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The clinical, cost-effectiveness and service impact of sorafenib (Nexavar) in the NHS of England and Wales for the treatment of patients with advanced renal cell carcinoma

A submission by Bayer Schering Pharma to the National Institute for Health and Clinical Excellence (NICE)

Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma

Health Technology Assessment

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Executive Summary

Advanced RCC, an orphan disease, is the most common form of primary kidney malignancy, and has a bleak prognosis with a median survival of 8-12 months and a five year survival of less than 10%. There is a compelling unmet clinical need for effective treatments to improve the prognosis of these patients. Sorafenib, which has designated orphan drug status, is an oral multi-kinase inhibitor licensed for use in patients with advanced RCC who have failed prior therapy with interferon alpha or interleukin-2, or are unsuitable for such therapy. Sorafenib's efficacy was confirmed in the largest-ever randomised controlled trial (RCT) in advanced RCC (TARGET study) and in a randomised discontinuation study. These placebo-controlled studies showed clinically and statistically significant improvements in progression free survival. Overall survival was also improved in the Phase III RCT, after adjusting for placebo patients who crossed-over to active treatment. In addition to the Phase II and III RCTs, there are 2 expanded access programmes, altogether involving over 4200 patients. Sorafenib is generally well tolerated, with most adverse events being mild to moderate. The cost per QALY of treating these patients may be larger than the traditionally accepted thresholds. However, these do not necessarily take into account the poor prognosis and relatively low quantity of life remaining for patients diagnosed with advanced RCC. Without sorafenib, there are no other RCT evidence-based treatment options available for patients with advanced RCC who have either failed or are unsuitable for cytokine therapies. The budget impact of treating approximately 880 patients is equivalent to £3.5 million per annum over five years.

Renal Cell Carcinoma (RCC) is the most common form of primary kidney malignancy, accounting for over 80% of cases. Unlike most other tumours, the incidence of RCC is increasing. RCC now accounts for 2-3% of all newly diagnosed malignancies in the UK. It is more prevalent in men than women (male:female ratio 3:2), and the incidence increases with age, with rates rising steeply after the age of 40. Risk factors include age, smoking, chemicals, and certain inherited conditions. For early-stage tumours, surgery (partial or radical nephrectomy) is the mainstay of treatment, and can offer a good prognosis, with 5-year survival rates up to 90-95%. However, around 40% of patients undergoing partial or radical nephrectomy eventually experience a relapse. In addition, because RCC often has few or no specific symptoms in the early stages, 20-25% of patients already have advanced (metastatic or unresectable) disease by the time they present. In this situation, the prognosis is bleak, with a median survival of 8-12 months, and a five-year survival of less than 10%. Consequently, there is a compelling clinical need for effective treatments in order to improve the prognosis for these patients with advanced RCC.

The four new products under consideration (sorafenib, sunitinib, bevacizumab, and temsirolimus) will have impacts at different parts of the patient's care pathway. Sorafenib is licensed for use after interferon-alpha and interleukin-2 or when these therapies aren't suitable. Other options in these patient populations are best supportive care (BSC) or sunitinib. Sorafenib is the sole drug to have RCT data supporting its use in the post-first-line or cytokine-unsuitable setting. Furthermore this place in treatment is reflected in the European Association of Urology guidelines produced in March 2007, where it is stated that 'Tyrosine kinase inhibitors should be considered as first- or second-line treatment for mRCC patients (grade A recommendation). Sorafenib is advised as a second-line treatment for mRCC (grade A recommendation). Sunitinib is advised as first-line therapy in good-and intermediate-risk patients (grade A recommendation). Temsirolimus should be considered as first-line treatment in poor-risk patients (grade A recommendation).'

Sorafenib is an oral multi-kinase inhibitor which has demonstrated significant progression free survival (PFS) and placebo-censored overall survival (OS) benefits for RCC patients over placebo. Sorafenib's efficacy and tolerability in RCC has been demonstrated in two large, randomized, multicentre, placebo-controlled trials, providing the highest level of clinical evidence (Jadad score).

In the Phase III study (TARGET), sorafenib demonstrated highly statistically significant benefits over placebo. In fact, the study was stopped early due to highly significant positive results at the first interim analysis - a doubling of progression-free survival (PFS) compared to placebo.

As a result of this, patients in the placebo arm were allowed to cross-over to receive sorafenib, potentially confounding the results, and the final OS analysis did not achieve significance. However, in a pre-planned, placebo-censored analysis at crossover, sorafenib also demonstrated a statistically significant prolongation of overall survival (OS) compared to placebo.

In the same study, sorafenib additionally showed significant benefits compared with placebo for the secondary and tertiary efficacy-end-points: time to progression, tumour response, and disease control rate.

Sorafenib-treated patients demonstrated a significantly improved quality of life versus those receiving placebo in 4 out of 15 domains of the FKSI instrument (coughing; worrying about worsening RCC; fevers; ability to enjoy life). Moreover, sorafenib produced a significant delay in symptomatic deterioration (measured by FACT-G and FKSI) compared to placebo.

Sorafenib demonstrated non-inferiority to placebo with respect to quality of life (as measured by FKSI-10, FKSI-15 and FACT-G PWB). In other words, the clinical benefits gained from sorafenib treatment do not appear to be at the expense of quality of life.

The Phase II randomised discontinuation study also showed a statistically significant benefit from sorafenib, with PFS almost quadrupled compared to placebo. This corroborates the evidence from the Phase III TARGET study, and suggests that sorafenib is able to restabilise disease in patients with progressive malignancy.

The results from the randomised controlled trials (RCT) were further supported by 2 large expanded access programmes across Europe and North America, indicating that the results of the two pivotal RCTs are reproducible in the current clinical setting.

In order to be able to consider both the benefits and costs of treatment with sorafenib a Markov model was developed where the patient population considered reflected that of the TARGET study in the licensed indication in RCC.

The model incorporated three disease states: progression-free survival (PFS); progression; and death and the structure of the model includes time-variant transition probabilities to allow for the fact that the risk of death or disease progression may vary over time.

Over a 10-year time horizon, patients receiving sorafenib accrued total costs of £37,079 per patient – £23,849 more than those receiving BSC. Although use of sorafenib increased patients' treatment costs, treatment also enabled a gain of 0.415 life years and 0.263 QALYs per patient. The associated incremental cost per LYG and QALY is £57,456 and £90,630 respectively for sorafenib compared with BSC.

Sorafenib produced more QALYs and more LYG than BSC across all the sub groups. The greatest health gain was observed in those patients unsuitable for cytokine therapy. This sub group also had the lowest cost per additional QALY and LYG; [redacted] and [redacted] respectively.

The cost per QALY of treating these patients may be larger than the traditionally accepted thresholds. However, these do not necessarily take into account the poor prognosis and relatively low quantity of life remaining for patients diagnosed with advanced RCC. Without sorafenib, there are no other RCT evidence-based treatment options available for patients with advanced RCC who have either failed or are unsuitable for cytokine therapies.

For the overall indicated patient group, it is predicted that the budget impact to the NHS in England and Wales would be a total of £17 million over a five year period, the equivalent of £3.4 million per year, based on 880 patients being treated over the next five years.

In those groups where patients have a poor clinical status, sorafenib is particularly beneficial. The five year budget impact of treating either patients with liver metastases or those unsuitable for cytokine therapy is £4.5 million and just under £7.5 million respectively; the equivalent of £900,000 and £1.5 million per annum over five years.

A positive NICE recommendation is sought for the use of sorafenib in patients who have failed, or are unsuitable for, first-line therapy for RCC. This appraisal brings the opportunity to improve clinician and patient choice, a vital ingredient in the modern NHS as defined in the Cancer Reform Strategy (2007).