Resubmission

sunitinib, 12.5mg, 25mg, 50mg hard capsules (Sutent®) No. (275/06)
Pfizer Ltd

09 October 2009

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 resubmission

Sunitinib (Sutent®) is accepted for use within NHS Scotland for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesilate treatment due to resistance or intolerance.

Sunitinib compared with placebo delayed tumour progression by approximately five months. Treatment with sunitinib should not be continued if there is evidence of unacceptable toxicity or progression of disease.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of sunitinib. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland.

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 mesilate treatment due to resistance or intolerance.

Dosing information

Sunitinib 50mg orally daily for 4 consecutive weeks followed by a 2-week rest period to comprise a 6-week cycle. Dose modifications in 12.5mg steps may be applied based on individual safety and tolerability. Daily dose should not exceed 75mg nor be decreased below 25mg.

Therapy with sunitinib should be initiated by a physician experienced in the treatment of GIST.

Product availability date

August 2006

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 (BSC) and were randomised in a 2:1 ratio to sunitinib 50mg daily or placebo for the first four weeks of six-week cycles. 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 unblinded early, after one year, at an interim analysis when pre-defined efficacy stopping-criteria had been reached and placebo-treated patients were offered treatment with sunitinib.

Using data from the double-blind period,.estimated median TTP with sunitinib was significantly longer than placebo: 27.3 vs. 6.4 weeks, with a hazard ratio (HR) (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 HR (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 with placebo; 14 patients (6.8%) in the sunitinib group had a partial response and no patients in the placebo group had a tumour response.

Enrolment continued until May 2005 when the ITT population had increased to 361 patients randomised to sunitinib (n=243) or placebo (n=118). Eighty-four per cent of patients in the placebo group (n=99) crossed over to sunitinib treatment during the study. The median TTP of the entire study (blinded and open-label phases) including these 99 patients was 28.6 weeks (95% CI, 22.0, 41.0).

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 HR (sunitinib: placebo) for death of 0.49 (95% CI: 0.29, 0.83, p=0.007).

An analysis of the May 2005 ITT population using the Kaplan-Meier approach demonstrated no significant difference in estimated median overall survival between the sunitinib and placebo groups, 72.7 and 64.9 weeks, respectively (HR, 0.88; 95% CI, 0.68, 1.13). A further post-hoc analysis of overall survival in this population aimed to avoid selection bias and correct for cross-over by using rank preserving structural failure time (RPSFT) models for survival outcomes. Despite median overall survival estimates of 73 and 39 weeks for the sunitinib and placebo groups respectively, the width of the confidence intervals rendered the treatment difference non-significant (HR, 0.50, 95% CI, 0.26, 1.13).

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

Summary of evidence on comparative safety

The most frequently reported treatment-related adverse events in the pivotal study were haematological. In addition, fatigue, diarrhoea, skin discolouration and nausea were commonly reported.

Hypertension was reported in 11% of sunitinib treated patients during the double-blind phase but increased to 19% over the combined double-blind and open-label treatment period. Similarly, the incidence of hypothyroidism increased from 4.0% in the sunitinib group of the double-blind phase to 13% over the combined double-blind and open-label treatment period.

The nine patients who were intolerant to imatinib on study entry tolerated sunitinib without recurrence of the toxic effects that they had previously experienced on imatinib.

Summary of clinical effectiveness issues

In the pivotal study the cross-over of patients from placebo to sunitinib confounded the ITT overall survival results. A post-hoc analysis was performed based on RPSFT models of survival outcomes which relate a patient's observed event time in the placebo group to an event time that would have been observed if no cross-over to sunitinib treatment had been administered, assuming treatment has a multiplicative effect on a patient's lifetime

(accelerated failure time model). Hence it provides an unbiased test of the null hypothesis that otherwise is not possible in the presence of non-random switching. The analysis suggested a median overall survival benefit of around 8 months for sunitinib. The (non-significant) hazard ratio for overall survival produced using the RPSFT model (0.50) was consistent with the hazard ratio produced at the interim ITT analysis before crossover had occurred (0.49), thereby adding support to the RPSFT results.

Subgroup analysis of the pivotal study 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 with 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 platelet-derived growth factor receptor alpha (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 study population, which would affect the magnitude of clinical benefit that would be expected with sunitinib in Scottish practice.

Almost all study 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.

A randomised controlled study to investigate the safety and effectiveness of sunitinib (37.5mg daily) or imatinib (800mg daily) in patients with GIST who have had progressive disease while on imatinib (400mg daily) is currently ongoing.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing sunitinib treatment to BSC in patients with unresectable and/or metastatic malignant GIST after failure of imatinib mesilate treatment due to resistance or intolerance. The comparator was appropriate given the lack of active treatment options for this patient group. The model used a six-year time horizon and included states to account for progression-free survival, progressive disease and death.

Progression-free and overall survival estimates for the economic model were derived from the results of the pivotal study. Given the significant cross-over that occurred in the study, the economic model used the post-hoc RPSFT analysis of trial data rather than the ITT results.

Utility values were derived from quality of life data collected as part of the clinical study and resulted in a lower value for patients treated with sunitinib who did not experience progression compared to patients who had no progression while receiving BSC only, which therefore took account of any adverse effects associated with treatment. Resource use was largely estimated using information provided by Scottish clinicians.

The result indicated an ICER of £32,600 (incremental costs of £16,320 and incremental QALYs of 0.5).

A Patient Access Scheme (PAS) was submitted by the manufacturer and assessed by the Transitional Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Through this scheme each patient would receive the first

cycle of sunitinib free of charge. This decreased the incremental cost-effectiveness ratio (ICER) to £27,485 (incremental cost of £13,681 and incremental QALYs of 0.5) after taking into account the costs of operating the PAS in NHS Scotland.

Sensitivity analysis showed that the results were sensitive to the inclusion of the cost of sunitinib used in 22% of patients in the trial after disease progression. If this were included the base case estimates rose to £31,938 with the PAS or £37,502 without the PAS. Therefore, the most plausible base case estimate of cost effectiveness is likely to be between £27,485 and £31,938. including benefits of the PAS.

Probabilistic sensitivity analysis suggested a 59% chance that sunitinib was cost-effective at a willingness to pay for a QALY of £30,000 if the PAS operated or 36% without the PAS. Analysis was also provided using survival data from a sunitinib expanded-access programme. This found an increased overall median survival and time to progression that the data used in the base case and, when used in the economic evaluation, gave an ICER of £47,598 with the PAS and £52,293 without the PAS. These figures should however be interpreted with caution given the nature of the study on which they were based.

The model structure and approach were generally appropriate but there were some weaknesses with the analysis:

- The overall survival in the economic model is greater than that predicted by the post-hoc analysis reported in the clinical section of the submission though this is explained by the appropriate use of mean, rather than median, survival gain in the economic model;
- Cross-over within the trial meant that the true survival benefit of sunitinib is not known. While the statistical technique used has attempted to adjust for this issue, the resulting hazard ratio was non-significant and the sensitivity analysis has not taken account of the uncertainty in the hazard ratio;
- The results were sensitive to the inclusion of the costs of sunitinib post-progression, which arguably should have been included in the base case analysis. The impact of this issue is noted above.

The SMC modifiers used in appraising new medicines were considered and the Committee was of the view that there is an absence of other therapeutic options of proven benefit for the disease in question and provided by the NHS and there is evidence of a substantial improvement in life expectancy associated with the treatment. Although there were some limitations in the economic analysis the economic case was demonstrated when the modifiers were taken into account and the benefits of the PAS were included.

Summary of patient and public involvement

Patient Interest submission: Sarcoma UK and GIST Support UK.

Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) published “Gastrointestinal Stromal Tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up” in June 2009. This states that complete surgical resection is standard treatment for localised disease, with imatinib as standard treatment in locally advanced inoperable patients and metastatic patients. On tumour progression it is recommended that the imatinib dose is increased from 400 to 800mg daily. On progression or intolerance on imatinib, second-line treatment is sunitinib.

The National Institute for Health and Clinical Excellence (NICE) is reviewing technology appraisal guidance (TAG 86, October 2004) on imatinib as a multiple techology appraisal (MTA). The draft scope for this MTA, published in June 2009, covers imatinib (including continued 400mg dose and escalated dose), and the comparators; sunitinib and best supportive care. Outcomes to be measured include overall survival, disease-free survival, adverse effects of treatment, health-related quality of life, progression-free survival and time to treatment failure.

Additional information: comparators

No other medicines are licensed for the treatment of GIST after failure of imatinib treatment due to resistance or intolerance. It is estimated that 15% to 20% of patients will not respond to or are unable to tolerate imatinib. The relevant comparator would be BSC. There is some off-label use of imatinib 800mg daily in clinical practice (28 days treatment costs £2994).

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)
sunitinib	**50mg daily for 4 weeks of a 6-week cycle**	**3,139**

Costs from eVadis on 21 July 2009. Although the recommended sunitinib dose is 50mg daily, dose modifications may be necessary between minimum and maximum recommended daily doses of 25 and 75mg for which the corresponding costs per cycle are £1569 and £4708 respectively.

Additional information: budget impact

The manufacturer provided budget impact estimates with and without the PAS. Under both scenarios 4 new patients were assumed to be treated with sunitinib in year one, and then 14 patients in each year thereafter, representing 24% and 80% of eligible patients respectively.

With the PAS in operation the manufacturer estimated the gross budget impact at £55k in year one and £239k in year five. Taking account of costs associated with BSC, the manufacturer estimated a net budget impact of £39k in year one and £174k in year five. The drug budget only impact was £41k in year one and £163k in year five.

Without the PAS in operation, the gross budget impact was estimated at £66k in year one and £276k in year five. Taking account of costs associated with BSC, the manufacturer estimated a net budget impact of £50k in year one and £211k in year five. The drug budget only impact was estimated as £52k in year one and £200k in year five.

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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. In March 2009 the Cabinet Secretary for Health and Wellbeing announced that patient access schemes would be introduced in NHS Scotland according to an agreed national framework. The intention is that a Patient Access Scheme Assessment Group (PASAG) will be established under the auspices of NHS National Services Scotland to review and advise NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG will operate separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards together with the SMC advice.

This assessment is based on data submitted by the applicant company up to and including 5 October 2009.

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.

**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/*

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Demetri GD. Oosterom A, Garrett CR et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. The Lancet 2006; 368 (9544):1329-1338

European Medicines Agency (EMEA), European public assessment report (EPAR). Sunitinib (Sutent) 19/07/06 EMEA H/C/687 http://www.emea.europa.eu

Casali PG, Jost L, Reichardt P et al. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009; 20 (Suppl 4): iv64-iv67.