergillosis.

Immune dysregulation associated with SARS-CoV-2[8,13,14]

Inflammation resulting from immune dysregulation may result in an environment favouring fungal pathogenesis. Examples associated with SARS-CoV-2 include IL-1 hyperactivity, increased levels of IL-6, potential damage to T-cells and leukopenia.

COPD, chronic obstructive pulmonary disease; IL, interleukin.

Considerations when treating COVID-19 associated pulmonary aspergillosis

Suspicion and early diagnosis are critical determinants of outcomes for invasive pulmonary aspergillosis.[8,15]

While there are approved treatments for invasive aspergillosis, differences in coverage, tolerability and PK[1,16-18] mean that a considered, individualised assessment should be made for every patient, with particular attention given to the following.

Drug-drug interactions

- Interactions with concomitant medications in COVID-19 patients should be considered[8]
- CYP3A4-metabolised treatments may limit the use of voriconazole[16]

Renal insufficiency

- SARS-CoV-2 has renal tropism[8]
- IV voriconazole includes cyclodextrin – a potentially nephrotoxic excipient[16,20]
- Liposomal amphotericin B is also potentially nephrotoxic[21,22]

Pharmacokinetic profile

- Treating seriously ill COVID-19 patients can be challenging – an antifungal with a predictable PK profile and low requirement for drug monitoring may be beneficial[8]

QTc prolongation

- COVID-19 can significantly affect cardiac function and multiple medications used in COVID-19 patients are pro-arrythmic[23]
- Minimising the risk of QT prolongation may therefore be an important treatment consideration

IV, intravenous; PK, pharmacokinetics; TDM, therapeutic drug monitoring.

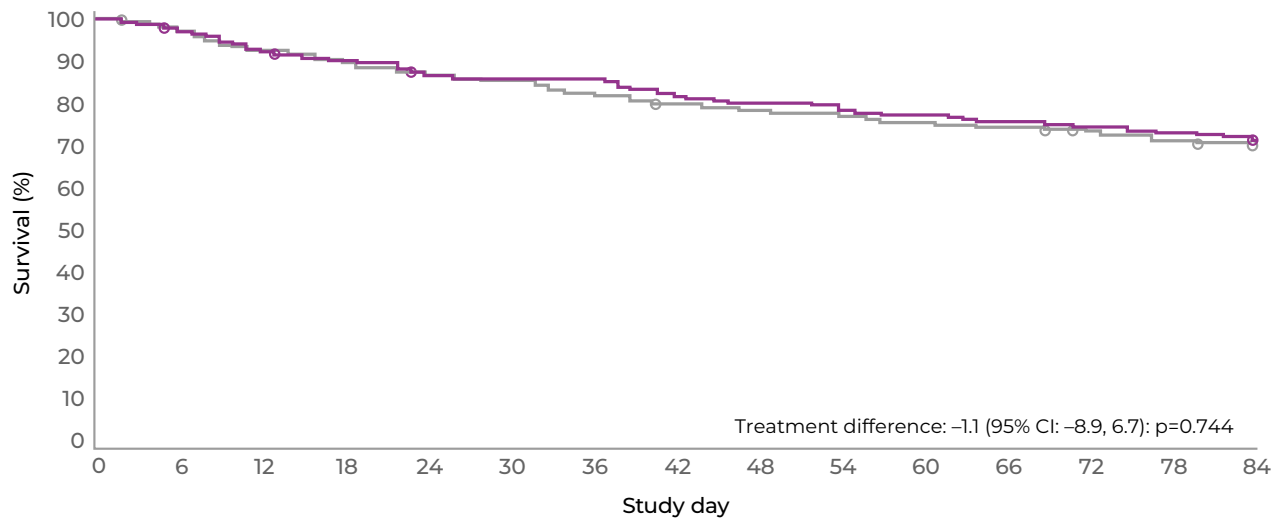
CRESEMBA® (ISAVUCONAZOLE)

CRESEMBA® is a recommended first-line treatment for invasive aspergillosis[15,24]

As effective as the standard of care...

In invasive aspergillosis, CRESEMBA® offers survival rates that are comparable with voriconazole:[24]

- In the SECURE registration trial, both survival and response rates were non-inferior to voriconazole



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 rates with CRESEMBA® and voriconazole in the SECURE study. Adapted from Maertens *et al.* 2016.[24]

...with improved safety and tolerability[b]

- Patients treated with CRESEMBA® had a lower incidence of drug-related AEs in certain system organ classes (42% vs 60%, p<0.001) and events leading to discontinuation (8% vs 14%)[24]
- In particular, AEs typically observed with voriconazole are significantly less common with CRESEMBA®[24]

	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

System organ classes with significantly fewer drug-related AEs with CRESEMBA® vs voriconazole in the SECURE trial. Adapted from Maertens *et al.* 2016.[24]

b. Improvements in targeted AEs. There was no significant difference in overall treatment-emergent AEs between CRESEMBA® and voriconazole in the SECURE trial.[24] Refer to the SmPC for a full list of AEs associated with CRESEMBA®.

AE, adverse event.

CRESEMBA® (ISAVUCONAZOLE)

CRESEMBA® has several attributes that may help you achieve your treatment goals even in complex clinical scenarios

Suitable for patients with renal impairment

- No dose adjustment required in patients with any degree of renal impairment, including ESRD[1]
- No cyclodextrin in the IV formulation,[1] reducing the potential for renal toxicity

Fewer and more manageable drug-drug interactions than other azoles

- Compared with other azoles, CRESEMBA® has fewer CYP450 effects[19]
- It can be administered with several medications without dose adjustments[1]

Concomitant medication	Proton pump inhibitors Statins Warfarin Methadone Methotrexate Repaglinide	Immunosuppressants (tacrolimus, sirolimus and ciclosprorin only) Short-acting opiates Digoxin Anticancer agents (other than methotrexate)	Antiretrovirals Dabigatran etexilate Midazolam Colchicine
Recommendation	**No dose adjustment for either CRESEMBA® or the concomitant medication**	**Monitoring of concomitant medication and dose adjustment if required**	

Recommendations for the coadministration of CRESEMBA® with some common concomitant agents[1,c]

Does not cause QTc prolongation

- While voriconazole and posaconazole prolong the QTc interval, CRESEMBA® shortens it[1,16,17,d]
- This may be a valuable consideration in patients with proarrhythmic risk

Simple dosing

- 200 mg every 8 hours for 48 hours (loading dose) then 200 mg once daily, for IV and oral administration – the two formulations are interchangeable[1]
- CRESEMBA® has a linear PK profile up to 600 mg, with low inter-patient and intra-patient variability. TDM may be needed but is not routinely recommended[1,25–27]

c. CRESEMBA® is contraindicated for co-administration 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. For further details and a full list of drug interactions, please consult the CRESEMBA® Summary of Product Characteristics.[1]
d. Due to CRESEMBA® shortening the QTc interval, it 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.[1]

ESRD, end-stage renal disease.

COVID-19[e] associated pulmonary aspergillosis: a new and emerging threat

Evidence of a risk of aspergillosis in COVID-19 ICU patients is growing, particularly in ARDS[8]

Diagnosis of COVID-19 associated pulmonary aspergillosis is difficult, and no guidelines currently exist for its management[8]

Risk factors may include severe lung damage, corticosteroid use, widespread broad-spectrum antibiotic use and underlying medical conditions, such as hypertension and diabetes[8]

Clinicians should carefully consider the characteristics of the therapy and the status of their patient when choosing a suitable antifungal treatment to combat COVID-19 associated pulmonary aspergillosis

CRESEMBA® is an effective antifungal therapy with a first-line recommendation for invasive aspergillosis[1,15]

European Confederation of Medical Mycology recommendations for treating COVID-19 associated pulmonary aspergillosis[28]

- The ECMM recommends CRESEMBA® (isavuconazole) and voriconazole as first-line treatment options
- Refer to the full ECMM guidelines for further information

e. CRESEMBA® is not indicated for the treatment of COVID-19.

ECMM, European Confederation of Medical Mycology.

CRESEMBA® (ISAVUCONAZOLE)

References

1. CRESEMBA® Summary of Product Characteristics. 2020.

2. Lin SJ *et al. Clin Infect Dis* 2001;**32**(3):358–366.

3. Bassetti M *et al. Infect Dis Ther* 2018;**7**(1):17–27.

4. ECDC. Influenza-associated invasive pulmonary aspergillosis, Europe. 2018. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/aspergillus-and-influenza-rapid-risk-assessment-november-2018.pdf. Accessed October 2020.

5. Taccone FS *et al. Crit Care* 2015;**19**:7.

6. Baddley JW. *Med Mycol* 2011;**49**(sup1):S7–12.

7. Verweij PE, *et al. Intensive Care Med* 2020;**46**(8):1524–1535.

8. Arastehfar A *et al. J Fungi (Basel)* 2020;**6**(2):91.

9. Alanio A *et al. Lancet Respir Med* 2020;**8**(6):e48–e49.

10. Rutsaert L, *et al. Ann Intensive Care* 2020;**10**(1):71.

11. Zhu XJ, *et al. Virus Res* 2020;**285**:198005.

12. Wang J, *et al. Crit Care* 2020;**24**:299.

13. Thompson GR, *et al. Open Forum Infect Dis* 2020;**7**(7):ofaa242.

14. Zheng HY, *et al. Cell Mol Immunol* 2020;**17**(5):541–543.

15. Ullmann AJ, *et al. Clin Microbiol Infect* 2018;**24**:e1–38.

16. VFEND Summary of Product Characteristics. 2020.

17. Noxafil Summary of Product Characteristics. 2019.

18. AmBisome Summary of Product Characteristics. 2019.

19. Natesan SK and Chandrasekar PH. *Infect Drug Resist* 2016;**9**:291–300.

20. Donnelley MA *et al. Infect Drug Resist* 2016;**9**:79–86.

21. Patel GP *et al. J Med Toxicol* 2011;**7**(1):12–15.

22. Shigemi A *et al. Int J Antimicrob Agents* 2011;**38**(5):417–420.

23. Wang Y *et al. J Arrhythm* 2020;**36**:827–836.

24. Maertens JA *et al. Lancet* 2016;**387**(10020):760–769.

25. Kaindl T *et al. J Antimicrob Chemother* 2018;**74**(3):761–767

26. Andes D *et al. Antimicrob Agents Chemother* 2018;**62**(7)

27. Desai AV *et al. Antimicrob Agents Chemother* 2017;**61**(12)

28. Koehler P *et al. Lancet Infect Dis* 2020. [Epub ahead of print].

Prescribing information

Please click the links below to be directed to the EMA website

CRESEMBA® - SmPC

VFEND® - SmPC

CRESEMBA® (ISAVUCONAZOLE)