HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

5 March 2008

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

Applicant: BAYER SANTE

sorafenib

List I
Medicinal product available only on hospital prescription. Prescribable only by oncology, haematology and cancer specialists. Medicinal product requiring specific monitoring during treatment

Date of initial marketing authorization (centralized procedure): 19 July 2006
Date of extension of indication: 29 October 2007

Orphan drug

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use in the extension to the indication: “treatment of hepatocellular carcinoma”.

Health Technology Assessment Division

1 CHARACTERISTICS OF MEDICINAL PRODUCT

1.1. Active ingredient

sorafenib

1.2. 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 are considered unsuitable for such therapy.
Indication already evaluated by the Committee (see opinion of 6 September 2006)

NEXAVAR is indicated for the treatment of hepatocellular carcinoma."

1.3. 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 (two 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.

Dosage adjustments
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 (< 18 years) and adolescents due to a lack of data on safety and efficacy.

Elderly patients: No dose adjustment is required in the elderly (patients above 65 years of age).

In patients with renal impairment: no dose adjustment is required in patients with mild, moderate or severe renal impairment. No data is available in patients requiring dialysis.

In patients with hepatic impairment: No dose adjustment is required in patients with mild to moderate hepatic impairment. No data is available in patients with severe hepatic impairment.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification 2007

L	Antineoplastic and immunomodulator agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XE	Protein kinase inhibitors
L01XE05	sorafenib

2.2. Medicines in the same therapeutic category

None.

2.3. Medicines with a similar therapeutic aim

- epirubicin (FARMORUBICIN, injection), indicated for the treatment of hepatocellular cancer
- medicinal products based on doxorubicin (which are used in practice but do not have marketing authorization for the treatment of hepatocellular carcinoma)

3 ANALYSIS OF AVAILABLE DATA

The company submitted the results of 2 studies:

- a non-comparative phase II trial (trial 10874) which included 137 patients suffering from advanced hepatocellular carcinoma
- a comparative placebo-controlled randomized double-blind phase III trial (trial 10554), which comprises 602 patients suffering from advanced hepatocellular carcinoma. Only the results of this comparative trial will be described in the present opinion.

3.1. Efficacy results of trial 10554

Objective: to evaluate the efficacy and safety of sorafenib (NEXAVAR) compared with a placebo in the treatment of advanced hepatocellular carcinoma

Methodology:

Comparative placebo-controlled randomized double-blind phase III trial, which included 602 patients (299 in the sorafenib group, and 303 in the placebo group).

Inclusion criteria after a 28-day pre-selection period (ITT population):

- life expectancy: at least 12 weeks
- ECOG performance index: 0, 1 or 2 (see Appendix 1)
- histologically or cytologically confirmed hepatocellular carcinoma
- patients ineligible for surgical or locoregional treatment
- at least one measurable lesion not previously treated locally or systemically
- stage of cirrhosis: Child-Pugh Class A only (see Appendix 2)

Dosing regimen:
The dosage of sorafenib was 400 mg twice daily.
The treatment continued until symptomatic progression, death, or appearance of adverse effects.

Primary endpoints:
- overall survival
- time to symptomatic progression, defined as:
  - at least a 4-point reduction compared with the baseline value in the score evaluated by the patient according to the FHSI-8 (FACT Hepatobiliary Symptom Index) questionnaire,
  - a deterioration in ECOG performance to 4,
  - or death

Statistical methods:
The number of patients required was calculated on the basis of the estimated survival rate.
The protocol required:
- the inclusion of 560 patients (280 in each treatment group) to observe 424 deaths[1]
- a first intermediate analysis after 170 deaths
- a second intermediate analysis after 300 deaths.

The significance threshold for terminating the trial was established at 0.0077 by the protocol, according to the O'Brien Fleming method, based on the "overall survival rate".

Secondary endpoints:
- time to radiological progression
- rate of global control of the illness, assessed by an independent committee and defined as the proportion of patients presenting a total or partial response or stabilization of the illness for at least 28 days according to the RECIST criteria
- quality of life, estimated according to the FACT-Hep questionnaire[2] : proportion of patients with an 8-point variation in the total FACT-Hep score

Results
The median duration of treatment was 23 weeks in the sorafenib group and 18.6 weeks in the placebo group.

➢ Main characteristics of the patients included
The patients' initial demographic and tumoral characteristics were similar in the two treatment groups (table below).

[1] With a beta risk of 90.45% according to the O'Brien-Fleming method, taking account of inflation of the alpha risk due to the intermediate analyses
[2] The FACT-Hep analysis is based on the total scores for the 45 items in the questionnaire. The total score ranges between 0 and 180. FACT-Hep evaluates the following factors: physical well-being, functional well-being, emotional well-being and social well-being.

	Placebo (no. = 303) no. (%)	Sorafenib (no. = 299) no. (%)
Gender Male Female	 264 (87) 39 (13)	 260 (87) 39 (13)
Age (years): <65 ≥65 mean (SD)	 108 (36) 195 (64) 66,3 (10,2)	 124 (41) 175 (59) 64,9 (11,2)
General state (ECOG score) 0 1 2	 164 (54) 117 (39) 22 (7)	 161 (54) 114 (38) 24 (8)
Child Pugh score A B C	 297 (98) 6 (2) 0 (0)	 284 (95) 14 (5) 1 (0,3)
Vascular invasion and/or extra-hepatic metastases Absent Present	 91 (30) 212 (70)	 90 (30) 209 (70)
BCLC stage (see Appendix 3) B C D	 51 (17) 252 (83) 0 (0)	 54 (18) 244 (82) 1 (0,3)
Hepatic cirrhosis Histological Clinical Histological and clinical Not confirmed	 95 (31) 86 (28) 38 (13) 84 (28)	 91 (30) 86 (29) 33 (11) 89 (30)
Prior treatments Surgery Locoregional treatment Radiotherapy Systemic treatment (hormonal or cytotoxic)	 288 (95) 123 (40,6) 15 (5) 15 (5)	 284 (95) 116 (38,8) 13 (4,3) 9 (3)

- Primary endpoints: (ITT analysis)

The available results are those of the second intermediate analysis.

- Overall survival:

The overall survival rate was 71% for the sorafenib group vs. 61% for the placebo group after 6 months, and 44% vs. 33% after 12 months *(value of p not available)*

The median overall survival rate was 46.3 weeks [40.9; 57.9] in the sorafenib group vs. 34.4 weeks [29.4; 39.4] in the placebo group (RR = 0.6931, CI 95%: [0.5549; 0.8658], p=0.0006).

During this second intermediate analysis, the significance limit (p= 0.0077) specified by the protocol was reached. The data review committee considered that the trial was positive for this endpoint, and should therefore be terminated. The patients being treated with the placebo were therefore transferred to the sorafenib treatment group.

- Time to symptomatic progression:

No statistically significant difference was observed between the two treatment groups.

➢ Secondary endpoints:

- Time to radiological progression:

The median time to radiological progression, assessed by an independent committee, was 24 weeks in the sorafenib group vs. 12.3 weeks in the placebo group (HR = 0.5764, CI 95% [0.4484; 0.7410], $p<10^{-3}$).

The investigators' evaluation of 403 radiological progressions (222 in the placebo group and 181 in the sorafenib group) attributed a median time to progression of 17 weeks in the sorafenib group vs. 11.9 weeks in the placebo group (HR = 0.6889, CI 95% [0.5634; 0.8423], p=0.00013).

- Rate of global control of the illness:

The rate of control of the illness was 43.5% in the sorafenib group (130/299) vs. 31.7% in the placebo group (96/303), p=0.0016.

There was no complete response. A partial response was observed in two patients in the placebo group and seven patients in the sorafenib group. The duration of the response was not estimated.

Stabilization of the illness was observed in 70.6% of patients in the sorafenib group (211/299) and 67.3% of patients in the placebo group (204/303).

Disease progression was observed in 18.1% of patients in the sorafenib group (54/299) and 24.1% of patients in the placebo group (73/303).

- Quality of life :

The quality of life analyzed according to the FACT-Hep questionnaire did not differ statistically between the sorafenib group and the placebo group.

3.2. Safety data

Adverse events associated with the treatment were more frequent in the sorafenib group than the placebo group (79.5% of patients vs. 52.3%).

The main adverse effects observed in the sorafenib group compared with the placebo group were: diarrhoea (55.2% vs. 25.2%), weight loss (30.9% vs. 9.9%), anorexia (28.6% vs. 17.5%), hand-foot syndrome (21.2% vs. 3.0%), rash/desquamation (18.5% vs. 13.9%), vomiting (14.8% vs. 10.9%) and alopecia (14.1% vs. 1.7%).

The most frequent adverse events of grade 3-4 were diarrhoea (32 patients in the sorafenib group vs. 6 patients in the placebo group) and hand-foot syndrome (reported in 23 patients treated with sorafenib vs. 2 patients in the placebo group).

These adverse events led to discontinuation of the treatment in 31.6% of patients in the group treated with sorafenib (94/297) and 35.4% of patients in the placebo group (107/302).

3.3. Conclusion

The efficacy and safety of sorafenib in the treatment of hepatocellular carcinoma were evaluated in a phase III comparative, randomized, double-blind, placebo-controlled trial including 602 patients suffering from advanced hepatocellular carcinoma. The trial was conducted on patients with a good prognosis (good general state of health, hepatic cirrhosis at Child-Pugh stage A) who were ineligible for first-line surgical or locoregional treatment or after failure of those treatments.

Two primary endpoints were analyzed: overall survival and time to symptomatic progression. The available results are those of the second intermediate analysis required by the protocol.

The median overall survival rate was 46.3 weeks (11.5 months) in the sorafenib group vs. 34.4 weeks (8.5 months) in the placebo group (RR = 0.6931, CI 95%: [0.5549-0.8658], p=0.0006), ie. a gain of 3 months.

In view of this result, the trial was terminated and the patients in the placebo group were transferred to the sorafenib treatment group. However, this survival benefit is modest.

No statistically significant difference was observed between the two treatment groups for the second primary endpoint (time to symptomatic progression).

A benefit was therefore only demonstrated for one of the two primary endpoints analyzed.

Analysis of quality of life according to the FACT-Hep questionnaire showed no difference between the two groups.
The most frequent adverse events observed in the patients treated with sorafenib were gastrointestinal (diarrhoea) and dermatological (hand-foot syndrome, rash/desquamation).
The Committee regrets that it has no efficacy or safety data for sorafenib in the population of more fragile patients, at Child Pugh stage B or C.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Liver tumours are often asymptomatic. The most frequent primary malignant tumour is hepatocellular carcinoma. The associated risk factors are cirrhosis, alcohol and infection with the hepatitis B or C virus. This carcinoma can be life-threatening. The 5-year survival rate for hepatocellular carcinoma with cirrhosis is under 5%. The 2-year survival rate is 20-50%. In the event of hepatocellular carcinoma in a healthy liver, this survival rate is 30-40%.
This proprietary product is classed as a palliative treatment.
The efficacy/adverse effects ratio is high in patients with a good prognosis suffering from hepatic cirrhosis at Child-Pugh stage A and who are ineligible for first-line surgical or locoregional treatment or have proved unresponsive to those treatments.
This ratio has not been established in patients with a less favourable prognosis, suffering from hepatic cirrhosis at Child Pugh stage B or C, in the absence of data for that population.
This medicinal product is a first-line therapy administered to patients who are ineligible for first-line surgical or locoregional treatment or have proved unresponsive to those treatments.
There is no approved alternative medication.

Public health benefit:
Hepatocellular carcinoma (HCC) constitutes a major public health burden. In the sub-population of patients liable to benefit from NEXAVAR, the burden is low, as this sub-population is small compared with the total population of HCC patients.
Improving the treatment of this disorder constitutes a public health need.
In view of the findings of the phase III trial on the median overall survival rate, sorafenib can be expected to have a low impact in terms of mortality in patients who are ineligible for or unresponsive to locoregional treatment, in a good general state of health, and suffering from cirrhosis at Child-Pugh stage A. This impact cannot be extrapolated for a larger population, and the risk of negative impact cannot be ruled out if the product is used in patients eligible for locoregional treatment or for whom no benefit has been demonstrated. The available data are insufficient to assess the impact of sorafenib on quality of life.
The transposability of the experimental data is not guaranteed, as the trial population was significantly different from the population to be treated in practice, in view of the breakdown of the patients according to the etiology of cirrhosis (some 50% of the patients in the trial had viral cirrhosis, whereas in France, the vast majority of cases of cirrhosis are alcohol-related). Moreover, a risk of deterioration in the real quality of life cannot be ruled out in view of the frequency of adverse events.
Consequently, no public health benefit is expected for NEXAVAR in this extension to the indication.

However, the actual benefit is substantial for patients with a good prognosis and hepatic cirrhosis at Child-Pugh stage A who are ineligible for first-line surgical or locoregional treatment or unresponsive to those treatments.

4.2. Improvement in actual benefit

As the demonstration is limited to a population with a good prognosis, the extent of the effect observed and the safety profile, the Transparency Committee considers that NEXAVAR provides a minor improvement in actual benefit (IAB IV) for patients suffering from advanced hepatocellular carcinoma, with intact liver function (Child Pugh stage A), who are ineligible for or unresponsive to surgical or locoregional treatment.

4.3. Therapeutic use[3]

Hepatocellular carcinoma usually develops in patients with cirrhosis, more rarely in those with chronic non-cirrhotic liver disease, and exceptionally in a healthy liver.
The choice of treatment depends of the status of the hepatocellular carcinoma.

Curative treatments are represented by transplant (indicated for a tumour strictly localized in the liver, and for a single tumour measuring under 5 cm in diameter or, in the event of multiple tumours, if there are not more than 3 nodules not exceeding 3 cm in diameter, in the absence of thrombosis of the portal system), surgery (a single tumoral nodule, normal bilirubin, ALAT < 2 N, in the absence of signs of portal hypertension) and percutaneous ablation.

Palliative treatments, namely lipiodol chemoembolization (LCE) and arterial embolization (AE), are used for inoperable patients who cannot receive percutaneous treatment.
The benefit of LCE and AE in patients suffering from hepatocellular carcinoma with alcoholic cirrhosis is controversial: clinical trials, especially trial FFCD 9402[4], have not shown any gain in terms of survival. However, two phase III trials and two recent meta-analyses showed increased survival among the treated patients[5, 6, 7, 8]. In these trials, the patients were selected (patients with intact liver function, mainly suffering from hepatocellular carcinoma with chronic liver disease of viral origin). Moreover, the methods of conducting LCE and post-treatment monitoring are not consensual. AE and LCE present technical difficulties of administration. The role of sorafenib compared with AE and LCE is unknown.
As regards systemic chemotherapy, no medicinal products used in monotherapy or in combination have proved superior to doxorubicin, which in turn has not proved superior to palliative care in terms of survival[9]. A recent trial[10] which compared nolatrexed (antifolate) with doxorubicin in patients suffering from metastatic hepatocellular carcinoma or who were ineligible for surgical treatment, showed that doxorubicin provided a greater benefit in terms of the median overall survival rate.
(NB: an indirect comparison with a study relating to sorafenib is impossible, because the patients included in this trial have a less favourable prognosis.)

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[3] Thésaurus de cancérologie de la Société Nationale Française de Gastroentérologie. Novembre 2006

[4] Doffoël M, Vetter D, Bouché O, Bonnetain F, Abergel A, Fratté S, et al. La chimioembolisation lipiodolée améliore-t-elle la survie et la qualité de vie des patients ayant un carcinome hépatocellulaire sur cirrhose ? Résultats d'un essai prospectif, randomisé et multicentrique (FFCD 9402) (abstract). Gastroenterol Clin Biol 2005;29:A148.

[5] Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte JJ et al Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial Lancet. 2002 May 18;359(9319):1734-9.

[6] Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-71.

[7] Cammà C, Schepis F, Orlando A, Albanese M, Shahied L, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma : meta-analysis of randomized controlled trials. Radiology 2002 ;224:47-54.

[8] Llovet JM, Bruix J, Barcelona-Clinic-Liver Cancer Group. Systematic review of randomized controlled trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003 ;37:429-42.

[9] Yeo W, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst 2005;97:1532-38.

[10] EPAR for NEXAVAR
Gish RG et al. Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. J Clin Oncol. 2007 Jul 20; 25 (21) : 3069-75

Thus there is no reference chemotherapy for the treatment of advanced hepatocellular carcinoma.

Sorafenib therefore constitutes a new first-line treatment method for advanced hepatocellular carcinoma in patients with a good prognosis, at Child Pugh stage A, who are ineligible for or unresponsive to surgical or locoregional treatment.

4.4. Target population

The target population of NEXAVAR is represented by patients suffering from advanced hepatocellular carcinoma, with an intact liver function (Child Pugh stage A), who are ineligible for or unresponsive to surgical or locoregional treatment.
This population can be estimated from the following data:
- the incidence of hepatocellular carcinoma was 7,289 new cases in 2007.
According to the experts:
- 50% of hepatocellular carcinomas are discovered at an intermediate or advanced stage (stage B and C of the BCLC classification), and 50% are diagnosed at Child Pugh stage A
- 80% of patients suffering from intermediate or advanced hepatocellular carcinoma at Child Pugh stage A are unresponsive to surgical or loco-regional treatment.

The total target population of NEXAVAR can be estimated at approximately 1,500 patients.

4.5. Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use and various public services in the extension to the indication, at the dosage specified in the marketing authorization.

4.5.1. Packaging: appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%

APPENDICES

APPENDIX 1: ECOG score

The ECOG (Eastern Cooperative Oncology Group) value scale is a scale that assesses the patient's general state of health, and a prognosis factor. It is a 5-point scale (0 to 4):

- 0: Fully active, able to carry on all pre-disease performance without restriction
- 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
- 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX 2: Child-Pugh Classification of Severity of Liver Disease

Points scored for	1	2	3
Encephalopathy	0	+	++
Ascites	0	+	++
Serum albumin (g/l)	>35	28-35	<28
Total bilirubin (mg/l)	<20	20-30	>30
Prothrombin time (%)	>70	45-70	<45

Child-Pugh stage A: 5-6 points
Child-Pugh stage B: 7-9 points
Child-Pugh stage C: 10-15 points

APPENDIX 3: BCLC (Barcelona Clinic Liver Cancer) classification

Stage		ECOG score	Tumour morphology	Okuda stage	Liver function
early	A1	0	single, < 5 cm	I	No PHT, normal bilirubin
	A2	0	single, < 5 cm	I	PHT, normal bilirubin
	A3	0	single, < 5 cm	I	PHT, hyperbilirubinaemia
	A4	0	3 lesions, < 3 cm	I – II	Child-Pugh A - B
intermediate	B	0	multinodular	I – II	Child-Pugh A - B
advanced	C	1-2	vascular invasion, metastases	I – II	Child-Pugh A - B
terminal	D	3-4	irrelevant	III	Child-Pugh C

PHT: Portal hypertension
Stage A and B: all criteria must be fulfilled
Stage C and D: one criterion is sufficient