NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Sunitinib for the treatment of gastrointestinal stromal tumours

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide clarification on:

- **whether the patients in the trial were generalisable to UK practice due to a large number receiving higher doses of imatinib for first-line treatment than is currently recommended in the UK**
- **the difference in median overall survival between the Demetri (2008) publication and the submission**
- **the rank preserved structural failure time (RPSFT) method used to control for crossover**
- **which treatments were considered as best supportive care as modelled for estimating the cost effectiveness**
- **the sensitivity analyses using the unadjusted intention-to-treat ITT data for all effectiveness estimates**
- **how the utility values were calculated**
- **whether the Department of Health had agreed to accept one free cycle of sunitinib for patients with GIST**
- **the number of patients who continued to receive sunitinib after disease progression.**

The ERG noted an error in the submitted model with regard to the calculation of the incremental cost-effectiveness ratio (ICER) using the unadjusted ITT data for the best supportive care arm. The manufacturer acknowledged the error.

Licensed indication

Sunitinib (Sutent, Pfizer) has a UK marketing authorisation for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) after failure of imatinib treatment due to resistance or intolerance.

Key issues for consideration

- Is the Committee satisfied that the rank preserved structural failure time (RPSFT) method used by the manufacturer to control for crossover is appropriate? If so, what are the implications of the wide confidence intervals around the hazard ratio derived from the RPSFT analysis in interpreting the clinical and cost effectiveness of sunitinib compared with best supportive care?
- What is the Committee's view of the identified errors and omissions in the probabilistic sensitivity analyses identified by the ERG and the implications for certainty in the cost-effectiveness estimates?
- Given that 54 patients continued to take sunitinib after disease progression, but that the economic model only included costs of sunitinib during the progression-free health state, does the Committee accept the revised analyses conducted by the ERG that incorporate the additional sunitinib costs?
- How generalisable are the results to clinical practice, given that the randomised controlled trial (RCT) only included patients with a good performance status, and that approximately 4% had experienced intolerance to imatinib?
- In England and Wales, NICE guidance states that first-line treatment for unresectable and/or metastatic malignant GIST is a maximum of 400 mg of imatinib per day. How generalisable are the results to UK clinical practice, given that in the RCT more than 80% of patients had previously received daily imatinib doses of more than 400mg, to which their disease did not respond?

- Does the Committee consider the sensitivity analysis, which included single-dose imatinib as a component of best supportive care, to be appropriate?
- Does the Committee have concerns that the patients in the cohort study had longer time to disease progression compared with the RCT given that many of these patients had a poorer prognosis? However it should be noted that most of these patients had previously only received 400mg of imatinib compared with patients in the RCT who in the main had received escalated doses, up to 800mg, of imatinib.

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	People with unresectable and/or metastatic malignant GISTs after failure of imatinib treatment due to resistance or intolerance
Intervention	Sunitinib
Comparators	Best supportive care
Outcomes	• Overall survival • Time to tumour progression • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life
Economic evaluation	Outcomes to be included: • Incremental cost per quality-adjusted life year • Incremental cost per life year gained • Resource utilisation • Cost of treating adverse events The time horizon (6 years) for the economic evaluation reflects the life expectancy of patients with GIST. The costs were considered from a NHS and Personal Social Services perspective. As agreed with the Department of Health the first cycle of sunitinib is free for all patients.
Other considerations	Best supportive care is taken to mean treatment to control, prevent and relieve complications and side effects and to improve comfort and quality of life. Within the model it is assumed to include palliative interventions but explicitly excludes the use of active therapy.

1.2 Evidence Review Group comments

1.2.1 Population

The population considered by the manufacturer was people with unresectable and/or metastatic malignant GISTs after failure of imatinib treatment due to

resistance or intolerance. This matched the marketing authorisation for sunitinib and was in accordance with the scope.

1.2.2 Intervention

The intervention, sunitinib, was in accordance with the scope and marketing authorisation.

1.2.3 Comparators

The ERG noted that the definition of best supportive care used by the manufacturer was different from that in the scope; however the ERG commented that the definition used by the manufacturer is in accordance with clinical practice.

1.2.4 Outcomes

The ERG stated that the outcomes considered by the manufacturer were appropriate and clinically relevant, although the ERG highlighted that the primary outcome, time to tumour progression, was not specified in the scope and progression-free survival is a more common outcome measure in cancer research.

1.2.5 Economic evaluation

The time horizon of 6 years in the manufacturer's economic evaluation was considered appropriate.

1.2.6 Treatment pathway

The manufacturer provided a diagram that represented the typical treatment pathway for people with unresectable and/or metastatic malignant GIST (see Figure 1, page 13 of the MS). First-line treatment in the diagram was 400 mg of imatinib per day; this is in accordance with previous NICE guidance (Imatinib for gastrointestinal tumours. NICE technology appraisal guidance 86 [2004]. Available from www.nice.org.uk/TA86) see Appendix B for the guidance section of TA no. 86. However, if progressive disease is

experienced after receiving 400 mg of daily imatinib then, in the diagram, there is an option for an escalated dose of imatinib (600 mg or 800 mg per day). An escalated dose of imatinib is not a recommended treatment option in the previous NICE guidance 86; however since this guidance was published the license for first-line imatinib use does now state that there is limited clinical evidence to allow dose escalation to 800 mg of imatinib per day (NICE technology appraisal no. 86 is due to be reviewed). In the diagram, the manufacturer stated that sunitinib could be given to people who have experienced disease progression or 'no response' after receiving 400 mg, 600 mg or 800 mg of imatinib per day or after experiencing primary imatinib intolerance.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer presented data from one randomised controlled trial (RCT) that compared sunitinib plus best supportive care with placebo plus best supportive care. Best supportive care was defined as the monitoring of progression, symptom control and palliative care without active treatment. Summary details of this RCT are presented in Table 1.

Table 1: Summary of key sunitinib RCT, A6181004

Trial name	Design/duration	Participants	Intervention/ comparator	Primary outcome
A6181004 n = 312	Blinded, randomised, controlled, multicentre phase III trial The blinded phase of the trial was stopped early as results met pre-specified efficacy endpoints. All patients were then offered open-label sunitinib	People with imatinib-resistant or intolerant malignant GIST	Sunitinib + BSC (n = 207) versus placebo + BSC (n = 105)	Time to tumour progression [a]
[a]Defined as time from randomisation to first documentation of objective tumour progression BSC, best supportive care				

The baseline characteristics of the patients in the two treatment arms were generally similar and relatively balanced in terms of previous duration and amount of previous imatinib treatment. Approximately 4% of patients in each treatment arm had experienced primary imatinib intolerance.

Patients were stratified according to the following factors:

- Best outcome of previous imatinib treatment (progressive disease within 6 months of starting treatment versus progressive disease after 6 months of starting treatment or imatinib intolerance).
- Baseline McGill Pain Questionnaire score (0 versus more than or equal to 1).

The blinded phase of the RCT was terminated early when an interim analysis showed that there was significantly longer time to progression for patients who received sunitinib plus best supportive care compared with those who

received placebo plus best supportive care. A total of 84% of patients randomised to receive placebo plus best supportive care crossed over to the sunitinib plus best supportive care arm. The manufacturer also stated that 54 (22%) patients continued to receive sunitinib plus best supportive care after disease progression.

The manufacturer also provided details of additional studies that are currently ongoing. Of note is a large expanded access programme (EAP). This open-label cohort study was established to allow access to sunitinib for people with GIST who might benefit and who, due to trial inclusion criteria or lack of regulatory approval where they live, might otherwise not have access to sunitinib. As of December 2007, 1126 people were enrolled in the EAP and the intention-to-treat (ITT) population comprised 1117 people. Patients in the EAP were of Eastern Cooperative Oncology Group (ECOG) performance status 0 to 4, and 55% of patients had received 400 mg or less of daily imatinib treatment before entering the EAP. In the EAP, sunitinib treatment was given for as long as there is evidence of disease control according to the judgment of the trial investigator. The EAP is scheduled to end in December 2009.

The manufacturer also highlighted that there is an ongoing RCT of double dose (800 mg) imatinib compared with sunitinib that is currently recruiting patients who have experienced disease progression after treatment with 400 mg imatinib.

2.1.1 Results of the A6181004 RCT and EAP

The ITT population analyses of the RCT showed that the time to tumour progression was significantly longer for those who received sunitinib plus best supportive care compared with those who received placebo plus best supportive care, with a hazard ratio of 0.33 (95% confidence interval [CI] 0.23 to 0.47, $p < 0.0001$) using the interim effectiveness data gathered during the blinded phase of the study. The median time to tumour progression for the patients who crossed over from placebo plus best supportive care to sunitinib

plus best supportive care was similar to those randomised to receive sunitinib plus best supportive care.

The ITT population analyses of the RCT showed that overall survival was significantly longer for those who received sunitinib plus best supportive care compared with those who received placebo plus best supportive care, with a hazard ratio of 0.491 (95% CI 0.290 to 0.831, $p < 0.007$) during the blinded phase of the study. The analysis of the entire study (that is blinded plus open-label phase) showed that there was no statistically significant difference in overall survival for those who received sunitinib plus best supportive care compared with those who received placebo plus best supportive care, with a hazard ratio of 0.876 (95% CI 0.679 to 1.129, $p = 0.306$).

The manufacturer also presented analyses of overall survival using a rank preserved structural failure time (RPSFT) model. The RPSFT model is a 'post-hoc' approach taken by the manufacturer to control for the crossover that occurred from the placebo plus best supportive care arm to the sunitinib plus best supportive care arm after the study was unblinded. The RPSFT analysis demonstrated a statistically significant longer overall survival for patients who received sunitinib plus best supportive care compared with those who received placebo plus best supportive care, with a hazard ratio of 0.505 (95% CI 0.388 to 0.658, $p < 0.001$) for the entire study. Following external recommendation, the manufacturer revised the 95% CI associated with the hazard ratio derived when using the RPSFT approach. The revised 95% CI was 0.262 to 1.134, meaning that the difference in overall survival was no longer statistically significant. Summary results from the RCT are presented in Table 2.

Table 2: Summary of results from the A6181004 RCT

Outcome; phase of study (analysis method)	**Sunitinib + BSC; Median weeks (95% CI)**	**Placebo +BSC; Median weeks (95% CI)**	**Hazard ratio (95% CI, p-value)**
TTP; blinded	27.3	6.4	0.33

phase (ITT)	(16.0 to 32.1)	(4.4 to 10.0)	(0.23 to 0.47, p < 0.0001)
OS; blinded phase (ITT)	NR	NR	0.491 (0.290 to 0.831, p = 0.007)
OS; entire study (RPSFT)	72.7 (61.3 to 83.0)	39.2 (28.0 to 54.1)	0.505 (0.388 to 0.658, p<0.001) **OR** 0.505 (0.262 to 1.134)*
OS: entire study (ITT)	72.7 (61.3 to 83.0)	64.9 (45.7 to 96.0)	0.876 (0.679 to 1.129, p=0.306)
TTP: time to tumour progression; OS: overall survival; NR: not reached; RPSFT: rank preserved structural failure time; ITT: intention-to-treat *Amended 95% CI presented by the manufacturer after correspondence with statistical expert			

Quality of life was measured in the RCT using the EuroQoL (EQ-5D) health state profile. More than 75% of patients completed the EQ-5D questionnaire at each time point and there were no statistically significant differences reported between the treatment groups.

Treatment-related adverse events and serious adverse events were more common in the sunitinib plus best supportive care arm than the placebo plus best supportive care arm. In the RCT, 83% of patients in the sunitinib plus best supportive care arm and 59% of patients in the placebo plus best supportive care arm experienced adverse events of any severity. A total of 9% of patients in the sunitinib plus best supportive care arm and 8% of patients in the placebo plus best supportive care arm stopped treatment due to adverse events. The most common adverse event of any severity was fatigue: 34% of patients in the sunitinib plus best supportive care arm and 22% of patients in the placebo plus best supportive care arm experienced fatigue. Other serious adverse events experienced more frequently in the sunitinib plus best

supportive care arm than the placebo plus best supportive care arm were: hand-foot syndrome; diarrhoea; hypertension; and serious haematological adverse events. The manufacturer stated that the adverse events reported were generally of mild to moderate intensity and could be easily managed by dose reduction, dose interruption or standard supportive medical treatments. For further details of safety associated with sunitinib treatment, see the MS pages 43–46.

The results of other secondary outcome analyses and subgroup analyses of the RCT can be found on pages 40-42 of the MS.

The ITT population analyses of the time to tumour progression and overall survival in the EAP were also presented by the manufacturer. At the time of data analysis, 50% of the ITT population was alive. The median time to tumour progression was 41 weeks (95% CI 36 to 47) and the median overall survival was 75 weeks (95% CI 68 to 84). In the EAP, the most commonly experienced adverse events were fatigue, diarrhea and nausea, which were generally mild to moderate in severity. Treatment-related adverse events related to cardiac function included heart failure, congestive heart failure, myocardial infarction, reduced ejection fraction and pulmonary oedema; however the manufacturer stated that only 1.7% of patients in the EAP experienced such adverse events. A total of 23 people died due to treatment-related reasons during the EAP follow-up period. The results of subgroup analyses of the EAP can be found on page 54 of the MS.

2.2 Evidence Review Group comments

The ERG identified several strengths in the manufacturer's clinical-effectiveness evidence:

- The literature search strategy was appropriate and reproducible. The ERG commented that it is unlikely that there are any other relevant and good quality studies that have not been identified by the manufacturer.

- The included RCT was of good quality.

The main areas of concern and uncertainty highlighted by the ERG on the clinical effectiveness included the following:

- In the RCT, a total of 84% of the patients randomised to receive placebo plus best supportive care crossed over to receive sunitinib plus best supportive care. The ERG commented that the RPSFT method to control for the high level of crossover seemed appropriate as the technique allows for analysis over a longer follow-up period than censoring the data. However, the ERG highlighted that the RPSFT method was an uncommon technique and the ERG has been unable to confirm whether it was correctly applied.

- The population in the RCT was restricted to patients with a good performance status (ECOG score of 0 or 1). This means that the results from the RCT may not be generalisable to all people with unresectable and/or metastatic malignant GIST whose condition is resistant or intolerant to imatinib.

- In the RCT, 83% of those randomised to receive sunitinib plus best supportive care experienced an adverse event of any severity, compared with 59% of those randomised to receive placebo plus best supportive care.

2.3 Statements from professional/patient groups and nominated experts

Patient and clinical experts stressed that the cohort eligible for second-line sunitinib treatment in England and Wales is small, between approximately 90 and 150 patients per year. It was also highlighted that there are currently no alternative treatment options for people with unresectable and/or metastatic GIST after resistance or intolerance to first-line imatinib treatment. This could be considered as a substantial improvement in the second-line treatment of

unresectable and/or metastatic malignant GIST, although consultees noted that imatinib was the first targeted therapy for this indication.

The type of *KIT* gene mutation of the GIST can be a valuable prognostic indicator of likely benefit from sunitinib treatment. However, diagnosing *KIT* mutations is not considered as part of current standard practice. Patient and clinical experts highlighted that there are some significant adverse effects associated with sunitinib treatment; however these are generally not life-threatening and are manageable (most commonly with dose reductions). Sunitinib should only be given in specialist centres by oncology teams experienced in the treatment of GIST and in the use of sunitinib. Currently, there are regional variations in the prescribing of sunitinib for GIST.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer identified two published cost-effectiveness studies, which estimated the cost effectiveness of sunitinib compared with best supportive care for the treatment of people with GIST whose condition was intolerant or resistant to imatinib. Both of the studies used the interim effectiveness data gathered during the blinded phase of the A6181004 RCT and the studies were performed from the perspective of a Canadian and a Mexican healthcare system. The published studies reported base-case cost-effectiveness estimates of Can$79,884 and US$46,108 per quality-adjusted life year (QALY) gained, respectively, for sunitinib compared with best supportive care (see pages 58–59 of the MS for further details).

The ERG also identified a model-based analysis that the manufacturer had submitted to the Scottish Medicines Consortium. Resource use in this model was estimated from Scottish treatment guidelines, trial resource use and expert opinion. The ERG assumed that the effectiveness data were from the published interim analyses. The analysis reported a base-case cost-effectiveness estimate of £65,000 per QALY gained for sunitinib

compared with best supportive care. It was not clear whether the one free cycle had been agreed with the Department of Health at the time of this submission.

The manufacturer developed a Markov model to assess the cost effectiveness of sunitinib compared with best supportive care (it was assumed by the manufacturer that patients in the placebo arm would receive best supportive care until death, and that patients in the sunitinib arm received best supportive care in the progressive disease state) in people with unresectable and/or metastatic malignant GIST after failure of imatinib treatment due to resistance or intolerance. The model had three distinct health states: progression-free; progressive disease (no active therapy); and death. All patients entered the progression-free state of the model, based on the assumption that their condition failed to respond to imatinib treatment. The model had a cycle length of 6 weeks and the time horizon was 6 years; the manufacturer stated that this reflected the maximum life expectancy of the patient population in the model. A half-cycle correction was modelled. No subgroup analyses were conducted by the manufacturer.

The model used effectiveness data extrapolated from the empirical evidence from the RCT. The manufacturer used unpublished, updated effectiveness evidence from the RCT that had superseded the published results from 2006 and 2008. The follow-up of the mature data was about 4.5 years. For progression-free survival, Weibull curves were fitted to the unadjusted ITT data from the placebo plus best supportive care and sunitinib arms independently (see Figure 1). For overall survival, Weibull curves were fitted to the unadjusted ITT data from the sunitinib arm and to the RPSFT-adjusted data from the placebo plus best supportive care arm independently (see Figure 2). In a sensitivity analysis, the manufacturer fitted a Weibull curve to the unadjusted ITT data for overall survival with placebo plus best supportive care.

Figure 1: progression-free survival curves

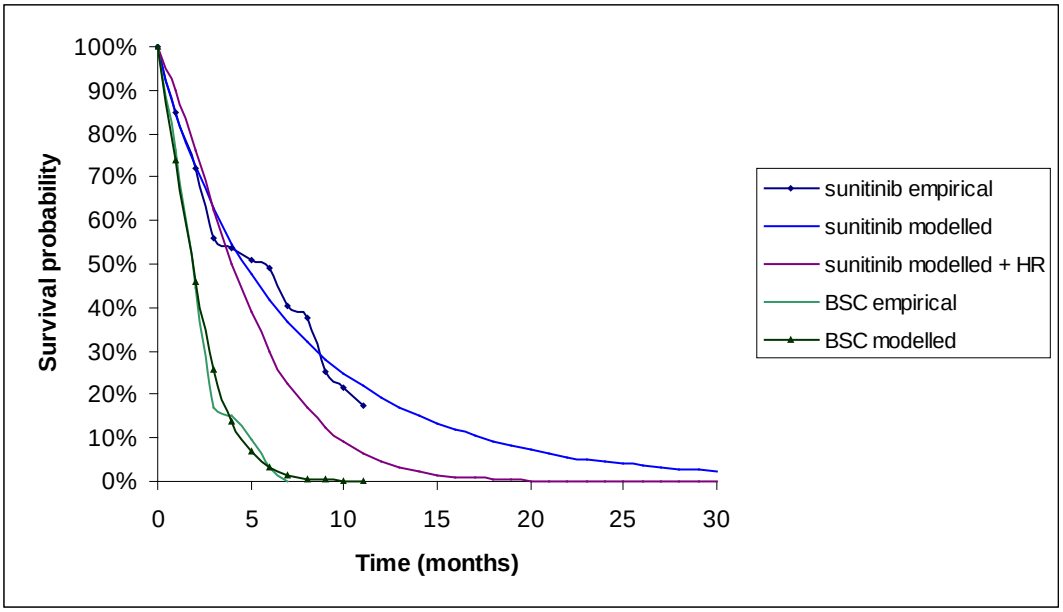
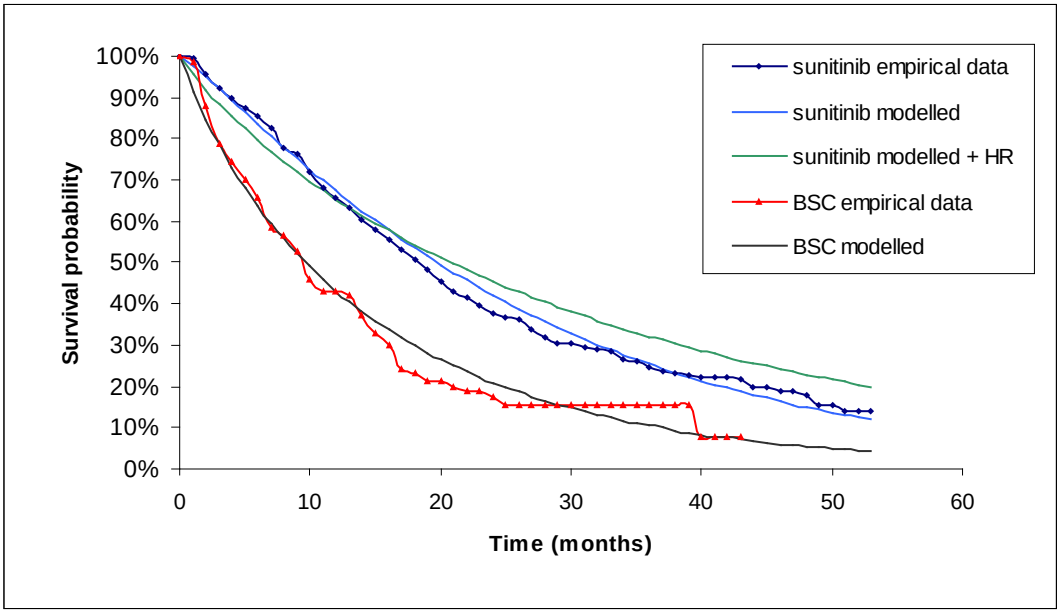


Figure 2: overall survival curves



The utility values used in the model were taken from the RCT, in which the EQ-5D questionnaire was used. In the progression-free health state, a utility value of 0.731 was assigned to patients receiving sunitinib and a utility value of 0.781 was assigned to patients receiving placebo plus best supportive care.

In the progressed disease health state, a utility value of 0.577 was assigned to both arms. The manufacturer did not model the effect of adverse events on utility, and stated that the reduced utility values assigned to the sunitinib arm would account for disutility from adverse events.

Resource use was not measured directly within the RCT, although the drug usage and relative dose intensity estimates were derived from the RCT and the manufacturer consulted four consultant oncologists currently treating patients with GIST in the UK. In the model, the manufacturer assumed a relative dose intensity of 88.6% for sunitinib and cost data were taken from the 'British national formulary' (BNF 56, 2008). The manufacturer has agreed a patient access scheme with the Department of Health in which the first cycle of sunitinib is free to the NHS. The details of the cost variables included in the model can be found on pages 75–76 of the MS.

3.1.1 Results

The results of the manufacturer's base-case analysis are presented in Table 3.

Table 3 - Results of the manufacturer base-case cost-effectiveness analysis

	sunitinib	BSC	sunitinib vs. BSC
Time on treatment (months)	7.3	n/a	7.3
Life years	1.98	1.21	0.77
Mean time in Progressed Disease (years)	1.38	1.02	0.36
QALYs	1.23	0.73	0.50
Drug costs	£12,391	£0	£12,391
Total costs	£19,767	£6,315	£13,699
Cost per life year gained			£17,695
Cost per QALY			**£27,365**

The manufacturer presented a variety of univariate sensitivity analyses to explore the impact of: time horizon; costs associated with death; costs

associated with best supportive care in the progressed disease health state; cost of monitoring outpatients; costs of adverse events; dose intensity; survival curves (sunitinib progression-free survival and overall survival curve extrapolation based on application of the hazard ratio from trial to best supportive care curves); and discount rates. The resulting ICERs from the deterministic sensitivity analyses can be found in Table 27 (pages 83–84) of the MS, and Table 22 (page 80) of the ERG report. Particularly of note was sensitivity analysis using the unadjusted ITT data to model the best supportive care overall survival curve. The results of this sensitivity analysis are presented in Table 4.

Table 4: Sensitivity analysis using the unadjusted ITT method for best supportive care overall survival

	sunitinib	BSC	sunitinib vs. BSC
Time on treatment (months)	7.3	n/a	7.3
Life years	1.98	1.79	0.77
Mean time in Progressed Disease (years)	1.38	1.60	-0.22
QALYs	1.23	1.07	0.17
Drug costs	£12,391	£0	£12,391
Total costs	£19,767	£7,017	£12,750
Cost per life year gained			£66,010
Cost per QALY			**£77,107**[a]

[a] This ICER is higher than that of £34,649 per QALY gained as presented in the MS, Table 27 p84. The ERG noticed an error in the original submission, which was corrected and confirmed by the manufacturer during clarification.

The manufacturer also conducted probabilistic sensitivity analyses to address uncertainty around the key clinical and cost values used in the model. The results of the probabilistic sensitivity analysis is shown in Figure 15 (page 82 of the MS).The cost-effectiveness acceptability curves are shown in Figure 16 (page 83 of the MS) and the manufacturer stated that sunitinib has a 50% probability of being cost effective compared with best supportive care, at a willingness-to-pay threshold of £30,000 per QALY gained.

3.2 Evidence Review Group comments

The ERG considered that the approach to the economic modelling was appropriate for the decision problem. The ERG noted that the sources and justification of estimates used in the model were generally reasonable, and that the overall survival data used in the model were relatively mature and thus the survival curves fitted the data well. The ERG stated that there were no apparent logical errors or internal inconsistencies in the manufacturer's economic model.

There were three major areas of concern and uncertainty highlighted by the ERG with regard to the economic model submitted by the manufacturer:

- The ERG acknowledged that the RPSFT method as used to model overall survival in the best supportive care arm in the manufacturer's base case appeared reasonable. However the ERG highlighted that the RPSFT method is uncommon and that the ERG has been unable to determine whether the method was applied correctly by the manufacturer (see page 83 of the ERG report). The ERG highlighted that this parameter is the key driver in the economic model.

- The ERG highlighted a number of errors and omissions in the probabilistic sensitivity analyses (see pages 90–91 of the ERG report). In particular, the ERG stated that the uncertainty in the progression-free survival and overall survival has not been modelled fully. The ERG was concerned, given the wide confidence interval (as recommended by an external expert to the manufacturer) around the estimate for the overall survival hazard ratio using the RPSFT method, that the uncertainty in the base-case ICER is substantial and is likely to be higher than that presented by the manufacturer in the probabilistic sensitivity analyses.

- In the manufacturer's model, patients were assumed to receive sunitinib until disease progression; however the ERG noted that in the RCT, 54 (22%) patients received sunitinib after disease progression. The

manufacturer did not include these additional costs of sunitinib in the model, and provided further details of the 54 patients during clarification. The ERG calculated that the additional incremental sunitinib costs in progressed disease were £2,237 in the model. When the ERG incorporated these additional sunitinib costs into the model, the base-case ICER increased from £27,400 to £31,800 per QALY gained. When the additional costs of sunitinib were incorporated into the sensitivity analyses that used the unadjusted ITT data, the ICER increased from £77,100 to £90,500 per QALY gained (see pages 92–93 of the ERG report).

The ERG also highlighted further potential limitations of the economic model submitted by the manufacturer:

- In the EAP, the median overall survival was similar to that used by the manufacturer in the economic model: 75 weeks and 73 weeks, respectively. However, the ERG noted that the median time to tumour progression was longer in the EAP than that used by the manufacturer in the economic model: 41 weeks and 23 weeks respectively. The ERG stated that it is not clear why the patients in the EAP experienced a longer time to tumour progression than those in the RCT, particularly as only those patients with a good ECOG performance status of 0 or 1 participated in the trial. In an exploratory analysis performed by the ERG, when the sunitinib progression-free survival curve was adjusted to produce a median of 41 weeks, the ICER increased from £27,400 to £46,300 per QALY gained. The ERG stated that the increase in the ICER was mainly due to the increased costs of sunitinib; the economic model assumed that treatment with sunitinib is given until disease progression (see page 86 of the ERG report).

- The ERG accepted that the utility values for the progression-free health state had been calculated appropriately by the manufacturer. The ERG noted some inconsistencies with the utility data used by the manufacturer for the progressed disease health state of 0.577 used in the economic

model. The ERG sought further clarification from the manufacturer and the ERG was unable to reconcile the data that the manufacturer supplied in clarification with those presented in the submission. The ERG noted that the utility values for progressed disease supplied during clarification were higher than those originally assigned to the progression-free health state. However, the ERG highlighted that the cost-effectiveness estimate is relatively insensitive to variations in the utility values.

- No subgroup cost-effectiveness estimates were calculated by the manufacturer. The ERG highlighted that the RCT population was stratified by previous imatinib treatment and baseline pain score. The ERG also noted that time to tumour progression data were also presented according to several prognostic factors (see page 42 of the MS).

3.3 Further considerations following premeeting briefing teleconference

In order to allow the Appraisal Committee to consider the applicability of the 'end of life' criteria, the following section summarises the pertinent parameters:

- The marketing authorisation for sunitinib is for people with unresectable and/or metastatic malignant GIST whose condition is intolerant or resistant to first-line imatinib treatment. The patient population is between approximately 90 and 150 people in England and Wales per year.

- The median overall survival in the RCT for people with unresectable and/or metastatic malignant GIST after the failure of first-line imatinib treatment was approximately 40 weeks with best supportive care. However, this figure is taken from the RPSFT method which controls for the crossover that occurred in the RCT. The manufacturer and the patient and clinical experts stated that 5-year survival rates are poor and very few people survive beyond 5 years.

- The median overall survival in the RCT and EAP was increased to approximately 75 weeks for people receiving second-line sunitinib treatment. This represents an increase in survival of around 35 weeks with sunitinib treatment.

- There are currently no alternative treatment options for people with unresectable and/or metastatic malignant GIST who have experienced intolerance or resistance to first-line imatinib treatment. Therefore, sunitinib could be considered as a substantial improvement in the second-line treatment of unresectable and/or metastatic malignant GIST, although patient and clinical experts stated that imatinib was the first targeted therapy for this indication.

4 Authors

Rebecca Trowman and Joanna Richardson, with input from the Lead Team (Peter Clark and Eugene Milne).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG):

- Bond M, Hoyle M, Moxham T et al, The clinical and cost effectiveness of sunitnib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer, January 2009.

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Pfizer

II Professional/specialist, patient/carer and other groups:

- Association of Upper GI Surgeons of GB and Ireland (AUGIS)
- NCRI/RCP/RCR/JCCO/ACP
- Plymouth Teaching PCT
- Royal College of Nursing
- Sarcoma UK - GIST Support UK (GSUK)

Appendix B: Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. NICE technology appraisal guidance 86 (2004)

1. Guidance

1.1. Imatinib treatment at 400 mg/day is recommended as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic gastro-intestinal stromal tumours (GISTs).

1.2. Continuation with imatinib therapy is recommended only if a response to initial treatment (as defined in Section 1.5) is achieved within 12 weeks.

1.3. Responders should be assessed at intervals of approximately 12 weeks thereafter. Continuation of treatment is recommended at 400 mg/day until the tumour ceases to respond, as defined in Section 1.5.

1.4. An increase in the dose of imatinib is not recommended for people receiving imatinib who develop progressive disease after initially responding (see Section 1.5).

1.5. For the purpose of this guidance, response to imatinib treatment should be assessed on the basis of the results of diagnostic imaging to assess size and density of the tumour(s), patients' symptoms and other factors, in accordance with the Southwest Oncology Group (SWOG) criteria detailed in Appendix D. For the purpose of this guidance, response to therapy is defined as the SWOG classifications of complete response, partial response or stable disease.

1.6. The use of imatinib should be supervised by cancer specialists with experience in the management of people with unresectable and/or metastatic GISTs.