HAUTE AUTORITÉ DE SANTÉ

INFECTIOUS DISEASE
New medicinal product
March 2016

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

CRESEMBA (isavuconazole), antifungal

No clinical added benefit demonstrated by comparison with other reference antifungals in the management of invasive aspergillosis and mucormycosis

Main points

- CRESEMBA is a new azole antifungal available in oral and intravenous forms, with Marketing Authorisation in the treatment of invasive aspergillosis and mucormycosis in patients for whom treatment with amphotericin B is inappropriate.
- It has not demonstrated a clinical added benefit compared with voriconazole (VFEND) in terms of efficacy in the treatment of invasive aspergillosis.
- Limited data are available in the treatment of mucormycosis
- Like other azole antifungals, its safety profile is marked by disturbances of liver function and skin disorders.
- It is a first-line therapeutic option in the treatment of invasive aspergillosis and second-line in the treatment of mucormycosis, especially in patients with renal failure.

Therapeutic use

- Initial treatment of invasive aspergillosis is based on intravenous administration of voriconazole (VFEND) or liposomal amphotericin B (AMBISOME) in case of contraindication for voriconazole. A switch to oral voriconazole or posaconazole is then considered. Surgical excision of the aspergillosis lesion may also be used in addition to antifungal treatment.
- In case of suspected mucormycosis, an adapted antifungal treatment must be offered urgently to avoid spread and necrosis, especially in rhino-orbital-cerebral forms. The first-line antifungal treatment is liposomal amphotericin B at high doses (≥ 5 mg/kg). Posaconazole (NOXAFIL) is used in the second-line, off-label, in patients refractory or intolerant to amphotericin B or as step-down oral therapy upon satisfactory serum concentration. Wide surgical treatment is combined with drug treatment as soon as possible.
- **Role of the medicinal product in the therapeutic strategy**
  CRESEMBA is an alternative to the first-line therapeutic options in the treatment of invasive aspergillosis, especially in patients with renal failure.
  It is a second-line therapeutic option in patients who cannot receive amphotericin B (refractory, intolerant or with a contraindication) in the treatment of mucormycosis.

Clinical data

- In the treatment of invasive aspergillosis, a study versus voriconazole was carried out in 516 patients who had not received azole antifungal-based prophylaxis. The median treatment duration was 54 days [1 to 102 days] with isavuconazole and 51 days [1 to 88 days] with voriconazole. The non-inferiority of isavuconazole compared with voriconazole was demonstrated on the all-cause mortality rate 42 days after the start of treatment (primary endpoint). These results should be interpreted with caution due to the significant number of early discontinuations of treatment (more than half of patients), the questionable threshold of the non-inferiority limit selected (10% in terms of mortality) and the absence of drug monitoring for voriconazole.
  As this is a non-inferiority study in a disease that causes significant mortality, the overall clinical response should have been the primary efficacy endpoint, more clinically relevant. For this mortalityendpoint, the results favour

voriconazole. Treatment discontinuations due to insufficient therapeutic response were more numerous in the isavuconazole group and the outcome of patients who failed (potentially difficult to treat thereafter) was not reported. Deaths due to an infection were also more numerous in the isavuconazole group (15% versus 9% in the voriconazole group) and three deaths related to a fungal infection occurred in the isavuconazole group.

- In treatment of mucormycosis, the data are very limited in this rare indication (descriptive study conducted in 37 patients with mucormycosis, in which only 11 finished the treatment with isavuconazole). Amphotericin B currently remains the best documented treatment in this indication and the Marketing Authorisation for isavuconazole is restricted to patients for whom treatment with amphotericin B is inappropriate. In these patients, the lack of comparative data versus amphotericin B or posaconazole may be regretted.
- The safety data are still limited, but the medicinal product profile seems to be in line with that expected for an azole antifungal, in particular with disturbances of liver function and skin disorders. The most commonly observed adverse effects during clinical studies were: elevated liver function tests, nausea, vomiting, dyspnoea, abdominal pain, diarrhoea, injection site reactions, headaches, hypokalaemia and skin rashes. In the comparative study versus voriconazole, isavuconazole was overall better tolerated (with fewer hepatic, ocular or cutaneous adverse effects), except for respiratory effects and in particular observations of dyspnoea.
- During the development of isavuconazole, fungal strains with reduced susceptibility were identified in vitro. The mechanisms of resistance seem to be similar to those of other azole antifungals and suggest the existence of cross-resistance.

Special prescribing conditions

- Medicine for hospital prescription.

Benefit of the medicinal product

- The actual benefit* of CRESEMBA is substantial.
- CRESEMBA provides no clinical added value** (CAV V) in the management of invasive aspergillosis and mucormycosis.
- Recommends inclusion on the list of reimbursable products for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 16 March 2016 (CT-14849) and is available at **www.has-sante.fr**

* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".