Scottish Medicines Consortium

sunitinib 50mg capsule (Sutent®) No. (343/07)

Pfizer

12 January 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises 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 after failure of interferon-alpha 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.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of advanced and/or metastatic renal cell carcinoma after failure of interferon-alpha or interleukin-2.

Dosing information

50mg daily for first 4 weeks of 6-week cycle

Product availability date

1 August 2006: This drug is designated with Orphan Drug status for this indication.

Summary of evidence on comparative efficacy

Sunitinib inhibits tyrosine kinase enzymes in multiple receptors that are implicated in tumour growth, pathological angiogenesis and metastatic progression of cancer.

Two open-label trials recruited 63 and 106 adults who had Eastern Co-operative Oncology Group (ECOG) performance scores ≤ 1 and unidimensionally measurable metastatic renal cell cancer, with the larger trial including only patients with tumours of clear cell histology. The smaller study included patients who had disease progression or unacceptable toxicity on only one previous cytokine-based therapy (interferon-alpha (IFN-α), interleukin-2 (IL-2) or a combination of these). The larger study included patients who had disease progression (as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) or World Health Organisation (WHO) criteria) during or within nine months of completion of only one of these cytokine-based therapies. Patients received sunitinib 50mg daily for the first four weeks of six-week cycles; doses could be reduced or delayed in the event of toxicity in both studies and, in the smaller study, daily doses could be increased to 62.5mg or 75mg at the discretion of the medical monitor. The primary outcome of overall objective response (defined as confirmed complete or partial response on RECIST criteria) was assessed by an independent laboratory blinded to the investigators' assessments in the larger trial and, in the smaller study, was assessed by investigators, with only data that had been interpreted by them as showing a response forwarded to an independent laboratory for confirmation. In the second interim analysis (August 2005) of the larger trial, 36 patients had confirmed partial responses based on independent laboratory assessments and the objective response rate (95% CI) was 34% (25% - 44%). Based on investigators' assessments 1 and 45 patients had confirmed complete and partial responses respectively, and the objective response rate (95% CI) was 44% (34% - 53%). Using independent laboratory assessments, median progression-free survival (95% CI) was 8.3 months (7.8 - 14.5) and median overall survival could not be estimated, as 71% of patients were still alive. In the smaller study, in which patients were initially treated for up to one year with sunitinib, 16 patients had confirmed partial responses verified by the independent laboratory and the objective response rate (95% CI) was 25% (15% - 38%), with 23 patients having confirmed partial responses on the investigators' assessments corresponding to an objective response rate (95% CI) of 36.5% (25% - 50%). Median time to tumour progression (95% CI) was 8.7 months (5.5 - 10.7 months).

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In the trials of sunitinib in patients with metastatic renal cell cancer the most common adverse events were gastrointestinal and dermatological. Haematological adverse effects were reported: neutropenia (10%), anaemia (9.5%) and thrombocytopenia (9%). Fatigue/asthenia (64%), anorexia (28%), dysgeusia (42%) and hypertension (17%) were also common.

Summary of clinical effectiveness issues

Patients recruited to the trials described previously had good performance status with ECOG scores of 0 or 1. Therefore, there are no data on the benefits that could be expected with sunitinib in patients with poorer performance status. All the patients recruited to the larger sunitinib trial and the majority (87%) of those in the smaller study had renal cell cancer of clear cell histology. While this histology represents 85% of renal cell cancers, there are limited data on the benefits that could be expected with sunitinib in patients with renal cell cancers of other histology.

The trials of sunitinib described previously primarily assessed tumour response and did not include a control arm, either placebo or an active treatment, therefore the absolute size of the clinical benefits, such as progression-free survival and overall survival, with sunitinib are unknown. However, the European regulatory authority noted that the tumour response rates in these studies were very high and very likely to translate into clinically relevant effects on progression-free and overall survival. To support these limited data, the European regulatory authority subsequently reviewed additional data on progression-free survival from a randomised trial comparing sunitinib with IFN-α in treatment-naïve patients with metastatic renal cell cancer. As these data relate to first-line, rather than second-line treatment, the size of benefits on progression-free survival to be expected in practice with second-line use of sunitinib (in patients who have failed on a cytokine-based therapy) cannot be estimated accurately.

There are no trials directly comparing sunitinib with sorafenib, the other drug licensed for the treatment of patients with metastatic renal cell cancer who have an inadequate response or intolerance to a previous cytokine-based therapy, therefore, relative efficacy and safety are unknown. In a double-blind trial sorafenib, compared to placebo, increased progression-free survival by approximately 3 months and improved tumour response, with 2.1% of patients achieving a confirmed partial response and other patients having tumour reductions, which were below the 30% threshold required for a RECIST partial response.

Summary of comparative health economic evidence

The manufacturer provided a cost utility analysis comparing sunitinib treatment with best supportive care (BSC) in patients with advanced and/or metastatic renal cell carcinoma following disease progression with IFN-α or IL-2. BSC was defined as monitoring of disease progression by physicians, palliative care for pain, symptom management and personal care support from social services. Outcomes for patients treated with sunitinib were taken from a phase II non-comparative study with a two-year follow-up period but the model examined the costs and outcomes over a six-year period by extrapolation. Survival data for patients treated with BSC were averaged from two sources: a published case series and a USA Medicare database. Utility values were derived from EQ-5D data collected as part of a

sunitinib clinical trial. Resource use and unit cost data were sourced from published literature and supplemented with opinion from clinical experts.

The results of the model indicated an incremental cost effectiveness ratio of £39,000 per quality adjusted life year (QALY); £30,066 per life year gained; and £55,000 per progression-free year gained. One-way sensitivity analysis indicated that the results were most sensitive to the method used to estimate survival for BSC patients: changing the method altered the cost per QALY to a low of £34,000 and a high of £81,000. Given the lack of directly comparative trial data between BSC and sunitinib, alternative methods for deriving a more robust value for survival with BSC are limited.

The analysis was clear, concise and well conducted but given the comparatively high cost for health gain, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The September 2002 National Institute for Health and Clinical Excellence (NICE) guidance on cancer services: improving outcomes in urological cancers notes that IFN-α can increase survival time in patients with metastatic or advanced renal cancer. Around 5% of patients experience complete and sometimes long-lasting responses to treatment with IFN-α or IL-2. However, spontaneous remission is known to occur occasionally in untreated patients. A triple regimen, which includes IL-2, 5-fluorouracil and IFN has been linked to the highest reported response rates in non-randomised and in a randomised controlled trial in which it was compared with tamoxifen. However, toxicity problems increase when additional agents are given in combination with IFN, and other studies have failed to confirm that improved response rates are associated with enhanced survival. Research into a variety of forms of treatment, particularly combination therapies based on biological agents, is continuing.

Additional information: previous SMC advice

Following review of a full submission, the Scottish Medicines Consortium issued advice on 6th October 2006 that sorafenib 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.

Additional information: comparators

The multikinase inhibitor, sorafenib, is licensed in the UK for the same indication as sunitinib: treatment of patients with advanced renal cell carcinoma who have failed prior INF-α or IL-2 based therapy or are considered unsuitable for such therapy.

Additional information: costs

Drug	Dose range	Annual cost (£)
Sunitinib	**50mg daily for first 4 weeks of 6-week cycle**	**28,635**
Sorafenib	400mg twice daily	32,560

Doses are shown for general comparison and do not imply therapeutic equivalence

Additional information: budget impact

The manufacturer estimated the net budget impact of using sunitinib over BSC would be £1.2m in 2007 rising to £3.2 m by 2011. It was estimated that there would be 306 eligible patients with metastatic renal cell cancer in Scotland in 2007 rising to 347 new patients by 2011. Using market share projections of 15% in 2007 and 30% in 2011 the manufacturer estimated that 46 eligible patients would be treated in 2007 rising to 104 new patients by 2011. The net cost estimates included monitoring costs, community nursing/home care costs and the costs associated with terminal care, not just direct drug costs.

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 13 December 2006

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:* http://www.scottishmedicines.org.uk/

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 undernoted references were supplied with the submission.

Motzer RJ, Michaelson D, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet derived growth factor receptor, in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology 2006; 24: 16-24

Motzer RJ, Rini BI, Bukowski, et al. Sunitinib in patients with metastatic renal cell carcinoma. Journal of the American Medical Association 2006; 295: 2516-2524