Scottish Medicines Consortium

sunitinib 50mg capsule (Sutent®) No. 275/06

Pfizer

8 September 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 NHSScotland. 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 unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

Sunitinib compared to placebo delayed tumour progression by approximately five months. The economic case has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

Dosing information

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

UK launch date

1 August 2006

Comparator medications

No other medicines are licensed for the treatment of malignant gastrointestinal stromal tumour (GIST) after failure of imatinib treatment due to resistance or intolerance. The relevant comparator would be best supportive care. Sunitinib has been granted orphan drug status.

Cost of per treatment period

Sunitinib costs £3304 per treatment cycle.

Summary of evidence on comparative efficacy

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

A double-blind study recruited 312 adults with GIST who experienced unacceptable toxicity or developed progressive disease, defined by response evaluation criteria in solid tumours (RECIST) or World Health Organisation (WHO) criteria, during imatinib treatment and had an Eastern Co-operative Oncology Group (ECOG) performance score ≤1. They received best supportive care and were randomised in a 2:1 ratio to sunitinib 50mg per day for the first four weeks of six-week cycles or placebo. The daily dose of sunitinib could be reduced to 37.5mg or 25mg for patients experiencing toxicity. Randomisation was stratified by prior imatinib response (progressive disease in <6 months; progressive disease after ≥6 months; or intolerance) and McGill pain questionnaire's present pain intensity scale (MPQ-PPI) (0 or ≥1). Blinded treatment continued until disease progression, when treatment assignment was unblinded and placebo-treated patients offered open-label sunitinib and sunitinib-treated patients also offered open-label sunitinib, if there was sufficient evidence of clinical benefit in the opinion of the investigator. The primary endpoint, time to tumour progression (TTP), with progression defined by RECIST criteria and verified by an independent laboratory, was assessed in the intention-to-treat (ITT) population, which comprised all randomised patients, using the Kaplan-Meier method and compared between the two groups with a two-sided unstratified log-rank test. The trial was stopped early, after one year, at an interim analysis when pre-defined efficacy stopping-criteria had been reached. At this time the trial was unblinded and placebo-treated patients offered treatment with sunitinib. Using data from the double-blind period, median TTP with sunitinib was significantly longer than placebo: 27.3 vs. 6.4 weeks, with a hazard ratio (sunitinib : placebo) for disease progression of 0.33 (95% confidence intervals (CI): 0.23, 0.47). In a similar analysis where tumour progression was verified by investigative site radiologist, the corresponding results were 28.9 vs. 5.1 weeks,

with a hazard ratio (95% CI) for disease progression of 0.28 (0.20, 0.40). The proportion of patients achieving a confirmed tumour response, defined as a RECIST complete or partial response, was significantly greater with sunitinib compared to placebo; 14 patients (6.8%) in the sunitinib group had a partial response and no patients in the placebo group had a tumour response.

Survival

At the interim analysis 29 (14%) and 27 (26%) patients in the sunitinib and placebo groups, respectively, were known to have died and median overall survival had not been reached in either group. In analyses, including data from placebo-treated patients who had experienced disease progression on blinded treatment and received open-label sunitinib, the first quartile of overall survival in patients initially assigned to sunitinib was 40.0 weeks (95% CI: 29.7, upper limit not yet calculable) and in patients initially assigned to placebo was 15.9 weeks (95% CI: 11.3, 33.7), with a hazard ratio (sunitinib : placebo) for death of 0.49 (95% CI: 0.29, 0.83, p=0.007).

Quality of life

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

Summary of evidence on comparative safety

In the trial described previously, treatment-related adverse effects occurring more commonly with sunitinib than placebo included gastrointestinal related effects, such as diarrhoea (29% vs. 8%), nausea (24% vs. 12%), anorexia (19% vs. 6%), taste disturbance (18% vs. 2%), stomatitis (15% vs. 2%), vomiting (15% vs. 6%), dyspepsia (11% vs. 1%) dry mouth (6% vs. 1%), mucosal inflammation (12% vs. 0%) and glossodynia (6% vs. 0%). Skin discolouration occurred in more sunitinib-treated patients (25% vs. 6%) and the summary of product characteristics notes that sunitinib has been associated with depigmentation of hair or skin. In the trial described previously, other dermatological treatment-related adverse effects occurring more commonly with sunitinib included palmar-plantar erythrodysaesthesia syndrome (14% vs. 2%) and rash (13% vs. 5%). Treatment-related anaemia (12% vs. 1%), neutropenia (9% vs. 1%) and thrombocytopenia (8% vs. 0%) were more common with sunitinib than placebo, as were treatment-related fatigue (34% vs. 22%) and asthenia (12% vs. 4%) and hypertension (10% vs. 4%).

Summary of clinical effectiveness issues

Subgroup analysis of the trial described previously indicated that time to disease progression with sunitinib was longer in patients who had achieved control of their disease for more than 6 months with previous imatinib treatment compared to patients who had had disease progression during the first 6 months of previous imatinib treatment. These patients made up about 80% and 20% of the study population respectively. Some physicians have defined disease progression within the first 6 months of imatinib treatment as primary resistance and it has been noted that the progression is generally multifocal with tumours frequently exhibiting specific mutations of KIT or PDGFRα proteins. It is not clear whether there are differences between the prevalence of patients achieving less than 6 months disease control with imatinib in the Scottish population compared with the trial population, which would affect the magnitude of clinical benefit that would be expected with sunitinib in Scottish practice.

In the trial described previously almost all patients had a good performance status, ECOG performance score of 0 or 1, therefore, there are no data on the benefits which could be expected with sunitinib in practice in patients with poorer performance status.

Summary of comparative health economic evidence

The manufacturer provided a cost utility analysis comparing sunitinib treatment with best supportive care in patients with malignant GIST who are intolerant, unresponsive or who develop progressive GIST after treatment with imatinib. The model extrapolated data from the double-blind phase of the key clinical trial in order to estimate the cost-effectiveness over a six-year period. Best supportive care was comprised of a range of health and home support services given following a palliative care needs assessment. Utility values were derived from the EQ-5D data collected as part of the clinical trial and included an allowance for lower quality of life experienced during the treatment cycle. Resource use was estimated using a combination of Scottish treatment guidelines, trial resource use and expert opinion.

The results of the model indicated an incremental cost effectiveness ratio (ICER) of £65000 per QALY or £52000 per incremental progression-free life year. Satisfactory sensitivity analysis was provided to show that the results were relatively robust to changes in input variables.

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

Patient and public involvement

Patient Interest Group Submission: Sarcoma UK

Budget impact

The budget impact, net of the cost of best supportive care, was £53k in 2006 rising to £102k in 2010. These figures were based on 4, 10, 12, 13 and 14 patients being on sunitinib treatment in years one to five respectively. These figures were arrived at taking into account incidence/prevalence, the number of patients treated with imatinib who have treatment failure or are intolerant, projected uptake of sunitinib as a second line treatment and also mortality

when receiving sunitinib. Seventy-five percent of patients were assumed to have disease progression on imatinib within two years and 15% were assumed to have intolerance to imatinib. The manufacturer estimated that treatment uptake would be 40% in the first year and 80% in subsequent years.

Guidelines and protocols

The October 2004 National Institute for Health and Clinical Excellence (NICE) technology appraisal number 86, imatinib for the treatment of unresectable and/or metastatic GIST, recommends imatinib 400mg daily for first-line management of people with KIT (CD117)-positive metastatic GISTs. Continuation of therapy is recommended only if a response (as defined by Southwest Oncology Group (SWOG) criteria as complete or partial response or stable disease) is achieved within 12 weeks. Responders should be assessed at intervals of about 12 weeks thereafter. Continuation of treatment is recommended at 400mg daily until the tumour ceases to respond. An increase in the dose of imatinib is not recommended for people receiving imatinib who develop progressive disease after initially responding.

Additional information

A joint marketing authorisation application was made to the European Medicines Agency (EMEA) for sunitinib in the treatment of GIST after failure of imatinib therapy and in the treatment of metastatic renal cell carcinoma after failure of cytokine-based therapy. On 27th April 2006 the Commiitee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending to grant a conditional marketing authorisation for sunitinib.

After review of a full submission the Scottish Medicines Consortium (SMC) issued advice in August 2003 that imatinib is recommended for restricted use within NHS Scotland, under the supervision of an oncologist for patients with KIT-positive GIST.

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 02 October 2006.

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

** 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/