Scottish Medicines Consortium

sunitinib 12.5mg, 25mg, 50mg capsules (Sutent®) No. (384/07)

Pfizer Ltd

8 June 2007

The Scottish Medicines Consortium 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

sunitinib (Sutent®) is not recommended for use within NHS Scotland for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC). In a planned interim analysis, sunitinib improved progression-free survival and objective response rate when compared with interferon alfa. However, as yet there is insufficient information available on overall survival.

The manufacturer did not present a sufficiently robust economic analysis and their justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of advanced and/or metastatic renal cell carcinoma.

Dosing information

50 mg dose orally, taken daily for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks.

Product availability date

February 2007

Summary of evidence on comparative efficacy

Sunitinib is an oral inhibitor of multiple tyrosine kinases. Overexpression of tyrosine kinases is implicated in the malignant transformation, tumour angiogenesis, tumour growth and metastasis of many renal cell carcinomas.

The pivotal study supporting the licensed indication is still ongoing and the evidence presented here is an interim analysis, the second of three planned analyses. This phase lll, open-label, comparative study to evaluate efficacy and safety, randomised 750 patients with confirmed metastatic renal cell carcinoma with a component of clear cell histology, Eastern Cooperative Oncology Group performance status 0 or 1 and no previous systemic treatment for renal call carcinoma, in a 1:1 ratio, to sunitinib 50mg daily, in repeated six-week cycles (four weeks treatment with sunitinib followed by two weeks rest) or subcutaneous interferon alfa, in six-week cycles on three non-consecutive days per week: 3 million units (MU) per dose the first week, 6 MU per dose the second week, and 9 MU per dose thereafter. Dosage reductions were allowed in both groups to manage adverse events. Treatment was continued until disease progression, unacceptable adverse events, or withdrawal of consent. The primary outcome measure was progression-free survival (PFS) based on independent core imaging laboratory assessment in the intention-to-treat population. PFS was defined as time from randomisation to the first documentation of objective disease progression according to RECIST (Response Evaluation Criteria in Solid Tumours) or to death from any cause, whichever occurred first. Secondary outcomes included the objective response rate, overall survival, patient-reported outcome assessments and safety.

At the time of the analysis, the median duration of treatment was 6 months (range 1 to 15) in the sunitinib group and 4 months (range 1 to 13) in the interferon alfa group. For the primary outcome, the median PFS for patients treated with sunitinib was 47 weeks and for patients treated with interferon alfa 22 weeks; hazard ratio 0.42 (95% CI 0.32 to 0.54, $p<0.001$). The secondary outcomes also favoured sunitinib. The objective response rate was significantly greater in the sunitinib group with 103 patients (28% (95%CI, 23-32%)) compared with 20 patients (5.3% (95% CI, 3.3 to 8.1) in the interferon alfa group achieving a partial response with no complete responses recorded. Ninety-two patients (24%) in the sunitinib group and 170 patients (45%) in interferon alfa group had discontinued due to disease progression. Overall survival for each treatment could not be compared in this analysis as the median overall survival had not yet been reached in either group. Health related quality of life and kidney disease related-symptoms were significantly better in the sunitinib group as measured by the patient reported outcome assessments. The between-treatment differences were considered clinically meaningful.

Summary of evidence on comparative safety

A significant adverse event profile was reported for both treatment groups. However, the median number of days on study was approximately 37% longer for patients receiving sunitinib, (169.0 days for sunitinib versus 123.5 days for interferon alfa). Adverse events considered related to study treatment were reported in 357/375 (95.2%) of sunitinib patients and 329/360 (91.4%) of interferon alfa patients with 116 (31%) patients treated with sunitinib compared with 79 patients (22%) treated with interferon alfa experiencing serious adverse events. One patient in the sunitinib group and two in the interferon alfa group died as a result of a treatment-related serious adverse event. Sunitinib-related events reported by ≥20% of patients, included constitutional events (fatigue, dysgeusia, anorexia, mucosal inflammation, and asthenia), gastro-intestinal events (diarrhoea, nausea, dyspepsia, stomatitis, and vomiting), cutaneous events (palmar-plantar erythrodysaesthesia syndrome and rash), and hypertension. Adverse events could be managed by dose reductions or interruptions. In the sunitinib group 142 (38%) and 121 (32%) patients had their dose interrupted or dose reduced compared with 115 (32%) and 77 (21%) for interferon alfa patients, respectively. Adverse events that resulted in treatment discontinuation occurred in 30 (8%) patients treated with sunitinib and 47 (12.5%) treated with interferon alfa.

Summary of clinical effectiveness issues

Metastatic renal cell carcinoma (about 85% with a component of clear cell histology) is amongst the most resistant of tumours to treatment and has a poor prognosis, with a median survival of approximately six to twelve months. Interferon alfa is the current standard of care for patients with predominantly clear cell histology. However, outcomes are poor with reported response rates low with only small improvements in median survival of around 3.8 months. Sunitinib significantly improved PFS and objective response rate when compared with interferon alfa. However, both PFS and response rate are surrogate outcomes and response rate in this disease is not always a reliable surrogate for survival. The results reported here are for an interim analysis with as yet no information on overall survival. Results of the final analysis are awaited.

Although the dose of interferon alfa in this study was not the maximum licensed dose for this indication, a recent Cochrane systematic review of immunotherapy for advanced renal cell cancer concluded that the optimal dose and schedule for interferon alfa has still to be determined but should be in the range 5-18MU three times a week. This review also noted that a range of response rates have been reported even for similar protocols. This may be due to the variable natural history of the condition which is sometimes associated with spontaneous remission. The response rate for interferon alfa in this study is at the lower end of that previously reported.

Favourable prognostic factors include performance status and prior nephrectomy (which itself has been shown to improve survival). All patients in the study had a ECOG performance status of 0 or 1 and around 90% had previous nephrectomy The number of patients included in the study with risk factors indicating a poor prognosis was small and although the results still favoured sunitinib the gain was less. There is no information on patients with renal cell carcinoma without a clear cell histology component.

Adverse events were managed through dose interruption or discontinuation. In the sunitinib group, 38% of patients had their dose interrupted and 32% their dose reduced. In response to this the European Medicines Agency (EMEA) have requested as a follow up measure, a complementary analysis of efficacy and safety in the subgroup of patients with reduced dose.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing sunitinib with interferon alfa. Interferon alfa was the appropriate comparator. The economic model had three health states; alive and progression-free, alive and progressed, and dead. Patients could not switch between treatments when disease progressed (as per trial protocol) and instead were offered best supportive care. The duration of the model was six years, and given the short term nature of the available trial data, extrapolation was required to estimate survival over this time period. Utility values derived during the clinical trial indicated that a patient with stable disease on sunitinib had a quality of life score of 0.77 falling to 0.72 when their disease progressed. This compared to a value of 0.79 for an interferon alfa patient with stable disease and 0.69 when their disease progressed.

A base case was presented that assumed the first cycle of sunitinib was free of charge. Policies in relation to cost sharing schemes are outwith the remit of SMC and therefore this was not considered further. An analysis excluding the cost-sharing proposal showed an incremental cost per QALY of £33,371, an incremental cost per progression-free life year gained of £61,611 and an incremental cost per life year gained of £28,345. In terms of outcomes, sunitinib produced an extra 0.82 life years and 0.69 QALYs.

There were several issues with the analysis. For overall survival, the data are sparse at this stage. This means that there is uncertainty in knowing the true magnitude of the survival advantage of sunitinib over interferon alfa in the extrapolated phase of the model. Statistical advice received on the progression-free and overall survival estimates suggested that they originated from a model with poorly fitted data. The results were sensitive to changes in the values of these parameters. A probabilistic analysis indicated a 36% chance of sunitinib being cost effective at a willingness to pay for a QALY of £30000.

Summary of patient and public involvement

Patient Interest Group Submission: Kidney Cancer UK
Patient Interest Group Submission: James Whale Fund for Kidney Cancer

Additional information: previous SMC advice

Following a full submission the SMC issued the following advice on 12 January 2007; sunitinib (Sutent) is not recommended for use within NHS Scotland for the treatment of advanced and/or metastatic renal cell carcinoma after failure of interferon-alfa or interleukin-2 therapy. In uncontrolled trials, sunitinib has been associated with tumour responses in patients who have metastatic renal cell cancer. However, the economic case has not been demonstrated.

Following a full submission the SMC issued the following advice on 6 October 2006; 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-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy. Sorafenib has been compared with best supportive care and has shown to increase progression-free survival, though the impact on overall survival is uncertain. The cost-effectiveness of sorafenib has not been demonstrated.

Additional information: comparators

Interferon-alfa and aldesleukin are licensed for the treatment of metastatic renal cell carcinoma.

Additional information: costs

Drug	Dose regimen	Cost per cycle or 6 weeks treatment (£)
Sunitinib	**50mg once daily for 4 weeks followed by 2 weeks off.***	**3139**
Interferon alfa-2a (Roferon-A)	18 x 10^6 IU subcutaneously three times per week**	1627
Aldesleukin	Week 1: 18 x 10^6 IU subcutaneously for 5 days then on weeks 2-4: 18 x 10^6 IU on days 1, 2 and 9 x 10^6 IU on days 3-5 One week rest and then the 4-week cycle is repeated.	1606***

*Dose may be adjusted in the range 37.5 to 87.5mg at a cost of £2354 to £5493

** The licensed dose differs from that used in the pivotal trial and is 3 x 10^6 IU three times a week for one week; 9 x 10^6 IU three times a week for one week and 18 x 10^6 IU subcutaneously three times per week thereafter. Cost of the first six weeks is £1265.

*** This is for a 5-week cycle. Over 6 weeks, including the first week of the next cycle, the cost is £2124

Doses are for general comparison and do <u>not</u> imply therapeutic equivalence.
Costs are based on eVadis prices accessed on 3rd April 2007

Additional information: budget impact

The manufacturer estimates the net budget impact of introducing sunitinib as a first line treatment to be £600k, £774k, £1.06m, £1.4m and £1.71m in years one to five respectively. This was the additional cost compared to all eligible first line patients (281 in year one) being treated with interferon alfa. The figures assume that all patients would receive the first cycle of sunitinib free of charge. Market share for sunitinib was assumed to rise from 12% in 2007 to 30% 2011. This resulted in 34 patients being given sunitinib in 2007 rising to 96 by 2011. Expert advice suggests that patient numbers would be higher and therefore the budget impact is likely to be higher than the manufacturer estimated.

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 15 May 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The references below, shaded grey, are additional to information supplied with the submission.

Motzer R, Hutson T, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New England Journal of Medicine. 2007; 356: 115-124

Coppin C, Porzsolt F Autenrieth M et al. Immunotherapy for advanced renal cell cancer. Cochrane Prostatic Diseases and Urological Cancers Group. Cochrane Database of Systematic Reviews. 1,2007.