HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

06 September 2006

Nexavar 200 mg, film-coated tablet
B/112 (CIP code: 376 137-2)

Applicant BAYER PHARMA

sorafenib

List I
Medicine for hospital prescription only. To be prescribed only by oncologists or haematologists, or doctors competent in oncology. Medicine requiring special monitoring during treatment.

Date of Marketing Authorisation: 19 July 2006

Reason for request: inclusion on the list of drugs reimbursed by National Insurance and approved for hospital use.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Sorafenib

1.2. Background

Sorafenib is a protein kinase inhibitor with a dual mechanism of antitumour action, i.e. a direct action through blocking cell proliferation and an action associated with anti-angiogenesis.

1.3. Indication

Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon alpha or interleukin 2 based therapy or who are considered unsuitable for such therapy.

1.4. Dosage

Nexavar treatment should be supervised by a physician experienced in the use of anticancer therapies. The recommended dose of Nexavar in adults is 400 mg (2 tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg). It is recommended that sorafenib should be administered without food or with a low or moderate fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Dose adjustment

Management of suspected adverse effects may require temporary interruption or dose reduction of Nexavar therapy. When dose reduction is necessary, the Nexavar dose should be reduced to two tablets of 200 mg once daily.

- *Paediatric patients:* Nexavar is not recommended for use in children and adolescents (<18 years) owing to a lack of data on safety and efficacy.
- *Elderly patients:* no dose adjustment is required in the elderly (patients over 65 years of age).
- *Renal impairment:* no dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance > 30 ml/min). No data are available in patients with severe renal impairment (creatinine clearance < 30 ml/min) or in patients requiring dialysis.
- *Hepatic impairment:* no dose adjustment is required in patients with mild to moderate hepatic impairment. No data are available on patients with severe hepatic impairment.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XE	Protein kinase Inhibitors
L01XE05	sorafenib

2.2. Medicines in the same therapeutic category

Sunitinib (Sutent)

2.3. Medicines with the same therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

The company submitted results from 2 studies:

- a phase II study (# 100391)
- a phase III study (# 11213).

Study 100391

Its aim was to evaluate progression-free survival in patients with stable disease (<25% reduction in tumour size) after a 3-month induction phase with sorafenib, compared to placebo.

- **Design and methodology**

This was a phase II, randomized, placebo-controlled trial of 569 patients with solid tumours, including advanced renal cell carcinomas. Overall, 202 patients had renal cell carcinoma refractory to conventional therapies (interleukin 2 and interferon).

During the induction phase, all patients with renal cell carcinoma (n=202) received sorafenib (2 X 200 mg tablets), twice daily, for 3 months. At the end of this phase, tumour response was evaluated by imaging. Patients were separated into 2 groups as follows:

- not stabilized (n=79): patients continued sorafenib. This group was not evaluated.
- stabilized (n=65): patients were randomized to receive placebo (n=33) or sorafenib (n=32).Their baseline characteristics are given in Table 1.

Table 1. Patient baseline characteristics

	Sorafenib (n=32)	Placebo (n=33)
Mean age (years)	58.4	56.7
ECOG score[1] (N))		
0	18 (56%)	18 (55%)
1	14 (44%)	15 (45%)
Prognostic risk (N)		
Poor	13 (40%)	14 (42%)
Intermediate	18 (56%)	15 (45%)
Previous treatment with IL2 and/or IFN (N)	26 (81%)	28 (85%)

The primary endpoint was the progression-free rate, defined as the percentage of randomized patients with stable disease or a response to treatment at 12 weeks after randomization.

- **Results**

Efficacy

The efficacy analysis concerned a group of 65 randomized patients (subgroup analysis as described in the protocol). Overall, 50% (16/32) of patients randomized to sorafenib and 18% (6/33) of patients randomized to placebo were progression-free 3 months after randomization (p=0.0077).

Median Progression-Free Survival was 5.4 months for patients randomized to sorafenib versus 1.3 months for patients randomized to placebo (p=0.0001).

Undesirable effects

The most common side effects during the induction phase and at 12 weeks of treatment are given in Tables 2 and 3, respectively.

Table 2. Most common side-effects during the 12-week induction phase

Events		Incidence (%)
Cardiovascular	Hypertension	35
Dermatological	Hand-foot syndrome	60
	Rash, skin exfoliation	62
	Alopecia	50
Gastrointestinal	Diarrhoea	46
	Stomatitis	27
General	Fatigue.	55

[1] The ECOG (Eastern Cooperative Oncology Group) scale is a scale graded from 0 to 4 that evaluates the patient's performance status which is a prognostic factor.
0: Fully active, able to carry out all pre-disease activities without restriction
1: restricted in physically strenuous activity, but ambulatory and able to carry out light work
2: ambulatory and capable of all self-care, but unable to carry out any work activities 50% of the time
3: capable of much more limited self-care. Confined to bed or chair > 50% of the time.
4: completely disabled. Cannot carry out any self-care. The patient is totally confined to bed or chair.

Table 3. Most common side-effects at 12 weeks

	Sorafenib %	Placebo %
Weight loss	25	6
Hand-foot syndrome	19	15
Diarrhoea	41	24
Nausea	19	9
Vomiting	16	6

- **Conclusion**

This study showed a statistically significant increase in progression-free survival in patients randomized to continue treatment with sorafenib after stabilization during an initial 12-week induction phase. Overall, 50% of patients on sorafenib (16/32) and 18% (6/32) of patients on placebo were progression-free at 12 weeks after randomization (p=0.0077).

The median Progression-Free Survival was 5.4 months for patients receiving sorafenib versus 1.3 months for patients on placebo (p=0.0001).

Study 11213 (unpublished)

- **Design and methodology**

This was a randomized, placebo-controlled trial to evaluate the efficacy and safety of sorafenib as a 2nd-line therapy (after failure of immunotherapy) in patients with advanced renal cell carcinoma (nonresectable and/or metastatic). A total of 903 patients were included: 451 received sorafenib (2 x 200 mg tablets), twice daily, and 452 matching placebo.

The primary endpoints were overall survival and progression-free survival. The protocol specified that:

- patients on placebo should not switch to sorafenib,
- a single analysis be performed when approximately 363 events (progression or death) had been recorded for assessment of progression-free survival,
- two analyses be performed for assessment of overall survival: an intermediate analysis when 270 deaths had occurred and a final analysis[2] when 540 deaths had occurred.

Secondary endpoints were objective response rate and quality of life[3].

- **Results**

The mean age of patients was 59 years. Most patients had an ECOG performance status score of 0 or 1, had previously received either interleukin-2 or interferon-alpha, and 99.8% had a good or intermediate prognostic score.

Analysis of progression-free survival

A first analysis based on radiological imaging was carried out in the first 769 patients (384 patients in the sorafenib group and 385 in the placebo group). Progression-free survival was

[2] With a type I (alpha) risk of 0.04 (two-sided test), 540 events would yield a statistical power of about 90% to detect an increase of 33.3% in overall survival rate.

[3] Measured using the FKSI-10 (Functional Assessment of Cancer Therapy - Kidney Symptom Index) score which evaluates 10 symptoms and concerns in patients with renal cancer (such as pain, fatigue, breathlessness, fear that their health will deteriorate) and FACT-G (Functional Assessment of Cancer Therapy - General) score

167 days (95% CI 139–174) (i.e. 5.5 months) in the sorafenib group versus 84 days (95% CI 78–91) (i.e. 2.8 months) in the placebo group, RR = 0.44, $p < 10^{-6}$.

A second analysis based on the clinical investigator's assessments was carried in all the patients (n=903). Median progression-free survival was 168 days (i.e. 5.6 months) for patients on sorafenib versus 84 days (i.e. 2.8 months) for patients on placebo (RR = 0.51, $p < 10^{-6}$).

Analysis of overall survival

In view of the encouraging results recorded for progression-free survival in patients treated with sorafenib, the study design was modified to allow patients on placebo to switch to sorafenib. A total of 216 patients on placebo (56%) switched to sorafenib (protocol amendment).

According to a first interim pre-crossover analysis, the median overall survival was 14.7 months in the placebo group but was not reached in the sorafenib group. Although results were provided for a second interim, post-crossover, analysis, these could not be used - except for information purposes - because some of the patients in the placebo group received sorafenib of their own free choice.

Tumour response rate

In the Nexavar group, 1 patient experienced a complete response, 43 patients (9.5%) a partial response, and 333 patients (73.8%) had disease stabilization.

In the placebo group, 8 patients (1.8%) had a partial response and 239 patients (52.9%) experienced disease stabilization.

Quality of life

After 24 weeks of treatment, an improvement was observed:
- in the FKSI-10 score, in 44% of patients on sorafenib versus 22% of patients on placebo
- in the FACT-G score, in 47% of patients on sorafenib versus 21% of patients on placebo.

Undesirable effects

The analysis was performed in 902 patients. The most commonly reported undesirable effects were dermatological (rash/skin exfoliation, hand-foot syndrome), cardiovascular (hypertension) and gastrointestinal effects.

Grade 3-4 adverse events were reported by 38% of patients receiving sorafenib compared to 28% of patients receiving placebo. The most common grade 3-4 adverse event was hand-foot syndrome. It was reported by 5.5% of patients on sorafenib but no patient on placebo.

Of the randomized patients, 10.2% of those receiving sorafenib and 8.2% of those on placebo discontinued treatment because of serious adverse events.

- **Conclusion**

In a phase III trial carried out only in patients (n=903) with advanced renal cell carcinoma (non resectable and/or metastatic) with a good or intermediate prognosis, after failure of first-line therapy with interferon-alpha or interleukin-2, sorafenib increased progression-free survival by about 3 months compared to placebo (5.6 months on sorafenib versus 2.8 months on placebo, $p < 10^{-6}$).

According to an intermediate analysis of survival performed before 216 patients switched from placebo to sorafenib, median overall survival was 14.7 months in the placebo group and was not reached in the sorafenib group.

The final analysis of overall survival is not available.

The adverse events most commonly reported by patients taking Nexavar were dermatological, cardiovascular and gastrointestinal events.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Renal cell carcinoma is the most common type of renal cancer and is a life-threatening disease. The most common clinical signs are urological signs (haematuria, lumbar pain) and general signs (weight loss, fever).

Nexavar is used as curative therapy.

The efficacy/undesirable effects ratio is high.

Nexavar is a second-line drug.

There is an alternative drug, sunitinib (Sutent).

Public health benefit

Advanced renal cell carcinoma represents a moderate public health burden.
Improving management of the disease is a public health need in the fight against cancer.
According to the results of clinical trials:

- Nexavar is expected, in theory, to have a moderate effect on morbidity, mortality and quality of life, despite the absence of a proven effect on overall survival. Because of the very small number of patients concerned in practice, the anticipated impact on morbidity, mortality and quality of life can only be low on a population scale.
- Nexavar can provide a partial response to the public health need.

Nexavar is therefore expected to be of benefit to public health. This benefit is minor.

The actual benefit is substantial.

4.2. Improvement in actual benefit

Nexavar provides substantial improvement in actual benefit (level II) in the management of advanced renal cell carcinoma in patients who have failed prior interferon alpha or interleukin 2 based therapy, or are considered unsuitable for such therapy.

4.3. Therapeutic use

Management of advanced renal cell carcinoma [4]

The aim of treatment of patients with metastatic disease is to improve overall survival and quality of life. However, until now, no treatment has been shown to improve quality of life because only few trials have been carried out with this objective.

- The gold standard drug therapy of metastatic disease is immunotherapy (interferon and interleukin 2).
- Nephrectomy increases the duration of survival in patients receiving interferon and with metastatic disease. In fact, in patients treated with interferon and with a good performance status, nephrectomy is likely to improve patient survival significantly.[5]

[4] Méjean A. et al. Tumeurs du rein. Progrès en Urologie 2004;14,997-1035

[5] Flanigan R., Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J. Med. 2001;345:1655-1659; Mickisch GH, Garin A, Van Poppel H et al: Radical nephrectomy plus interferon-alfa based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 2001; 358:966-970.

- Cytotoxic chemotherapy is not very effective. No randomized trial has shown a survival benefit of chemotherapy compared with a control group.

Interferon is one of the standard treatments for metastatic renal cell carcinoma, with a modest but real therapeutic benefit. Its use is associated with non serious undesirable effects, such as shivering and fever (flu-like syndrome). On the other hand, no trial has shown a benefit of interleukin 2 treatment in terms of survival.

Therapeutic use of Nexavar

In the absence of a therapeutic alternative after failure of immunotherapy, sorafenib, like sunitinib, is a new option as a second-line treatment of renal cell carcinoma.

4.4. Target population

The target population for Nexavar consists of patients with advanced or metastatic renal cell carcinoma who have failed prior interferon alpha or interleukin 2 based therapy and who are candidates for second-line therapy.

The target population can be estimated from the following data:
- in France, there are more than 8000 new cases of renal cancer a year.
- renal cell carcinoma accounts for 85%[6] of cases of renal cancer, i.e. 6800 cases per year.
- 50% of patients are diagnosed at an advanced or metastatic stage[7]. One third of the patients (i.e. 5440 patients) develop advanced or metastatic disease[8].
- Approximately 90% of these 5440 patients are given immunotherapy, and 70% of them fail to respond.

The overall estimated target population for Nexavar is about 3400 cases per year.

4.5. Committee Recommendations

The Committee recommended inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for use by hospitals and various public services for the indications and doses mentioned in the Marketing Authorization.

4.5.1. Packaging: appropriate for the prescription conditions

4.5.2. Reimbursement rate: 100%

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[6] EMEA - public summary of positive opinion for orphan designation of sorafenib tosylate for the treatment of renal cell carcinoma

[7] Godley PA, Taylor M. Renal cell carcinoma. Curr Opin Oncol 2001;13:199-203; Bleumer I, Oosterwijk E, De Mulder P, Mulders PF. Immunotherapy for renal cell carcinoma. Eur Urol 2003;44: 65-75.

[8] Godley PA, Taylor M. Renal cell carcinoma. Curr Opin Oncol 2001;13:199-203.