HAUTE AUTORITÉ DE SANTÉ

**INFECTIOUS DISEASE**
**New indication**
**July 2015**

**BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION**

# **VFEND** (voriconazole), antifungal agent

**No clinical benefit demonstrated when compared with NOXAFIL (posaconazole) as prophylaxis in haematopoietic stem cell transplant recipients at high risk for invasive fungal infections**

## Main points

- VFEND now has Marketing Authorisation in the prophylaxis of invasive fungal infections (IFI) in haematopoietic stem cell transplant recipients at high risk.
- No direct comparison has been made versus the other broad-spectrum antifungal agent, posaconazole (NOXAFIL) because of the concurrence of their development. An indirect comparison does not show a significant difference.
- The safety profile of VFEND reveals clinically significant abnormalities in liver function, vision disorders, and a risk of severe skin lesions or of cutaneous squamous cell carcinoma.

## Pre-existing indications

- VFEND has Marketing Authorisation in adults and children aged 2 years and older in the treatment of invasive aspergillosis, candidemia in non-neutropenic patients, fluconazole-resistant serious invasive Candida infections (including *C. krusei*), and serious fungal infections caused by *Scedosporium spp*. and *Fusarium spp*.
- This summary does not cover these indications.

## Therapeutic use

- Early initiation of an effective treatment, essential with regard to prognosis, justifies the use of a prophylactic antifungal treatment in high-risk patients, in the absence of detectable infectious agents and with no infection.
- The type of substances recommended varies according to the risk of IFI and the time since the graft procedure, especially in case of profound neutropenia or in situations of graft-versus-host disease requiring prolonged treatment with corticosteroids.
- **Role of the medicinal product in the therapeutic strategy**
  In IFI prophylaxis, VFEND is one of the first-line treatments in adults and children from age 2 years who receive a haematopoietic stem cell transplant and are at high risk for an invasive fungal infection.
  The injectable form of VFEND offers a benefit for patients with high-grade mucositis or with oral malabsorption.

## Clinical data

The assessment of VFEND in the prophylaxis of invasive fungal infections in haematopoietic stem cell transplant recipients is based on two comparative studies, one versus itraconazole (no Marketing Authorization in IFI prophylaxis in France) and the other versus fluconazole (ineffective against *Aspergillus*).

- The study versus itraconazole demonstrated the non-inferiority of antifungal prophylaxis with voriconazole versus itraconazole 180 days after transplantation, with 109 patients (48.7%) in the voriconazole group and 80 patients (33.2%) in the itraconazole group. The superiority of voriconazole compared with itraconazole, 100 days after transplantation, was demonstrated.

- The study versus fluconazole in IFI prophylaxis in haematopoietic stem cell transplant recipients was conducted in a context of protocolised treatment and at a dosage not strictly compliant with that of the Marketing Authorisation (no loading dose). The study did not show a difference in fungal infection-free survival rates after 180 days of transplant (primary efficacy endpoint).
- In the study versus itraconazole, gastrointestinal disorders, diarrhoea, nausea and vomiting were reported more frequently in the itraconazole group (from 11 to 16%) than in the voriconazole group (around 5%). Clinically significant abnormalities in liver function tests were observed in 22.2% of patients in the voriconazole group and 13.7% in the itraconazole group. Most of the hepatic adverse effects were of a mild to moderate intensity and none progressed to liver failure. However, the hepatic adverse effects led to permanent treatment discontinuation in 21.4% of patients in the voriconazole group and 7.1% in the itraconazole group. Vision disorders were more common in the voriconazole group (10.2%) than in the itraconazole group (3.5%).

- These studies did not allow assessment of the risk of severe skin lesions or cutaneous squamous cell carcinoma specifically linked to voriconazole, which can be estimated only on greater follow-up durations than that of these studies, a situation that may occur in case of graft-versus-host disease.

## Special prescribing conditions

Medicine for hospital prescription.

## Benefit of the medicinal product

- The actual benefit* of VFEND is substantial.
- VFEND does not provide clinical added value** (CAV V) in the prophylaxis of invasive fungal infections in haematopoietic stem cell transplant (HSCT) recipients at high risk.
- 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 22 July 2015 (CT-14287) and is available at **www.has-sante.fr**

[i] * 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".