REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Noxafil
100 mg gastro resistant tablets x 24
INN Posaconazole

Therapeutic indications	Posaconazole is indicated for the treatment of the following fungal infections in adults: - Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products; - Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B; - Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole; - Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products. - Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high-risk of developing invasive fungal infections; - Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high-risk of developing invasive fungal infections.
Start date - end date of procedure	22.04.2019 - 03.10.2019
Final decision	Rejects inclusion in the Positive Drug List.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Noxafil

Health problem

Invasive Aspergillosis: Aspergillosis develops only sporadically in patients with preserved immunity and high individual immunological reactivity. It mainly affects people with congenital or acquired immune deficiency, after long-term chemotherapy or treatment with corticosteroids, after organ or tissue transplantation. Patients with neutropenia, leukemia, chronic respiratory inflammatory diseases, mainly chronic obstructive pulmonary disease, asthma, cystic fibrosis are several times more likely to get ill. Infection of humans is carried out by airborne mechanism, after inhalation of microorganisms. Aspergillus produces many toxic metabolites that neutralize and render harmless the macrophages and neutrophils. They penetrate the body and are most often localized in the lungs. Treatment of patients with aspergillosis consists of conservative drug therapy with antifungals (Amphotericin B, Itraconazole, Voriconazole or Posaconazole) and surgical resection.

Fusariosis: Fusariosis is the second most common opportunistic mold after Aspergillus spp. in patients with neoplastic diseases. In immunocompetent usually infections caused by Fusarium spp. are superficial or confined to one organ, whereas in immunosuppressed patients, fusariosis is an invasive and disseminated infection. Fusariosis can be a localized skin infection, mycetoma, or pneumonia. Destruction of mucosa or skin barrier appears to be a major factor in the pathogenesis of invasive fusariosis. Treatment of disseminated fusariosis requires systemic antifungal therapy, if possible surgical removal of infected tissue, and immunotherapy. Azoles are currently considered most effective against Fusarium.

Coccidioidomycosis: Coccidioidomycosis is a lung or hematogenously disseminated disease caused by the fungi Coccidioides immitis and C. posadasii. It usually presents as an acute benign asymptomatic or self-limiting respiratory infection. Untreated disseminated coccidioidomycosis is usually fatal and, if meningitis is present, long-term and possibly lifelong treatment is required. Mortality in patients with advanced HIV infection exceeds 70% within 1 month of diagnosis. Treatment is usually with Fluconazole, Itraconazole, newer triazoles (Posaconazole) or Amphotericin B.

Chromoblastomycosis/Mycetoma: Chromoblastomycosis is a chronic fungal infection of the skin and subcutaneous tissue caused by traumatic inoculation of a specific group of fungi (usually Fonsecaea pedrosoi, Phialophora verrucosa, Cladosporium carrionii or Fonsecaea compacta) through the skin. Treatment options include oral Itraconazole (as monotherapy or with oral 5-flucitosine [5-FC]), topically applied heat therapy, cryosurgery, photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA), and combination therapy. Studies of

treatment with Posaconazole have shown better results than those obtained with Itraconazole or Terbinafine.

Epidemiological data

Nearly one billion people worldwide have fungal infections of the skin, nails and hair, and more than 150 million people have serious fungal diseases that have a major impact on their lives or are fatal. Data on epidemiology of invasive mycoses are difficult to ascertain because these are often treated empirically without an accurate diagnosis, which is often ascertained only at autopsy.

Efficacy data

An analysis of data on the therapeutic efficacy and safety of Posaconazole health technology was performed. The results of 5 clinical trials and 1 meta-analysis were compared and analyzed (Table).

Table Clinical trials, evaluating the efficacy and safety of posaconazole

Study (ID No.)	**P00041**	**RCT 316**	**P01899**	**P01893**	**C197-280**
Location, country	USA	Argentina, Australia, Austria, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Mexico, the Netherlands, Peru, Poland, Portugal, Saudi Arabia, Great Britain, USA	Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Dominican Republic, Ecuador, France, Germany, Greece, Hungary, Italy, Mexico, Netherlands, Panama, Peru, Poland, Portugal, Singapore, South Africa, Spain, Sweden, United Kingdom, United States	Germany, USA	USA
Study design & type	Phase 3, a multicenter, open-label clinical study investigating the safety and efficacy of posaconazole in patients with invasive fungal infection with refractory disease or intolerance to standard antifungal therapy.	Phase 3, a randomized, double-blind clinical study investigating the efficacy and safety of posaconazole versus fluconazole for the prevention of invasive fungal infections in immunosuppressed patients.	Phase 3, randomized, blinded to evaluators, evaluating the efficacy and safety of posaconazole versus fluconazole or itraconazole for the prevention of invasive fungal infections in neutropenic patients.	Phase 2, open-label, randomized study evaluating the safety, efficacy, and dosage of posaconazole for the empirical treatment of invasive fungal infection in neutropenic patients or for the treatment of refractory invasive fungal infection.	Multicenter, open, randomized study, safety assessment, tolerability and efficacy on posaconazole in patients with lung coccidioidomycosis engagement.
Duration of	12.1998 –	01.1999 – 02.2003	07.2002 – 04.2005	01.2001 – 3.2002	Not specified

study	03.2002 (3 y 3m)	(4 y и 1 m)	(2 y 9 m)	(1 y 2 m)	
Method of randomization	Not applicable	1:1	1:1	1:1:1	1:1 , subsequently 1 arm removed
Method of achieving anonymity (researcher, patient, evaluator of result)	open	Double blinded	Blinded for investigator	Not applicable	Not applicable
Intervention	posaconazole	posaconazole	posaconazole	posaconazole	posaconazole
Comparisons / controls (number)	Not applicable	Posaconazole vs fluconazole	posaconazole vs fluconazole/itraconazole	posaconazole 200 mg q.i.d. vs posaconazole 400 mg q.i.d. vs posaconazole 800 mg b.i.d.	posaconazole 800 mg/d (subsequently discontinued) vs posaconazole 400 mg/d
Primary results	Patients with cryptococcal meningitis Proportion of patients with response: 14 (48%) Patients with complete response: 4 Patients with partial response: 10 Patients without response: 15 (8 with treatment failure, 6 with stable disease, 1 with indeterminate condition) Patients with death: 12 (6 due to progression of fungal infection, 6 after discontinuation of posaconazole) Average duration of therapy: 81	Frequency of IFI during the fixed period of treatment posaconazole: 5.3% (OR 0.56; 95% CI, 0.30 to 1.07) fluconazole: 9.0% P = 0.07 Efficacy in relation to the incidence of proven or probable aspergillosis Rosaconazole with better efficacy than fluconazole (OR 0.31; 95% Cl, 0.13 to 0.75; P = 0.006) Efficacy in reducing the incidence of probable or proven IFI Rosaconazole with better efficacy than fluconazole (OR 0.30, 95% Cl, 0.12 to 0.71, P = 0.004) Efficacy with respect to invasive posaconazole aspergillosis with better efficacy than fluconazole (OR 0.17, 95% CI, 0.05 to 0.57, P = 0.001)	Patients with proven or probable IFI posaconazole: 7 (2%) fluconazole / itraconazole: 25 (8%) Absolute reduction in the posaconazole group: -6% (95% CI, -9.7 to -2.5, P <0.001) Patients with proven or probable fungal infection (100 days post-randomization) posaconazole: 14 (5%) fluconazole/ itraconazole: 33 (11%) P = 0.003 Mean (± SD) time to onset of IFI posaconazole: 41 ± 26 days fluconazole / itraconazole: 25 ± 26 days. Time to IFI In favor of posaconazole P = 0.003 Patients with posaconazole aspergillosis: 2 (1%) fluconazole/ itraconazole: 20 (7%) P <0.001 Patients with clinical success posaconazole: 195 (64%) fluconazole: 160 (54%) Patients with clinical failure posaconazole: 109 (36%)	Patients with rIFI with clinical response posaconazole 200mg /400mg: 6 (50%) posaconazole 400mg / 600mg: 1 (10%) posaconazole 800mg / 800mg: 4 (40%) Patients with rIFI with complete clinical answer posaconazole 200mg / 400mg:0 posaconazole 400mg / 600mg: 0 posaconazole 800mg / 800mg: 3 (30%) Patients with rIFI with partial clinical response posaconazole 200 mg / 400 mg : 6 (50%) posaconazole 400 mg / 600 mg: 9 (90%) posaconazole 800 mg / 800 mg: 6 (60%) Patients with rIFI with stable posaconazole disease 200 mg /400 mg : 1 (8)	Patients with response to therapy: 17 (85%) Mean MSG: (0-13) Decrease in MSG score relative to baseline: 63 (0-100) Patients treated with fluconazole after the end of the study: 5 (25%) Patients treated with itraconazole after the end of the study: 5 (25%) Patients without antifungal treatment after the end of the study: 10 (50%)

Network meta-analysis. Overall incidence of invasive mycoses, invasive Aspergillus infections and invasive Candida infections.

Of the 21 studies included, 20 reflect results for the overall incidence of IFI, and 16 reflect invasive Aspergillus infections and invasive Candida infections. All triazole antifungals, with the exception of itraconazole capsules, were significantly more effective than placebo at reducing invasive fungal infection. Posaconazole was significantly better than fluconazole (OR, 0.35 [95% CI, 0.16-0.73]) and itraconazole capsules (OR, 0.25 [95% CI, 0.06-0.97]), but not versus voriconazole (OR, 1.31 [95% CI, 0.43 to 4.01]), to prevent invasive mycosis.

Posaconazole was significantly more effective than placebo (OR, 0.12 [95% CI, 0.02 to 0.61]), fluconazole (OR, 0.07 [95% CI, 0.01 to 0.29]), itraconazole solution (OR, 0.10 [95% CI), 0.02 to 0.47] and voriconazole (OR, 6.46 [95% CI, 1.22 to 34.04]) for the prevention of invasive infections with Aspergillus. However, the effects of posaconazole treatment against voriconazole obtained by indirect evidence should be interpreted carefully. Voriconazole was significantly more effective in reducing invasive Aspergillus infections than fluconazole (OR, 0.42 [95% CI, 0.20 to 0.90]).

Total mortality and IFI-related mortality

19 and 14 studies were analyzed, respectively, which concern total mortality after 100 days plus mortality associated with invasive fungal infections. Posaconazole was associated with a significant reduction in overall mortality compared with placebo (OR, 0.49 [95% CI, 0.28-0.85]), fluconazole (OR, 0.54 [95% CI, 0.330.88]) and itraconazole solution. OR, 0.49 [95% Cl, 0.28 to 0.83]). Fluconazole (OR, 0.50 [95% CI, 0.28 to 0.88]), a solution of itraconazole (OR, 0.33 [95% CI, 0.16 to 0.70]) and rosaconazole (OR, 0.14 [95% CI, 0.04-0.43]) were with significantly greater efficacy than placebo in reducing mortality associated with invasive mycoses. Especially as concerns deaths due to IFI, rosaconazole has more favorable profile than fluconazole (OR, 0.27 [95% CI, 0.10-0.76]), but not over other agents. Although significance was not achieved, the general trend is in favor of voriconazole over other triazole antifungals with regard to risk reduction of both overall mortality and IFIs. In both cases, the effect of rosaconazole treatment against voriconazole was not statistically significant.

Empirical therapies

Fifteen studies concerning the use of empirical therapies were analyzed. With the exception of itraconazole capsules, significantly fewer patients required the initiation of empirical antifungal therapy when using triazole antifungal prophylaxis than with placebo. Fewer patients receiving prophylaxis with posaconazole required empirical therapies compared to fluconazole (OR, 0.35 [95% CI, 0.15-0.80]), itraconazole capsules (OR, 0.33 [95% CI, 0.12-0.95] OR, 0.37 [95% Cl, 0.15 to 0.91]). When voriconazole was administered, significantly

fewer patients received empirical therapies compared to fluconazole (OR, 0.66 [95% CI, 0.45-0.96]).

Ranking

Hierarchies of treatment effects have been established based on SUCRA values for prophylaxis against invasive fungal infections. A value of 1 indicates that the treatment is definitely the best, and a value of 0 indicates that it is definitely the worst. SUCRA values for the five treatments were as follows: posaconazole, 0.92; voriconazole, 0.80; itraconazole solution, 0.63; fluconazole, 0.36; itraconazole capsule, 0.27.

Network metaregression

Meta-regression analyzes show that the efficacy in terms of the overall incidence of invasive mycoses did not differ in performed procedures, follow-up duration, and test-specific error risk (P>0.05).

Studies P02387 and P02952

Study P02952 is a report comparing the results between P00041 and P02387, which should be considered with much attention, as P02387 is an external control group. A logistic regression model was used to compare posaconazole-treated and control groups in terms of overall response rate at the end of treatment in patients with invasive fungal infections due to aspergillosis. OR on the effects of treatment based on this model evaluates the efficacy of posaconazole relative to control. A two-way test (alpha = 0.05) was used to assess the significance of the treatment effect. Study P02387 is a retrospective study based on a review of medical records of patients refractory or intolerant to standard therapy of invasive mycoses. These patients represent an external control group that coincided in time with study P00041.

Table Patient disposition

	Number (%) of subjects	
	P00041 (N=330)	**P02387 (N=279)**
Disposition of subjects during the treatment phase - ITT subset		
Discontinued	193 (58)	109 (39)
Adverse events	102 (31)	5 (2)
Treatment failure	47 (14)	
Lost of follow-up	2 (1)	
Did not wish to continue	17 (5)	
Non-compliance with protocol	17 (5)	
Did not meet protocol eligibility	3 (1)	
Administrative	5 (2)	8 (3)
Death	*	96 (34)
Completed treatment phase	**137 (42)**	**170 (61)**

* *death reported separately.*

Safety data

Clinical study P00041

The most common drug-related adverse reactions include nausea (9%), vomiting (6%), headache (5%), abdominal pain (5%), diarrhea (3%), elevated alanine aminotransferase (ALAT) levels (3%), elevated levels of aspartate aminotransferase (ASAT) (3%) and rash (3%). Posaconazole did not cause QT prolongation or adverse cardiac inotropic effects. Long-term use of posaconazole (>6 months) does not result in a different safety profile compared with short-term use (<6 months).

Clinical trial RCT 316

The safety assessment included all 600 patients. The majority of adverse events were considered by researchers to be unrelated to treatment. The incidence of adverse events considered to be related to the studied drugs was similar in the two groups.

The frequency of discontinuation of the study drug due to an adverse event was similar in both groups (103 patients [34%] in the posaconazole group and 114 patients (38%) in the fluconazole group). The most common treatment-related adverse events leading to discontinuation are gastrointestinal disorders. In this study, a high frequency of treatment discontinuation was observed due to the severity of underlying disease; only 46% of patients in the posaconazole group and 41% of patients in the fluconazole group completed full 16-week therapy.

Clinical trial P01893

Most patients (84/98, 86%) received posaconazole for less than 3 months. In the general population (n=98), regardless of the dosing regimen, the most common treatment-related adverse reactions were gastrointestinal events. Serious or life-threatening adverse events were reported in 55% (54/98) of all randomized patients (49% of patients at 400 mg per day, 58% at 600 mg per day, 59% at 800 mg q.d.). 24% (24/98) of all randomized patients discontinued the study due to an adverse event; none of the events that led to the discontinuation were considered treatment-related. Laboratory tests do not show trends that suggest an effect of posaconazole treatment. No neurological abnormalities were reported. There are no clinically significant changes in the electrocardiograms. Serious adverse reactions were reported in 46% of all randomized patients. The overall mortality was 22% (22/98) for all randomized patients.

Clinical study C197-280

18 patients (90%) reported at least 1 adverse event. Twelve patients reported at least 1 adverse event that was likely related to posaconazole therapy. No event was considered severe or life-threatening. The most common treatment-related adverse events were dry mouth (25% of patients), headache (15%), skin nodules (15%), fatigue (10%) and rash (10%).

Studies P02387 and P02952

Serious Adverse Events (SAE)

In the group with invasive mycoses, 68% of patients reported SAE, most often fever (20%), respiratory failure and dyspnoea (10% each). Hypotension, acute myelogenous leukemia, sepsis, pneumonia, diarrhea and vomiting have also been reported in 6%-8%. Treatment-related SAEs occur in only 8% of patients.

Death cases

In the IFI pool, death occurred in 157 (37%) patients. Most of the death cases are due to complications or progression of the underlying disease.

Discontinuation of treatment due to adverse events (AE)

In the pool of invasive fungal infections, 46% of participants had AE that led to discontinuation of treatment, discontinuation of study, or death. Treatment-related AE that led to treatment discontinuation, study discontinuation, or death were reported in 6%.

Data on comparators

The available therapeutic alternatives for treatment and prevention of fungal infections in Bulgaria are:

Voriconazole - a broad-spectrum triazole antifungal. It is indicated in adults and children 2 years of age and older for treatment of invasive aspergillosis and serious fungal infections caused by Fusarium spp. Voriconazole should be used mainly in patients with progressive, potentially life-threatening infections. Voriconazole is also indicated for the prevention of invasive fungal infections in high-risk recipients with allogeneic hematopoietic stem cell transplantation.

Fluconazole - indicated for the prevention of fungal infections in immunocompromised patients considered to be at risk due to neutropenia after cytotoxic chemotherapy or radiation therapy, including patients after hematopoietic stem cell transplantation.

Pharmacoeconomic indicators

A health technology assessment is only available in France, identifying the benefits of the product as significant and recommending inclusion in the reimbursement list for hospital use. In the UK, Germany and Sweden, no evaluation has been performed.

Applied analysis

The applied CEA and CUA analyses reflect the Bulgarian therapeutic practice and treatment standards. The analysis was performed against 2 main alternatives - voriconazole and fluconazole. The model uses a health perspective and the payer's point of view - hospital health care facilities. The direct medical costs are estimated - for medicinal products, calculated for prices at wholesaler level and 100% reimbursement and for patients with invasive aspergillosis, the model includes Clinical Path № 042.1. The discount is 3.5%. A Markov model (computer simulation) with two mutually exclusive health conditions was applied: survival and death. Within the "survival" health condition, patients can either be treated or have successful treatment. The model is described as a Markov half-model, following the "area under the curve" approach to reflect differences in survival benefits as measured by overall survival (OS). A number of sensitivity analyses have been performed. According to the curve of acceptable cost efficiency, the probability that posaconazole therapy will be cost-efficient compared to voriconazole for the treatment of aspergillosis at a predetermined profitability threshold of BGN 38,000 / QALY reaches 67%. In the treatment of fusariosis according to the curve of acceptable cost efficiency, the probability that posaconazole therapy will be cost-effective compared to voriconazole at a pre-set profitability threshold of BGN 38,000 / QALY reaches 47%. In patients with AML and MDS, incremental sensitivity analysis shows superiority of fluconazole over posaconazole. In transplant patients, posaconazole therapy is 52% likely to be cost-effective compared to voriconazole at a pre-established profitability threshold of BGN 38,000 / QALY. The results of the one-way sensitivity analyses show that ICER is most strongly influenced by the health benefits of therapy with the evaluated technologies. The results of the analyses show that the cost of posaconazole therapy is 8000 to 14000 higher than the cost of the other two alternatives (voriconazole, fluconazole), the difference in efficacy is in favor of posaconazole, but the evidence is taken from clinical trials, rather than from meta-analyses. The probability of posaconazole being an acceptable alternative at a profitability threshold of BGN 38,000 varies between 47% and 67%, depending on the type of infection and the alternative.

Costs for the assessed health technology

The cost of therapy with Noxafil for individual diagnoses and according to the duration of treatment varies between 5313 and 112335 BGN.

The costs of therapy with competitive alternatives - voriconazole and fluconazole vary between BGN 214 and 721, depending on the duration of treatment and diagnosis, being again highest in the prevention of invasive infections during transplantation.

The budget impact in the treatment of patients with fusariosis is expected to lead to an additional cost of BGN 188,640, and in the prevention of transplanted patients - to an additional cost of BGN 2.9 million for 5 years.

Conclusion

The cost of treatment with posaconazole is many times higher than the cost of the main alternative voriconazole, as well as with already established fluconazole treatment. According to a meta-analysis, their effectiveness is similar and there is no reason to believe that posaconazole is superior to voriconazole or fluconazole in the intended indications. For the vast majority of incremental ratios posaconazole is not cost effective.

The price, respectively cost of treatment with posaconazole is not justified by the evidence of therapeutic effect, and the cost-effectiveness of the product has not been demonstrated.

Due to availability of enough alternatives with similar efficiency and lower costs, there are no ethical or moral aspects that the product Noxafil would raise for discussion.