

sorafenib 200mg tablets (Nexavar[®])

(No. 321/06)

Bayer Plc

6 October 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

sorafenib (Nexavar[®]) is not recommended for use within NHS Scotland for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alfa or interleukin-2 based therapy or are considered unsuitable for such therapy.

Sorafenib has been compared with best supportive care and has been shown to increase progression-free survival, though the impact on overall survival is uncertain. The cost-effectiveness of sorafenib has not been demonstrated.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

For the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alfa or interleukin-2 based therapy or are considered unsuitable for such therapy.

Dosing information

Recommended dose of 400mg twice daily without food or with a low to moderate fat meal. Treatment should continue for as long as clinical benefit is observed or until unacceptable toxicity occurs.

UK launch date

24 July 2006. Sorafenib has been designated an Orphan Drug for this indication.

Comparator medications

The most likely direct comparator is sunitinib which was launched in the UK at the beginning of August 2006 for the treatment of advanced and/or metastatic renal cell carcinoma after failure of interferon-alfa or interleukin-2 therapy. Sunitinib has yet to be reviewed by SMC.

Cost of relevant comparators

Product	Regimen	Cost per year (£)
Sorafenib tablets (Nexavar®)	400mg orally twice daily	£32,560
Sunitinib tablets (Sutent®)	50mg orally daily for 4 weeks followed by a two week rest period. This six week cycle is then repeated.	£28,635

Doses are shown for general comparison and do not imply therapeutic equivalence. A one year treatment period has been used for illustrative purposes only and in practice many patients will be treated for shorter durations.

Summary of evidence on comparative efficacy

The majority of kidney tumours are renal cell carcinomas which involve cells in the renal tubule. Although renal cell carcinoma accounts for approximately 2% of all adult cancers, it is the sixth leading cause of cancer death. At diagnosis about 25% of patients have metastatic or unresectable disease which is associated with a median survival time of 6 to 12 months and a 2-year survival rate of 10-20%. Sorafenib is a multikinase inhibitor with both anti-proliferative and anti-angiogenic properties. It has been designated an orphan drug for the treatment of advanced renal cell cancer in Europe.

One key phase III study has provided evidence of efficacy. This was a randomised, placebo-controlled, multi-centre study primarily designed to evaluate the effects on survival of sorafenib plus best supportive care against best supportive care alone. Eligible patients had unresectable and/or metastatic measurable renal cell carcinoma and had received no more than one systemic therapy for advanced disease during or after which the disease had progressed. In addition, patients had to have a life expectancy of at least 12 weeks, be of

good performance status (Eastern Co-operative Oncology Group (ECOG) scale 0 or 1) and rated as “low” or “intermediate” risk according to the Motzer scale. The Motzer scale assesses risk according to a number of associated prognostic factors including poor ECOG (≥ 2), high serum lactate dehydrogenase ($\geq 1.5 \times$ upper limit of normal), low serum haemoglobin, high corrected serum calcium ($\geq 10\text{mg/dl}$) and absence of prior nephrectomy.

Patients were randomised to receive sorafenib (400mg twice daily) (n=451) or placebo (n=452), stratified by country and Motzer risk category. Treatment was continued until a withdrawal criterion was reached (unacceptable toxicity, disease progression or death). Overall survival was the primary outcome and was defined as the time from randomisation to death from any cause. The main secondary outcome measure was progression free survival (PFS), defined as the time from randomisation to disease progression (radiological or clinical whichever was earlier) or death. In the primary analysis of PFS, radiological progression was assessed by an independent reviewer using Response Evaluation Criteria in Solid Tumours (RECIST) criteria, with subsequent analyses using investigator-assessed radiographs. Other secondary endpoints included response rate and measures of quality of life. Following results of an interim analysis in May 2005, after all patients had been enrolled, a protocol amendment allowed unblinding and the opportunity for placebo-treated patients to cross-over to sorafenib.

A first interim analysis of overall survival (May 2005) occurred after 220 deaths (123 in the placebo group and 97 in the sorafenib group), giving a hazard ratio for death of 0.72 (95% CI: 0.55, 0.95), $p=0.018$ (threshold for statistical significance $p=0.0005$). The median survival was 15 months in the placebo group and had not been reached in the sorafenib group. A second interim analysis (November 2005) after 367 deaths and after approximately 200 patients had crossed-over from placebo to active treatment found a hazard ratio of 0.77 (95% CI: 0.63, 0.95), $p=0.015$ (threshold for statistical significance $p=0.0094$). The median survival was 16 months in the placebo group and 19 months in the sorafenib group.

The primary analysis of PFS (January 2005), occurred after 769 patients had been enrolled and found a median PFS of 84 days in the placebo group (n=385) and 167 days in the sorafenib group (n=384). This corresponded to a hazard ratio of 0.44 (95% CI: 0.35, 0.55), $p<0.000001$. Subgroup analysis of PFS based on independent radiological review found more favourable treatment effects in terms of hazard ratios were found in patients with more aggressive disease. Similar results were observed in subsequent (May 2005) descriptive analyses, which used investigator-assessed radiographs.

In an analysis, which included data from patients randomised at least 6 weeks before the data cut-off in May 2005, investigator-assessed objective response (defined as a best response of complete or partial response by RECIST criteria) was achieved in 44/451 (9.8%) of sorafenib-treated patients and 8/452 (1.8%) of placebo patients. All responses were classed as partial with the exception of one complete response in the sorafenib group. In the respective groups 74% and 53% achieved a best response of stable disease.

Quality of life assessed by the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire and Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI) questionnaire, found that sorafenib treatment significantly delayed the time to deterioration in health status and a number of individual symptoms. However, significantly more sorafenib-treated patients reported side effects.

Further supportive data are available in the form of a phase II discontinuation study in patients with advanced refractory solid tumours. Results have been published for the subset of patients with renal cell carcinoma (n=202). All patients initially received sorafenib 400mg twice daily.

After 12-weeks, those patients with tumour shrinkage continued open-label sorafenib while those with tumour growth of at least 25% discontinued the study. Patients with stable disease were randomised to continue sorafenib or to receive placebo in a 12-week double-blind phase. The primary endpoint of progression-free rate 12-weeks post-randomisation was 50% (16/32) in the sorafenib-treated group and 18% (6/33) in the placebo treated group ($p=0.0077$).

Summary of evidence on comparative safety

The most commonly reported adverse events during sorafenib treatment were diarrhoea, rash, alopecia and hand-foot skin reactions. Hypertension was reported in more sorafenib than placebo treated patients but was usually mild to moderate, occurred early in the course of treatment and was manageable with standard antihypertensive therapy. However, regular blood pressure monitoring is recommended. An increased risk of bleeding has been associated with sorafenib therapy as well as increased INR in those patients also taking warfarin. In terms of laboratory findings, sorafenib treatment was associated with higher incidences of grade 3 or 4 lymphopenia, neutropenia, elevated lipase and hypophosphataemia than placebo. Sorafenib is considered to modestly suppress bone marrow function.

Summary of clinical effectiveness issues

The key phase III study was primarily designed to assess overall survival and mature data are awaited. The latest interim analysis appears to show improved survival with sorafenib but the difference over placebo did not reach statistical significance. A final analysis of survival is planned once 540 deaths have occurred. However, since patients have been allowed to cross over from placebo to sorafenib, the interpretation of these results may be limited.

The treatment effect demonstrated in terms of PFS, an absolute difference over placebo of 83 days, has been described by the European Medicines Agency (EMA) as “favourable and clinically meaningful”. Subgroup analysis suggested that larger treatment effects in terms of PFS were achieved in patients with more aggressive disease. Quality of life data suggest an advantage for sorafenib in several domains. However, this has to be balanced against an increased incidence of side effects.

Patients enrolled in this study had good performance status and were of “low” or “intermediate” Motzer risk categories. Therefore, the effects of sorafenib of patients with reduced performance status and “high” Motzer risk remain to be seen. As yet no biomarkers have been identified that would help optimise the predictive response to this multitargeted agent.

Although the phase II discontinuation study generally supports these results, the treatment effect reported may be different to that expected in the general population due to enrichment of those patients who entered the double-blind phase by the exclusion of those with side-effects or progressive disease before week 12 (and exclusion of patients who experienced at least 25% tumour-shrinkage before week 12).

No studies have been completed against the active comparator.

Summary of comparative health economic evidence

The manufacturer presented a cost utility analysis of sorafenib relative to best supportive care, an appropriate comparator given the current lack of active treatments. A Markov model was presented with three health states: progression free, disease progression and dead. The cycle length was 3 months with the 10 year time horizon requiring 40 model cycles. Transition probabilities for the first 4 cycles were drawn from the phase III trial. The 4th cycle transition probabilities were then reapplied 35 times. Modelling was undertaken separately for patients with ECOG performance status 0 (PS0) and ECOG performance status 1 (PS1), these being combined to give the overall estimate of cost effectiveness. Transition probabilities for the model were drawn from the phase III trial results.

Patients within the sorafenib arm received 400mg twice daily. Treatment with sorafenib was assumed to stop on disease progression, though the trial protocol permitted treatment to continue after progression if it was felt to be clinically justified. As a consequence, the estimate of the direct drug cost for sorafenib within the modelling may be biased, and possibly an underestimate. Other resource use was estimated through a survey of experts, this being valued at standard unit costs. These experts were also asked to use the EQ-5D questionnaire to evaluate patient quality of life in the progression-free health state and the “disease progression” health state. The higher rate of adverse events within the sorafenib arm were not factored into quality of life considerations as quality of life was only differentiated by the three health states and performance status but not by treatment. This may have led to bias.

The base case estimate was that among PS0 patients, sorafenib results in an additional 1.09 QALYs at an additional cost of £30,209, resulting in a cost effectiveness estimate of £27,689/QALY. For PS1 patients the respective quantities were 0.75 QALYs, £31,242 and a cost effectiveness of £41,687/QALY. Combining these gave an overall cost effectiveness estimate of £35,523/QALY.

The analysis was well handled over the period of the trial data. However, the degree of extrapolation and reapplication of the 4th cycle transition probabilities substantially reduces the confidence that can be placed in the longer-term estimates of cost effectiveness. The model anticipates that most patients will have progressed after two years. Shortening the time horizon of the analysis to two years raised the cost effectiveness ratio significantly.

The cost effectiveness of sorafenib has not been demonstrated.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

Based upon an average treatment duration of around 200 days, an eligible patient population of 134 patients in year 1 rising to 149 by year 5 and a market penetration of 40% rising to 50% over the same period, the direct drug cost of sorafenib is estimated by the manufacturer as being around £1m in year 1, rising to £1.4 million by year 5. Since sorafenib is broadly additional to best supportive care, no offsetting savings are anticipated.

Guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) produced service guidelines in September 2002 on Improving Outcomes in Urological Cancers. This document recommended interferon-alfa as the standard treatment for patients with metastatic renal cancer who are suitable for systemic anticancer therapy.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 19 September 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted reference was supplied with the submission

Ratain MJ, Eisen T, Stadler WM et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol, 2006; 24(16): 2505-12.