Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

sunitinib 12.5mg, 25mg, 37.5mg, 50mg hard capsules (Sutent®)

SMC No. (698/11)

Pfizer Limited

08 April 2011

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 full submission

sunitinib (Sutent®) is accepted for use within NHS Scotland.

Indication under review: Treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

Treatment with sunitinib improved progression free survival compared with placebo in patients with well-differentiated neuroendocrine carcinoma of the pancreas who were receiving best supportive care, including somatostatin analogues if required for symptomatic control.

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 or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults. Experience with sunitinib as first-line treatment is limited.

Dosing Information

Sunitinib 37.5mg taken orally once daily without a scheduled rest period. Dose modification in 12.5mg steps may be applied based on individual safety and tolerability. The maximum dose administered in the pivotal phase III study was 50mg daily. Dose interruptions may be required based on individual safety and tolerability.

Therapy with sunitinib should be initiated by a physician experienced in the administration of anti-cancer agents.

Product availability date

29 November 2010

Summary of evidence on comparative efficacy

Pancreatic neuroendocrine tumours (pNET) are rare, with an approximate prevalence rate of 10 per million. These heterogenous tumours may be functional, producing peptides which cause characteristic hormonal syndromes (insulinoma, gastrinoma, glucagonoma, vasoactive intestinal peptidoma), or non-functional but capable of causing general symptoms. Prognosis of pNET is unpredictable, however patients with unresectable, locally advanced or metastatic disease and recent disease progression have an expected survival of one to three years. In most patients surgery is not possible and treatment consists of symptom palliation. There is no standard of care and treatment strategies include surgery for primary and metastatic lesions and/or liver-directed therapies such as hepatic artery chemoembolisation, radiofrequency ablation therapy or ethanol injection. Somatostatin analogues are used for hormonal symptom control in functional tumours and their role as anti-tumour agents is under investigation. The main chemotherapy drug used in pNET is streptozocin (unlicensed in the UK), which has been combined with doxorubicin and/or fluorouracil.

Sunitinib inhibits tyrosine kinase enzymes in multiple receptors that are implicated in tumour growth, pathological angiogenesis and metastatic progression of cancer. It is the only drug licensed to treat pNET in the UK.

The main evidence supporting the licensed indication for pNET is from a phase III randomised, double-blind, placebo-controlled study that recruited 171 patients with a well-differentiated pancreatic islet cell tumour and locally-advanced or metastatic disease not amenable to surgery, radiation, or combined modality therapy with curative intent. Approximately 90% of patients in each treatment group had previously received surgery for pNET.

Sixty-six per cent (57/86) of sunitinib patients and 61% (72/85) of placebo patients had received previous systemic chemotherapy. Patients were randomised in a 1:1 ratio to receive sunitinib or placebo until progression of disease, unacceptable toxicity or death. Sunitinib at a daily dose of 37.5mg (adjustable between 25mg and 50mg) was administered continuously, although treatment breaks for severe toxicity were permitted. All patients received best supportive care that included somatostatin analogues if required for symptom control.

Tumour response and progression were assessed by the investigator according to Response Evaluation Criteria In Solid Tumours (RECIST) criteria. In patients whose disease had progressed randomisation was unblinded and treatment with open-label sunitinib (within one of two extension studies) was offered to all patients in the placebo group and according to the investigator's discretion to patients in the sunitinib group. Randomisation was unblinded for all remaining patients at the end of the double-blind study and they were offered access to open-label sunitinib in one of the extension studies.

The primary outcome was progression free survival (PFS), defined as time from randomisation to first documentation of objective tumour progression or death due to any cause. The study was designed to have an interim analysis at 130 PFS events and a final analysis at 260 events. However, it was stopped early by an independent data monitoring committee (DMC) based on their review of safety and efficacy data. Therefore, the primary analysis was based upon 30 PFS events in the sunitinib group and 51 in the placebo group in the intent-to-treat population (all randomised patients with study drug assignment designated according to initial randomisation, regardless of whether patients received any study drug or received a different drug from that to which they were randomised). Sunitinib improved investigator-assessed median PFS significantly compared with placebo: 11.4 versus 5.5 months for the sunitinib and placebo groups, respectively, hazard ratio (HR) 0.42 (95% confidence interval [CI]: 0.26 to 0.66).

Secondary efficacy outcomes included overall survival (OS), overall response rate and patient-reported outcomes. OS data were not mature at the time of the primary analysis. There were nine deaths in the sunitinib group and 21 deaths in the placebo group. Kaplan-Meier analysis demonstrated an improvement in OS with sunitinib, HR 0.41 (95% CI: 0.19 to 0.89). Median OS could not be estimated in either treatment group due to the high level of censoring. The proportions of patients remaining in the study when it was terminated were 48% (41/86) in the sunitinib group and 19% (16/85) in the placebo group.

An unplanned survival analysis performed 7.5 months after the double blind study was closed suggested an improvement in OS with sunitinib over placebo, HR 0.59 (95% CI: 0.34 to 1.04), despite the greater potential for confounding of the OS analysis due to treatment crossover.

Overall response rates (complete and partial) were significantly higher in patients treated with sunitinib compared with placebo: 9.3% (8/86) versus 0% (0/85), respectively.

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQC-30) questionnaire but the value of the results was limited by low patient numbers. There was no indication that treatment with sunitinib produced a significant deterioration in quality of life.

Supporting evidence for the pNET indication came from a cohort of patients in an open-label, uncontrolled, phase II study. Unlike the pivotal study, inclusion criteria did not specify that tumours be well-differentiated or that there had been disease progression in the previous 12

months. Sunitinib was administered in 6-week cycles: 50mg daily for 4 weeks then a rest period for 2 weeks. The primary endpoint of response rate (complete and partial) was 17% (11/66). Median time to progression was 33.4 weeks and, while the median OS could not be estimated due to the limited number of events, the lower 95% CI was estimated at 1.9 years.

Summary of evidence on comparative safety

There is no comparative safety evidence for sunitinib in patients with pNET. No new safety concerns emerged in the pivotal study. In that study, the most common treatment-related adverse events for sunitinib versus placebo were diarrhoea (53% versus 30%) and nausea (39% versus 22%). Other treatment-related adverse events include hair colour changes, neutropenia, fatigue, hypertension and palmar-plantar erythrodysaesthesia syndrome. Treatment-related serious adverse events were reported in more patients in the sunitinib group than the placebo group (13% [11/83] versus 7.3% [6/82]). The most commonly reported treatment-related serious adverse events in the sunitinib group were upper abdominal pain, nausea, and renal failure. Discontinuation because of a treatment-related serious adverse event occurred in 22% (18/83) patients in the sunitinib group and 17% (14/82) patients in the placebo group.

In the pivotal study, one death in each group was attributed to treatment with study drug: cardiac failure in the sunitinib group and dehydration in the placebo group. No treatment-related deaths occurred in those patients who continued to receive sunitinib in the open label extension studies.

The Medicines and Healthcare Products Regulatory Agency has recently advised that sunitinib is associated with a risk of osteonecrosis of the jaw, especially in patients who have been treated with bisphosphonates.

Summary of clinical effectiveness issues

Sunitinib is the only drug with a UK licence for pNET. It is formulated for oral administration and can be self-administered at home.

Treatment with sunitinib improved PFS compared with placebo in patients with well-differentiated neuroendocrine carcinoma of the pancreas who were receiving best supportive care that included somatostatin analogues if required for symptomatic control. There was no significant worsening of quality of life.

The pivotal study had several limitations. It was stopped early on the recommendation of the DMC when only 171 patients had been randomised instead of the intended sample size of 340 patients. The primary analysis did not account for the three safety reviews undertaken by the DMC.

Although possible unblinding of investigators as the result of known treatment-related adverse events had the potential to bias estimates of PFS, this outcome was validated through a blinded independent central review recommended by the European Medicines Agency (EMA). There was a high and uneven degree of censoring between treatment groups: 65% (56/86) patients in the sunitinib group and 40% (34/85) in the placebo group. There were several critical and major

deviations from the protocol. However all of these issues have been addressed to the satisfaction of the EMA by various sensitivity analyses and reviews.

At the start of the pivotal study several baseline characteristics favoured patients in the sunitinib group over those in the placebo group. Eastern Cooperative Oncology Group ECOG performance status (PS) was better in the sunitinib group (PS 0=62% and PS 1=38%), compared with the placebo group (PS 0= 48%, PS 1=51%, PS 2=1.2%). Extra-hepatic distant metastases were present in 24% of sunitinib patients and in 40% of placebo patients. Median time from diagnosis to study entry was 2.4 years for sunitinib patients and 3.2 years for placebo patients.

The submitting company carried out a post-hoc in-house analysis of OS data from the pivotal study using the Rank Preserving Structural Failure Time (RPSFT) model method to adjust for crossover that resulted in a hazard ratio for OS of 0.18 (95% CI: 0.06 to 0.68).

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis. This compared sunitinib plus best supportive care (BSC) with BSC alone, which was defined as medical management and approximately equal rates of somatostatin analogue use in each arm of the study. A Markov model was used which estimated costs and benefits over a 10-year time horizon.

Clinical data were taken from the main phase III clinical trial. Data on progression-free survival and overall survival were extrapolated using a Weibull method and included the use of the RPSFT method to allow for crossover between the arms of the clinical trial. The base case included events occurring in the extension period of the clinical study, after unblinding had occurred.

Utilities for the health states before and after progression were based on a conversion of EORTC quality of life questionnaire responses from the clinical study into utility values. The pre-progression value was 0.73 and the post-progression value was 0.596.

Costs included medicines, monitoring and supportive care, and terminal care. Medicines use was based on the clinical study and included adjustments for dose intensity and discontinuation. Monitoring and supportive care were based on the opinion of UK clinicians consulted by the manufacturer.

The manufacturer estimated the net cost of using sunitinib over the time horizon would be £33,518 and the quality adjusted life year (QALY) gain to be 1.39. The net cost per QALY was thus £24,098.

One-way analysis suggested the results were most sensitive to:

- RPSFT-based hazard ratio Method of modelling for the BSC PFS extrapolation (up to £37,722/QALY using the common-shape model and log-logistic method)
- Time horizon reduced from 10 years to 5 years (£29,233 per QALY)
- No discontinuation rate for prescribing in either treatment arm (£28,505 per QALY)

A Patient Access Scheme (PAS) was submitted by the manufacturer and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS the first cycle of sunitinib is provided free of charge. Using the base

case assumptions this was predicted to lower the net cost to £31,416. With the same QALY gain this lowered the cost per QALY to £22,660.

The main concern with the case presented was regarding the modelling of clinical benefits. The economic model predicted a gain of 2.33 life-years (or 1.39 QALYs) from 1.16 life-years in the BSC arm to 3.49 with sunitinib, so the gain is more than twice the predicted remaining life expectancy. This is a very substantial increase, and comparing the curves with the observed trial data suggests the model overestimates survival gains. The 'best fit' for the manufacturer's base case OS curve for the placebo group was with the patients in the clinical study who did not switch to sunitinib when the blinded phase was ended; these patients would only be typical of the overall experience of patients on placebo if those who switched to sunitinib had been randomly selected which seems unlikely. In addition, the uncertainty around the hazard ratio for death used in the base case was substantial, Finally, it seems to be at odds with some SMC expert clinical opinion and research evidence.

The manufacturer provided further support for their assumptions, including examples of survival rates from the literature. However, no figure could be provided that reflected the licensed indication for sunitinib and the figures quoted included some patients who did not have metastatic disease, while the ratios of functioning to non-functioning tumours were quite different to the population in the clinical study. The manufacturer also defended their selection of the RPSFT method to allow for cross-over in the trial.

The manufacturer also included a sensitivity analysis using a hazard ratio for death of 0.41, which is the value at the end of the blinded phase of the clinical study. This has the advantage of being based on observed data, with a slightly narrower confidence interval (0.19 to 0.89) than the base case. Based on this hazard ratio for death, the lifetime discounted cost per patient was estimated at £28,888 with a life-year gain of 1.24 (up from 1.61 to 2.85) and a QALY gain of 0.74 (up from 0.99 to 1.73). The added cost per QALY gained was thus £39,057. With the PAS the lifetime cost fell to £26,786 and the cost per QALY fell to £36,353, which may be considered a more conservative estimate of base case cost-effectiveness. This does not take account of the extension phase of the study. However, the manufacturer's extrapolations using a Weibull approach predicted some additional long-term survivors as a result of sunitinib treatment.

The final issue considered was the comparator treatment, which in this case was placebo. SMC clinical expert advice confirmed that the treatment pathway for this disease was unclear. However, a combination of streptozocin, 5-FU and doxorubicin was mentioned as a treatment option and this was not considered. SMC noted that streptozocin is not licensed for use in the UK.

SMC considered the likely range of cost-effectiveness ratios and the uncertainties above. Although there were some limitations in the economic analysis, the economic case was considered demonstrated when SMC modifiers, in particular those relating to the improvement in life expectancy and the absence of other therapeutic options of proven benefit, were applied.

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

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

In 2005, the UKNETwork for neuroendocrine tumours published Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. These guidelines pre-date the licensing of sunitinib for this indication. SMC experts have advised that updated guidelines are due to be published soon.

In 2009, the European Neuroendocrine Tumor Society (an international professional association composed of physicians and researchers) published ENETS Consensus guidelines for the standards of care in neuroendocrine tumours: chemotherapy in patients with neuroendocrine tumours. They do not mention sunitinib, but discuss the use of combinations of streptozocin + doxorubicin and/or 5-fluorouracil (5-FU), cisplatin + etoposide and dacarbazine.

Additional information: comparators

There is no standard treatment for unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression. SMC experts have advised that patients may be treated with unlicensed and off-label combination chemotherapy including unlicensed streptozocin or be entered into clinical studies.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Sunitinib	37.5 to 50mg orally daily	30,603 to 40,804

Costs from the manufacturer on 28.01.11

Additional information: budget impact

With the PAS, the manufacturer estimated an NHS budget impact of £454k and £764k in years one and five respectively. The submission did not include an estimate of the medicines budget impact. This was based on an estimate of 16 patients in year one rising to 24 in year five. This was broadly in line with clinical opinion consulted by SMC. The market share assumed was 60% per year. Given that this will be the first licensed treatment for this disease, this seemed plausible.

References

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

Pfizer Limited Clinical Study Report Protocol Number: A6181111. A phase III randomized, double-blind study of sunitinib (SU011248, Sutent®) versus placebo in patients with progressive advanced/metastatic well-differentiated pancreatic islet cell tumors 28 October 2009

Van Cutsem E, Dahan L, Patyna S et al. Evaluation of progression-free survival by blinded independent central review in patients with progressive, well-differentiated pancreatic neuroendocrine tumours treated with sunitinib or placebo. Presented at the 35th European Society for Medical Oncology (ESMO) meeting, Milan, Italy, October 8-12, 2010

Pfizer Limited Clinical Study Report Protocol Number: RTKC-0511-015. A phase II study of the efficacy and safety of SU011248 in patients with advanced unresectable neuroendocrine tumor 13 October 2006

European Medicines Agency (EMA) European Public Assessment Report. Sunitinib hard capsules (Sutent®). 21/10/2010 EMA/H/C/000687/II/0021 www.ema.europa.eu

Raymond E, Dahan L, Raoul JL et al. Sunitinib Malate for the treatment of pancreatic neuroendocrine tumors. NEJM 2011 364 501-13

Medicines and Healthcare Products Regulatory Agency: Drug Safety Update Jan 2011, vol 4 issue 6: A1.

**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/*

This assessment is based on data submitted by the applicant company up to and including 11 March 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates 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 prior to publication of SMC advice.

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.