HAUTE AUTORITÉ DE SANTÉ

INFECTIOUS DISEASE
Investigation
May 2016

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

VFEND IV (voriconazole), triazole antifungal

Major improvement in the management of invasive aspergillosis and serious infections with *Scedosporium spp*. or *Fusarium spp.*,
Minor improvement in the treatment of invasive candidiasis and candidemia, with resistance to fluconazole.

Main points

VFEND has been reassessed in curative treatment of:
- invasive aspergillosis and serious fungal infections with *Scedosporium spp*. or *Fusarium spp.,* where it retains its major therapeutic contribution as the standard treatment.
- for invasive candidiasis and candidemia, where it offers few advantages relative to fluconazole: fungistatic activity comparable to that of fluconazole, less sensitivity for *C. glabrata* with reduced fluconazole sensitivity and increased cross resistance among azole derivatives. It is mainly recommended as an oral relay treatment in candidiasis with *C. krusei* and *C. glabrata* sensitive to voriconazole.

Therapeutic use

- **Invasive aspergillosis**: Intravenous voriconazole (VFEND), is a first line curative treatment for aspergillosis with a loading dose on the first day, followed several days later by an oral treatment.
- **Fusariosis:** Voriconazole or liposomal amphotericin B are first line medicinal treatments for serious infections with *Fusarium spp*.
- **Scedosporiosis**: Voriconazole is the first line medicinal treatment for serious infections with *Scedosporium spp*.
- **Invasive candidiasis and candidemia**:
  - When haemoculture isolates yeast of the *Candida* genus, the initial treatment relies on IV caspofungin or micafungin. Switching to fluconazole is recommended if the strain is sensitive, for a total duration of two weeks after negative haemoculture.
  - In probabilist treatment for invasive candidiasis: fluconazole is recommended as first line when the clinical presentation is not severe, in a non-neutropenic patient, in whom there is no suspicion of an azole-resistant strain (*C. glabrata* or *C. krusei*, prior exposure to azoles).
  - In other situations, IV caspofungin is recommended. Amphotericin B (lipid derivative) is an alternative.

Clinical data

- **Invasive aspergillosis**: Voriconazole has demonstrated its superiority to conventional amphotericin B in terms of satisfactory overall response (53% versus 32%) and survival at 84 days after start of treatment (71% versus 58%), with a better safety profile. In one recent study, the non-inferiority of isavuconazole compared with voriconazole was demonstrated in terms of all-cause mortality 42 days after the start of treatment (18.6% versus 20.2%). The results on overall clinical response favoured voriconazole. Treatment discontinuations for insufficient therapeutic response were more frequent in the isavuconazole group (15% versus 9% in the voriconazole group). Deaths due to an infection were also more frequent 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 return, isavuconazole was overall better tolerated (with fewer hepatic, ocular or cutaneous adverse effects), except for respiratory effects (dyspnoea). Other antifungals with Marketing Authorisation in the treatment of invasive aspergillosis (caspofungin and posaconazole) have not been subject to comparative studies and their Marketing Authorisations are limited to patients resistant to or intolerant of amphotericin B and/or itraconazole.

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- **Candidemia and invasive candidiasis**: Voriconazole was evaluated in two non-comparative studies in compassionate use in patients with severe systemic resistant *Candida* infections (including candidemia, disseminated candidiasis and invasive candidiasis) for whom prior antifungal treatment, especially fluconazole (33 patients) and amphotericin B (18 patients), proved ineffective. A favourable response was observed in 24 patients. Voriconazole also demonstrated its non-inferiority relative to the conventional strategy of amphotericin B followed by fluconazole in the treatment of candidemia in non-neutropenic patients, in terms of clinical success (41% in each group) and mortality on the 98th day (36% versus 42%). Renal adverse events and serious adverse events were more common in the amphotericin B/fluconazole group than in the voriconazole group. In return, vision problems and treatment discontinuations due to adverse events were more common in the voriconazole group.
  In these indications, available data do not allow voriconazole to be ranked in relation to echinocandin class antifungals such as caspofungin (or even micafungin), the current treatment of choice for invasive candidiasis or candidemia, including fluconazole-resistant strains (*C. krusei and C. glabrata*).

- **Fusariosis and Scedosporiosis**: In these rare fungal infections, the efficacy of voriconazole was documented in a very limited number of patients. A favourable response was observed, however, in particular in patients intolerant of or resistant to prior antifungal treatment.

Prescribing conditions

- Medicine for hospital prescription.

Benefit of the medicinal product

- The actual benefit* of VFEND is substantial.
- VFEND
  - retains an major clinical added value ** (CAV I) in the management of invasive aspergillosis and serious fungal infections with *Scedosporium spp*. or *Fusarium spp*.,
  - provides a minor clinical added value ** (CAV IV) in the management of serious invasive infections with *Candida* or candidemia with fluconazole resistance
- Recommends continued 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 25 May 2016 (CT-14963) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. HAS Transparency Committee assesses the ACB, 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".

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