



Sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer

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Abstract

The submission's evidence for the clinical effectiveness and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours (GISTs) is based on a randomised controlled trial (RCT) comparing sunitinib with placebo for people with unresectable and/or metastatic GIST after failure of imatinib and with Eastern Cooperative Oncology Group (ECOG) progression status 0–1, and an ongoing, non-comparative cohort study of a similar population but with ECOG progression status 0–4. The searches are appropriate and include all relevant studies and the RCT is of high quality. In the RCT sunitinib arm overall survival was 73 median weeks [95% confidence interval (CI) 61 to 83] versus 75 median weeks (95% CI 68 to 84) for the cohort study. However, time to tumour progression in the cohort study was different from that in the RCT sunitinib arm [41 (95% CI 36 to 47) versus 29 (95% CI 22 to 41) median weeks respectively]. Median progression-free survival with sunitinib was 24.6 weeks (95% CI 12.1 to 28.4) versus 6.4 weeks (95% CI 4.4 to 10.0) on placebo (hazard ratio 0.333, 95% CI 0.238 to 0.467, $p < 0.001$). The manufacturer used a three-state Markov model to model the cost-effectiveness of sunitinib compared with best supportive care for GIST patients; the modelling approach and sources and justification of estimates are reasonable. The base-case incremental cost-effectiveness ratio (ICER) was £27,365 per quality-adjusted life-year (QALY) with the first cycle of sunitinib treatment not costed; when we included the cost of the first treatment cycle we estimated a base-case

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ICER of £32,636 per QALY. Pfizer's sensitivity analysis produced a range of ICERs from £15,536 per QALY to £59,002 per QALY. Weaknesses of the manufacturer's submission include that the evidence is based on only one published RCT; that 84% of the RCT control population crossed over to the intervention group, giving rise to the use of unusual rank preserved structural failure time (RPSFT) analysis to correct for possible bias; and that a number of errors and omissions were made in the probabilistic sensitivity analysis, meaning that it is not possible to come to firm conclusions about the cost-effectiveness of sunitinib for GIST in this patient population. In conclusion, during the blinded phase of the RCT, overall survival was significantly longer in the sunitinib arm than in the placebo arm (hazard ratio 0.491, 95% CI 0.290 to 0.831, $p < 0.007$). However, intention-to-treat analysis of the entire study showed no statistically significant difference in overall survival for those who received sunitinib (73 weeks) versus those who received placebo (65 weeks) (hazard ratio 0.876, 95% CI 0.679 to 1.129, $p = 0.306$).

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.¹ Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report² for the STA of the clinical and cost-effectiveness of sunitinib for gastrointestinal stromal tumours.

Description of the underlying health problem

Gastrointestinal stromal tumours (GISTs) represent the most common mesenchymal neoplasms of the gastrointestinal tract.^{3,4} GISTs are believed to originate from an intestinal pacemaker cell called the interstitial cell of Cajal.⁵ The incidence of GIST is estimated at 11–14.5 cases per million per year.^{6,7} The most frequent primary sites are gastric (50%) and small bowel (25%). Colorectal, oesophageal and peritoneal GISTs are less frequent. GIST can be diagnosed at any age, with a median age at diagnosis of 60 years.⁸

Estimates vary widely on the incidence of new cases of GIST, with figures between 200 and 2000 quoted⁹ with an apparent acceptance of an upper limit of 240. Approximately half of new cases of GIST are likely to be metastatic and/or unresectable on first presentation, the prognosis of which is poor, with few, if any, people surviving beyond 5 years in the absence of effective treatment.⁹

The clinical presentation of GIST is highly variable according to site and tumour size.¹⁰ GIST often remains clinically silent until tumours reach a large size, when mass effects, bleeding or rupture may ensue.¹¹

Scope of the ERG report

Research question

The research question that Pfizer addressed was: 'What is the clinical and cost-effectiveness of sunitinib for unresectable and/or metastatic GISTs after the failure of imatinib mesylate treatment due to resistance or intolerance?'

Intervention

The intervention is a multitargeted tyrosine kinase inhibitor produced by Pfizer with the brand name of Sutent[®] and the approved name of sunitinib malate.

Outcomes

The outcomes measured for clinical effectiveness are overall survival, progression-free survival, time to tumour progression, response rates, adverse effects of treatment and health-related quality of life. Those measured for cost-effectiveness are incremental cost per quality-adjusted life-year (QALY), incremental cost per life-year gained,

resource utilisation and the cost of treating adverse events.

Type of clinical/cost-effectiveness data used

In the clinical effectiveness evidence the type of data used is 'time to event'; this is reported as median time in weeks with the point estimates expressed as hazard ratios and 95% confidence intervals. To provide cost-effectiveness evidence Pfizer built a Markov model. The model was parameterised by effectiveness data and health state utilities [derived from the EuroQol 5 dimensions (EQ-5D) questionnaire] from a randomised controlled trial (RCT) by Demetri *et al.*^{12,13} and longer follow-up unpublished data from the same trial. Costs were based on an NHS and personal social services perspective.

Stated potential health effects

Pfizer stated that sunitinib potentially benefits patients as a second-line treatment for GIST by increasing the time to tumour progression, progression-free survival and overall survival through inhibiting vascular endothelial growth factor/platelet-derived growth factor receptors on cancer cells, vascular endothelial cells and pericytes, thus constraining the proliferation of tumour cells and the development of tumour blood vessels.

Stated costs

Pfizer reported that sunitinib malate is available at the following costs: 12.5-mg 28-capsule pack = £784.70; 25-mg 28-capsule pack = £1569.40; 50-mg 28-capsule pack = £3138.80; 12.5-mg 30-capsule pack = £840.75; 25-mg 30-capsule pack = £1681.50; and 50-mg 30-capsule pack = £3363.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The manufacturer's search strategy was reviewed by an Information Scientist and the searches were rerun with a more extensive RCT filter to see if any relevant trials had been omitted. The methods used by the manufacturer to report the clinical effectiveness were critiqued using the

principles found in the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care.¹⁴ We considered Pfizer's economic evaluation against the following study quality checklists: NICE reference case,¹⁵ Drummond *et al.*¹⁶ and Philips *et al.*¹⁷ for decision model-based economic evaluations. The model was rerun to check for wiring and parameterisation errors.

Results

Summary of submitted clinical evidence

The evidence for this submission is based on one RCT^{12,13} that compares sunitinib with placebo for people with unresectable and/or metastatic GIST after failure of imatinib due to resistance or intolerance and with Eastern Cooperative Oncology Group (ECOG) progression status 0–1 (the most physically able), and one, ongoing, non-comparative cohort study¹⁸ that gives expanded access to a similar population but with ECOG progression status 0–4.

The RCT was a double-blind, placebo-controlled, parallel-group, multicentre, phase III clinical trial. The blinded phase became open-label upon disease progression or at the time of interim analysis (54 weeks) when patients were allowed to cross over from placebo to treatment group.

The results for overall survival are similar in both studies with the RCT reporting results for the sunitinib arm of 73 median weeks [95% confidence interval (CI) 61 to 83 weeks] in comparison to 75 median weeks 95% CI 68 to 84 weeks] for the cohort study. However, the results for time to tumour progression in the cohort study (median weeks = 41, 95% CI 36 to 47 weeks) are quite different from those of the sunitinib arm of the RCT (median weeks = 29, 95% CI 22 to 41 weeks). These results may be influenced by the different ECOG performance status of the two study populations and a greater median overall survival for the ECOG grade 0–1 in the cohort study [RCT 73 weeks (95% CI 61 to 83 weeks), cohort 88 weeks (95% CI 77 to 97 weeks)].

The interim RCT results for progression-free survival showed that those in the sunitinib group had a significantly better chance of being alive and free from progressive disease than those in the placebo group. Median progression-free survival with sunitinib was 24.6 weeks (95% CI 12.1 to 28.4 weeks) compared with 6.4 weeks (95% CI 4.4 to

10.0 weeks) on placebo (hazard ratio 0.333, 95% CI 0.238 to 0.467, $p < 0.001$).

Summary of submitted cost-effectiveness evidence

The manufacturer used a Markov model, based on the renal cell carcinoma (RCC) model developed by the Peninsula Technology Assessment Group (PenTAG), to model the cost-effectiveness of sunitinib compared with best supportive care for GIST patients. This had a three-state structure: progression-free survival, progressive disease and death.

Pfizer's base-case analysis produced an incremental cost-effectiveness ratio (ICER) of £27,365 per QALY with the first cycle of sunitinib treatment not costed and using effectiveness estimates from their rank preserved structural failure time (RPSFT) analysis. When we included the cost of the first cycle of treatment we estimated that the value of the base-case ICER was £32,636 per QALY, again using RPSFT effectiveness data. Pfizer's sensitivity analysis produced a range of ICERs from £15,536 per QALY to £59,002 per QALY.

When a conventional method of unadjusted intention-to-treat (ITT) analysis is used to calculate the base-case ICER, values of £93,062 per QALY (first cycle costed) and £77,107 per QALY (first cycle free) are produced. However, this method does not account for the overestimated effectiveness results in the placebo arm due to crossovers; independent expert statistical opinion favours the RPSFT method.

Commentary on the robustness of submitted evidence

Clinical effectiveness

The searches are appropriate and include all relevant studies and the RCT is of high quality.

Cost-effectiveness

The approach taken to modelling is reasonable and the sources and justification of estimates are also generally reasonable.

Weaknesses

The evidence is based on only one completed and published RCT. The expanded access cohort

study is ongoing, is not comparative and is only published as an abstract at the time of this report.

The majority of the control population (84%) in the RCT crossed over to the intervention group. This gave rise to the use of unusual methods of analysis (RPSFT) to correct for the bias that this may have introduced. Although we believe this to be the correct approach we have been unable to check that it was applied correctly.

In their economic evaluation, Pfizer have presented a miscalculation of cost-effectiveness using the ITT overall survival data for best supportive care (Kaplan–Meier analysis). The stated ICER is £34,649 per QALY when it should have been £93,062 per QALY with sunitinib fully costed (or £77,107 per QALY if the first cycle of treatment is free). (Pfizer corrected this error following questions from us.)

A number of errors and omissions were also made in the probabilistic sensitivity analysis:

- Pfizer used the standard deviation rather than the standard error for the utilities
- in the model, Pfizer assume a standard deviation of 0.02 for progression-free survival, whereas the report says 0.20
- importantly, Pfizer have not modelled all of the uncertainty in the treatment effect for progression-free survival and overall survival
- there are errors in the Cholesky matrix decompositions in modelling the uncertainty of the fit of the Weibull curves for treatment effectiveness in worksheets 'PFS', 'overall survival_RPSFT analysis' and 'overall survival_ITT analysis'.

Conclusions

During the blinded phase of the RCT, overall survival was significantly longer for those in the sunitinib arm than for those who received placebo, with a hazard ratio of 0.491 (95% CI 0.290 to 0.831, $p < 0.007$). However, the ITT analysis of the entire study showed that there was no statistically significant difference in overall survival for those who received sunitinib (73 weeks) compared with those who received placebo (65 weeks), with a hazard ratio of 0.876 (95% CI 0.679 to 1.129, $p = 0.306$).

The degree of uncertainty (listed in the next section) in the cost-effectiveness analysis means

that it is not possible to come to firm conclusions about the cost-effectiveness of sunitinib for GIST in this patient population.

Areas of uncertainty

Given that there are several major errors in the probabilistic sensitivity analysis the precise degree of uncertainty in the base-case ICER is unknown. However, we can say that the uncertainty in the base-case ICER (reported as £27,365 per QALY – first cycle free) is substantial, given the wide (95%) CI for the hazard ratio of overall survival of 0.262 to 1.234 (using the RPSFT method).

The use of the RPSFT method of analysis has had a very large impact on cost-effectiveness; the ICER using this method (£32,636 per QALY – first cycle costed) is a great deal less than that based on the unadjusted ITT data analysis (£93,062 per QALY – first cycle costed). Expert statistical advice from Ian White (MRC Biostatistics Unit, Cambridge) indicates that the RPSFT is the correct method for analysis and that it appears to have been correctly applied. However, we cannot be sure of this.

We caution that the base-case ICERs may be slightly too low as Pfizer's calculation does not include the cost of sunitinib in progressive disease for some patients randomised to sunitinib (54 patients in the sunitinib arm carried on with this treatment after disease progression) who theoretically may have benefited.

Key issues

The use of the RPSFT method of analysis (instead of the conventional approach of censoring participants at the point of crossover) greatly affects the estimated cost-effectiveness of sunitinib for GIST. However, this is a common analysis issue in trials of cancer drugs that are found to be effective mid-trial, and the use of the RPSFT seems appropriate.

The lack of costing of sunitinib in progressive disease for patients initially randomised to sunitinib does not reflect the treatment of some patients in the RCT (22% continued with sunitinib after disease progression).

There is a large amount of uncertainty in the relative treatment effectiveness for overall survival between sunitinib and best supportive care under the RPSFT method.

Whether to assume that the first cycle of sunitinib is free to the NHS.

Patients in the expanded access cohort study had a longer median time to tumour progression than those in the RCT.

Summary of NICE guidance issued as a result of the STA

The Appraisal Consultation Document has yet to be issued by NICE.

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