HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

OPINION

31 May 2006

Noxafil 40 mg/mL, oral suspension
Box of 1 bottle (CIP: 370 239-8)

Applicant: Schering-Plough

posaconazole

list I
Medicine for hospital use only

Date of Marketing Authorisation (AMM): 25 October 2005

Reason for request: inclusion on the list of drugs approved for hospital use.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Posaconazole

1.2. Indications

Noxafil is indicated in the treatment of the following invasive fungal infections in adults:

- Invasive aspergillosis in patients whose disease is refractory to amphotericin B or itraconazole or in patients intolerant of these medicinal products;
- Fusariosis in patients whose disease is refractory to amphotericin B or in patients intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients whose disease is refractory to itraconazole or in patients intolerant of itraconazole;
- Coccidioidomycosis in patients whose disease is refractory to amphotericin B, itraconazole or fluconazole or in patients intolerant of these medicinal products.

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

1.3. Dosage

400 mg (10 mL) twice a day with a meal, or with 240 mL of a nutritional supplement. Patients unable to eat should take 200 mg (5 mL) four times a day.

Duration of therapy should be based on the severity of the patient's underlying disease, state of recovery from immunosuppression, and clinical response.

Use in renal failure: renal failure is not expected to affect the pharmacokinetics of posaconazole and no dose adjustment is recommended.

Use in hepatic failure: there are limited pharmacokinetic data in patients with hepatic failure. No recommendation for dose adjustment can therefore be made (see SPC sections 4.4 and 5.2).

Safety and efficacy in children and adolescents under 18 years of age have not been established. Posaconazole is therefore not recommended for patients under 18.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

J : GENERAL ANTIINFECTIVES SYSTEMIC
J02 : SYSTEMIC AGENTS FOR FUNGAL INFECTIONS
J02A : SYSTEMIC AGENTS FOR FUNGAL INFECTIONS
J02AC : TRIAZOLE DERIVATIVES

2.2. Medicines in the same therapeutic category

No medicine in the same therapeutic category is comparable to Noxafil in its therapeutic indications.

2.3. Medicines with a similar therapeutic aim

All systemic antifungals (see Table).

Therapeutic category	Substance	Brand name (formulation)
Polyenes	Amphotericin B	Abelcet (IV) Ambisome (IV) Fungizone (IV)
Nucleoside analogues	Flucytosine	Ancotil (IV/tabs)
Azoles	Fluconazole	Beagyn (caps) Triflucan (caps, os, IV)
	Itraconazole	Sporanox (caps, os)
	Ketoconazole	Nizoral (tabs)
	Voriconazole	Vfend (tabs, IV, os)
Echinocandins	Caspofungin	Cancidas (IV)
Various (cutaneous mycoses)	Griseofulvine Terbinafine	Grisefuline (tabs) Lamisil (tabs)

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

An uncontrolled study (P00041)[1] assessed the efficacy of Noxafil in a sample of 330 patients (age ≥ 13 years) with proven or probable invasive fungal infections refractory to or intolerant of standard antifungal treatments, and with an underlying immune deficiency conducive to infection (neutropenia, allogenic or autologous bone marrow transplant, solid organ transplant...). Patients were treated with Noxafil 800 mg/day in split doses for a maximum of 12 months. *Aspergillus* was the commonest of the pathogenic fungal agents involved.

The results of this study were compared with those of an external control group from a retrospective review of medical files of patients treated between April 30 1996 and April 30 2001 (protocol P02387)[2]. The external control group comprised 279 patients (age ≥ 13 years) with proven or probable invasive fungal infections refractory to or intolerant of standard antifungal treatments. Control group patients had been treated with the other drugs available as a last resort, for a maximum of 12 months, mostly during the same period and on the same sites as the patients treated with Noxafil.

An independent committee made a simultaneous blind assessment of the eligibility of each patient and the response to treatment, according to defined criteria.

Refractoriness was defined as progression of infection or failure to improve after a minimum of 7 days of treatment for aspergillosis and fusariosis, 90 days for chromoblastomycosis/ mycetoma, and 180 days for coccidioidomycosis.

The main assessment criterion was overall response (partial or complete) at the end of treatment in the modified intent-to-treat (mITT) population (eligible patients).

[1] Open-Label, Treatment Protocol For The Safety and Efficacy of Posaconazole (SCH56592) In The Treatment of Invasive Fungal Infections. Study period 11 February 1999 – 26 March 2002. Unpublished study.
[2] A Retrospective Study to Establish a Historic Database on the Efficacy of Standard Antifungal Therapy in Patients With Invasive Fungal Infection. Study period 23 October 2001– 17 September 2002. Unpublished study.

Responders:

- complete response: resolution of all attributable clinical signs and symptoms and radiographic, mycological or bronchoscopic abnormalities present at inclusion.
- partial response: significant improvement in attributable clinical signs and symptoms and radiographic, mycological or bronchoscopic abnormalities present at inclusion.

➢ ***Invasive aspergillosis***

The majority of aspergillosis cases were considered to be refractory to standard antifungal treatment in both the posaconazole group (88%) and the external control group (79%). More than 90% of patients were refractory to amphotericin B and 40–50% to itraconazole.

Invasive aspergillosis: Overall efficacy at the end of treatment

	Posaconazole N (%)	**External controls N (%)**
Total responders	45/107 (42)	22/86 (26)
Complete response	7 (6.5)	8 (9.3)
Partial response	38 (35.5)	14 (16.3)
- for all mycologically confirmed species	34/76 (45)	19/74 (26)
A. fumigatus	12/29 (41)	12/34 (35)
A. flavus	10/19	3/16
A. terreus	4/14	2/13
A. niger	3/5	2/7
- by underlying disease		
Neutropenia (ANC < 500/mm^3)	5/21	2/26
Bone marrow transplant	21/55 (38.2)	7/38 (18.4)
Solid organ transplant	7/12	5/7
- by reason for treatment		
Refractory with or without intolerance	40/94 (42.6)	13/68 (19.1)
Intolerance	5/13	9/18

However, this was not a prospective, randomized, controlled trial and any comparison with the external controls must therefore be considered with caution.

➢ ***Fusariosis***

Eleven patients out of 24 with documented or probable fusariosis were successfully treated with posaconazole 800 mg/day in split doses for 124 days (median) and up to 212 days. Seven of the 18 patients refractory to or intolerant of amphotericin B or itraconazole were classed as responders.

➢ ***Chromoblastomycosis/mycetoma***

Nine out of 11 patients were successfully treated with posaconazole 800 mg/day in split doses for 268 days (median) and up to 377 days. Five of these patients had chromoblastomycosis due to *Fonsecaea pedrosoi* and 4 had mycetoma, mainly due to species of *Madurella*.

➢ ***Coccidioidomycosis***

Eleven out of 16 patients were successfully treated with posaconazole 800 mg/day in split doses for 296 days (median) and up to 460 days.

3.2. Undesirable effects

The commonest undesirable effects were gastro-intestinal symptoms (nausea, diarrhoea, vomiting and abdominal pain), fever and headache.

The commonest serious undesirable effects were: fever, breathing difficulties, dyspnoea, hypotension and septicaemia (7–20%). Only 1% of cases were considered to be therapy-related.

Cardiac conditions (e.g. prolonged QTc/QT, abnormal ECG, atrial flutter…) were not common. However, the SPC includes a warning concerning the use of Noxafil with drugs known to prolong the QTc interval (CYP3A4 inhibitors) or in patients with conditions conducive to arrhythmia. As with other azoles, hepatic reactions have been reported (mildly to moderately elevated ALT or AST, alkaline phosphatase and total bilirubin), rarely requiring discontinuation of treatment. The SPC includes a recommendation that hepatic function should be monitored to prevent progression to more serious liver disease.

3.3. Conclusion

The efficacy of Noxafil in treating refractory invasive fungal infections (as specified in the therapeutic indications) has been assessed in a noncomparative study (P00041) in a sample of 330 patients with refractory invasive fungal infections and underlying immune deficiency conducive to infection (e.g. neutropenia, allogenic or autologous bone marrow transplant, solid organ transplant…).

Aspergillus was the commonest of the pathogenic fungal agents studied. Patients were treated with Noxafil 800 mg/day in split doses as last resort therapy.

In refractory invasive aspergillosis[3], a positive response (partial or complete resolution of the signs and symptoms present at the initial visit, by the end of treatment) was seen in 42% (45/107) of patients treated for a maximum of 12 months (complete response in 6.5% and partial responses in 35.5%).

In rare fungal infections, evidence of the efficacy of Noxafil was based on a very small number of patients. A favourable response was nevertheless seen in these infections (overall success: fusariosis 7/18, chromoblastomycosis-mycetoma 9/11, coccidioidomycosis 11/16).

Noxafil was well tolerated. The commonest undesirable events were gastrointestinal symptoms (nausea, diarrhoea, vomiting and abdominal pain), fever and headache, and they were considered to be therapy-related only in a small percentage of patients**.**

It is not possible to compare Noxafil with voriconazole, the present reference therapy for invasive aspergillosis, on the basis of the present data.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The conditions concerned by this drug can be life threatening, either immediately or as the result of complications.

The efficacy/safety ratio for this medicinal product in its therapeutic indications is substantial.

Noxafil is a secondary treatment in adult patients refractory to or intolerant of first-line antifungals.

There are few alternative therapies to this drug.

[3] Especially patients refractory or intolerant to amphotericin B or itraconazole.

Public health benefit

Invasive fungal infections in patients refractory to or intolerant of first-line therapies are a low burden on public health.

There is a need for an effective antifungal treatment for patients refractory to or intolerant of first line therapy, because these treatments are effective in only around half of cases.

Given that the impact of Noxafil on reducing morbidity and mortality in patients refractory to or intolerant of voriconazole cannot be assessed on the basis of the data available:
- it cannot be assumed that Noxafil will fulfil the need;
- the impact of Noxafil on reducing morbidity and mortality cannot be estimated.

In the current state of knowledge it is therefore not expected that Noxafil will benefit public health.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

In the absence of data enabling Noxafil to be compared to the current standard therapies for the management of invasive fungal infections, this product has not been shown to offer any improvement in actual benefit (IAB V) compared to available therapies.

However, the Committee considered that Noxafil offers an additional means of therapy in the management of invasive fungal infections.

4.3. Therapeutic use

- ***Invasive aspergillosis***

Noxafil is proposed as second-line therapy in forms refractory to amphotericin B or itraconazole or in patients intolerant of these drugs. It is therefore an oral-only alternative to caspofungin, which is available for the intravenous route only. On the basis of the information submitted by the applicant, it is not possible to determine the place of posaconazole in cases where voriconazole, the first-line therapy for invasive aspergillosis[4], is ineffective.

- ***Fusariosis***

Noxafil is proposed as second-line therapy in forms refractory to amphotericin B or in patients intolerant of this drug. Voriconazole is currently the first-line alternative to amphotericin B, with a specific Marketing Authorisation wording. On the basis of the results submitted, posaconazole can be accepted as a second alternative or when it is not possible to prescribe voriconazole, which has significantly more drug interactions. However, the efficacy of Noxafil remains to be proven beyond encouraging clinical results.

- ***Chromoblastomycosis/mycetomas***

Noxafil has been studied in a very small number of subjects, in particular those with mycetoma. However, it has been shown to be clinically effective against these disabling infections. No oral antifungal has a specific Marketing Authorisation for these indications requiring several months of therapy. In chromoblastomycoses, terbinafine is very effective. In fungal mycetomas, treatment is usually surgical; voriconazole has been of value in some cases.

[4] *Conférence de consensus commune SFAR, SPILF, SRLF: Prise en charge des aspergilloses et candidoses invasives de l'adulte.* Elsevier SAS. 2004. [Consensus conference on management of invasive aspergillosis and candidosis in adults]

- ***Coccidioidomycoses***

Treatment is continued over several months, or even for life when the central nervous system is affected, but these cases are not included in the indications for Noxafil. There are several alternatives to amphotericin B, notably fluconazole and itraconazole. However, having another antifungal for refractory infections or patients with intolerance would be very valuable. It should be noted that there is "little" information available on its efficacy in this mycosis, which is rarely encountered in France (fewer than 10 cases per year in France).

4.4. Target population

For invasive aspergillosis and fusariosis, the population is that of immunocompromised patients, and for chromoblastomycosis or mycetomas, that of migrants. Coccidioidomycosis occurs in patients who have spent time in an endemic zone, whether or not they are immunocompromised.

It is thought that around 1500–4000 patients are treated in France each year for invasive aspergillosis, and around 200 for rare fungal infections (fusariosis, chromoblastomycosis, mycetoma, coccidioidomycosis)[5].

The target population for Noxafil in the current management of invasive fungal infections coming under its therapeutic indications is difficult to estimate given their rarity and the vagueness of the data.

Noxafil is for use as an alternative, secondary treatment in patients refractory to or intolerant of first-line treatments (around 50% of patients). In practice, the number of patients likely to be treated with Noxafil is probably much lower because this treatment can only be considered when the oral route can be used. The absence of an intravenous form is a handicap for the treatment of patients in the acute stage of invasive aspergillosis, particularly in patients with mucositis or digestive malabsorption in GVH (graft-versus-host disease). Furthermore, the use of Noxafil when voriconazole (the current standard treatment for invasive aspergillosis) is ineffective, cannot be quantified on the basis of available data, not to mention the limited data on its efficacy in rare fungal infections. It should also be noted that even with antifungal treatment, mortality from these conditions is very heavy, at 50–100% depending on the underlying immune disease.

4.5. Transparency Committee Recommendations

The Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services for the indications and at the dosages given in the Marketing Authorisation.

[5] Data extrapolated from a study conducted by CEMKA based on an analysis of the literature, PMSI databases, the Hospital Market Survey study, and interviews with experts. Data submitted by applicant.