# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Overview

## Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of technology appraisal guidance 86)

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

# 1 Background

This multiple technology appraisal (MTA) is a part review of TA 86 to appraise imatinib at escalated daily doses of 600mg or 800mg for people with KIT (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) whose disease has progressed on treatment with imatinib at a dose of 400 mg/day compared with other treatment options. The comparators are therefore best supportive care and, following the publication of technology appraisal TA 179, sunitinib. The part review will therefore update recommendation 1.4 in TA86 (which currently specifies that an increase in the dose of imatinib is not recommended for people receiving imatinib who develop progressive disease after initially responding).

## *1.1 The condition*

Gastrointestinal stromal tumours (GISTs) are rare tumours of mesenchymal origin that occur in the gastrointestinal tract. Although GISTs can occur along the length of the gastrointestinal tract from the oesophagus to the anus, the majority arise in the stomach (60–70%). GISTs can also occur in the small bowel (25–35%), colon and rectum (5%). Most GISTs are associated with the overexpression of the marker KIT (CD117), a tyrosine kinase receptor, which

is thought to promote tumour growth or to inhibit tumour cell death through a signal transduction pathway.

Approximately one third of people with GISTs are asymptomatic during the early stages of the disease, however symptoms can include abdominal discomfort or pain, a feeling of abdominal fullness and the presence of a palpable mass. People have more severe symptoms when tumours metastasise or when they become large, rupture and bleed or obstruct the gastrointestinal tract. In metastatic disease, systemic symptoms such as fever, night sweats and weight loss are common.

Diagnosis of GIST is confirmed by clinical presentation and biopsy to determine the histological characteristics of the tumour, including positive KIT/CD117 protein expression. Approximately 4% of GISTs have clinical and morphological features but do not express the KIT/CD117 protein. Therefore it is important in these cases that other markers are investigated to confirm the diagnosis of GIST.

Retrospective studies carried out using KIT immunoreactivity have shown that GISTs have been under-diagnosed in the past. These studies estimate that the annual incidence of GIST in the UK is 15 cases per million, which is approximately 900 people. Prognosis is dependent on the resectability of the tumour; approximately 50% of GISTs are resectable at presentation. Without treatment GISTs are progressive and will eventually metastasise.

Although GISTs can occur at any age, the usual age of presentation is between 50 and 70 years. Tumour size, tumour growth rate and tumour location have been cited as prognostic factors, however tumour location may not be a reliable factor for estimating survival.

## *1.2 Current management*

Complete surgical resection is the current standard treatment for localised GISTs. However, recurrence generally occurs in 40–50% after complete

resection. For unresectable tumours, prognosis is very poor with survival generally less than 2 years without further treatment.

Conventional cytotoxic chemotherapy and radiotherapy are ineffective in treating advanced GISTs. Similarly, initial surgery to remove as much of the tumour as possible is not recommended unless there is an immediate clinical need, such as to remove an obstructing tumour.

NICE technology appraisal guidance 86 recommends imatinib treatment (400 mg/day) for the first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GISTs. It does not recommend an increase in the dose of imatinib for people who develop progressive disease after initially responding to 400 mg/day. Sunitinib is recommended as a treatment option for people with unresectable and/or metastatic malignant GISTs following treatment failure with imatinib because of resistance or intolerance (NICE technology appraisal guidance 179).

The treatment of people with unresectable and/or metastatic GISTs whose disease progresses after treatment with imatinib is generally decided on a case-by-case basis by multidisciplinary teams. Many clinicians advocate an initial dose escalation of imatinib up to 800 mg/day and then consider sunitinib 50 mg/day (for 4 weeks out of 6) for subsequent disease progression, although practice will vary depending on people's specific needs. Best supportive care (managing symptoms) is sometimes considered, but interrupting treatment can result in rapid disease progression in some people, and so imatinib is often continued, despite disease progression, as part of best supportive care.

# 2 The technology

**Table 1 Summary description of technology**

| | |
|---|---|
| Non-proprietary name | Imatinib mesilate |
| Proprietary name | Glivec |
| Manufacturer | Novartis Pharmaceuticals UK |
| Dose | Oral doses of 400, 600 or 800 mg/day |
| Acquisition cost (excluding VAT, BNF edition 59) | £13.37 per 100 mg tablet<br>(60-tablet pack = £802.04). Approximately £19,533 (400 mg/day), £29,300 (600 mg/day) or £39,067 (800 mg/day) per year. |

Imatinib is a signal-transduction inhibitor which selectively inhibits certain classes of tyrosine kinase, including the KIT receptor expressed in GISTs. Imatinib binds to activated KIT receptors and blocks the cell-signalling pathway to prevent uncontrolled cell proliferation.

Imatinib has a UK marketing authorisation for the treatment of adult patients with KIT (CD117)-positive unresectable and/or metastatic malignant GISTs. The summary of product characteristics recommends imatinib at a dose of 400 mg/day for the treatment of unresectable and/or metastatic GISTs. The marketing authorisation also states that limited data exist on the effect of dose increases of imatinib from 400 to 600 or 800 mg in patients whose disease progresses at the lower imatinib dose.

# 3 The evidence

NICE received a submission from the manufacturer of imatinib, which did not include an economic model, but highlighted that the evidence base has not changed significantly since the publication of technology appraisal 86. NICE also received submissions from patient groups, patient experts and professional organisations.

## *3.1 Clinical effectiveness*

The Assessment Group identified published and ongoing studies on the clinical effectiveness of escalated doses of imatinib prescribed with best supportive care for people with KIT (CD117)-positive unresectable and/or metastatic GISTs whose disease had progressed on treatment with imatinib 400 mg/day. The Assessment Group also found clinical-effectiveness studies of comparator treatments (sunitinib and best supportive care or best supportive care alone). The reference lists of these studies and submissions from the manufacturer and other consultees were searched to identify additional relevant studies.

Six papers and ten abstracts reporting four separate clinical trials and one additional retrospective cohort met the Assessment Group's inclusion criteria. An additional 49 papers were used for background information.

The Assessment Group did not identify any randomised controlled trials or non-randomised comparative studies comparing the effectiveness of escalated doses of imatinib (600 or 800 mg/day) with sunitinib or best supportive care that met their inclusion criteria.

Studies by Zalcberg et al. (2005) and Blanke et al. (2008a; 2008b) were the primary reports of the EORTC-ISG-AGITG (62005) trial, the S0033 trial and the B2222 trial respectively. Another study by Debiec-Rychter et al. (2006) was included to provide additional information from the EORTC-ISG-AGITG (62005) trial on treatment response after crossover, while a study by Demetri

et al. (2002) was used to provide interim data from the B2222 trial on response after crossover. All of these trials contained a treatment arm of imatinib 400 mg/day and reported data separately for people who received escalated doses of imatinib on disease progression. A non-randomised retrospective study by Park et al. (2009) was also included to provide separate outcome data for people with metastatic or unresectable GIST who received an initial dose of imatinib 400 mg/day that was escalated to higher doses on disease progression.

Seven abstracts were identified that provided interim results of an ongoing, open-label trial on the effectiveness of sunitinib in people whose condition failed to respond to treatment with different doses of imatinib. An abstract by Seddon et al. (2008) was considered the primary report for this trial.

Two confidential reports from the manufacturer were also included in the evidence base for the assessment report.

The characteristics of all of the people included in the trials who were randomised to receive an initial dosage of imatinib 400 mg/day are given in table 2.

**Table 2 Characteristics for people receiving an initial dosage of imatinib 400 mg/day (see assessment report, page 26)**

| | EORTC-ISG-AGITG* | S0033 trial (Blanke et al. 2008) | B2222 trial (Blanke et al. 2008) | Park et al. (2009) | Seddon et al. (2008) |
|---|---|---|---|---|---|
| **Included in this analysis** | **People randomised to imatinib 400 mg/day** | **People randomised to imatinib 400 mg/day** | **People randomised to imatinib 400 mg/day** | **People receiving imatinib 400 mg/day initially, with dose escalation on disease progression** | **People receiving sunitinib 50mg once daily (4 weeks on treatment, followed by 2 weeks off treatment)** |
| Number of people (N) | 473 | 345 | 73 | 24 | 1117 |
| Median age in years (range) | 59 (49–67) | 61.9 (18–87) | [redacted] | 52 (31–73) | 59 (10–92) |
| Sex (M/F) | 283/190 | 187/158 | [redacted] | 18/6 | 665/451 |
| ECOG/WHO performance status score 0 | 217 | [redacted] | [redacted] | 4 | 420 |

| | | | | | |
|---|---|---|---|---|---|
| 1<br>2<br>≤2<br>>2<br>Missing | 191<br>48<br>(456)<br>17 | <br><br>332<br>13 | [redacted] | 18<br>2 | 515<br>134<br>(1069)<br>38<br>10 |
| Race/ethnicity (N)<br>White<br>Black<br>Asian<br>Other/unknown | Not reported | <br>273<br>37<br>25<br>10 | [redacted] | Not reported | Not reported |
| Previous chemotherapy (N) | 156 (32.9%) | Not reported | [redacted] | 3 (12.5%) | 225 (20.1%) |
| Previous radiotherapy (N) | 26 (5.5%) | Not reported | [redacted] | Not reported | 78 (7.0%) |
| Previous surgery (N) | 410 (86.7%) | | [redacted] | 20 (83.3%) | Not reported |
| People who initially received imatinib 400 mg/day which was increased on disease progression | 133/473 (28.1%) | 118/345 (34.2%) | 43/73 (58.9%) | 24/24 (100.0%) | N/A |

* Study characteristics from Zalcberg et al. (2005) not reported, however these data were reported by Verweji et al. (2004) for the same trial.
† People in this study were part of a retrospective cohort. Treatment was not randomised. The population of interest received escalated imatinib doses.

Among the imatinib trials, i.e., EORTC-ISG-AGITG, S0033 and B2222, disease progressed in 28.1%, 34.2% and 58.9% of people initially randomised to imatinib 400 mg/day and they received an escalated dose. All the people included in Park et al. received an escalated dose of imatinib. In the sunitinib study by Seddon et al. disease failed to respond to treatment in 31.4% of people (whose disease previously failed to respond to imatinib ≤ 400 mg/day).

### Overall response

The results for people treated with an escalated dose of 600 mg/day following disease progression at imatinib 400 mg/day were reported in two studies (Blanke et al. 2008 [B2222] and Park et al. 2009). The Assessment Group noted that some of the people who crossed over were likely to have had an initial response to imatinib 400 mg/day before disease progression, because

only 11 people in the imatinib 400 mg/day arm showed a best response before progressive of the disease (Table 3).

**Table 3 Overall response for people treated with an escalated dose of 600 mg/day or 800 mg/day following disease progression at imatinib 400 mg/day**

| Parameter | Treatment with imatinib 600 mg/day following disease progression at imatinib 400 mg/day | | Treatment with imatinib 800 mg/day following disease progression at imatinib 400 mg/day | | |
|---|---|---|---|---|---|
| | Blanke et al. 2008 (B2222) | Park et al. 2009 | Blanke et al. 2008 [S0033 trial] | Zalcberg et al. 2005 [EORTC-ITG-AGITG trial] | Park et al. 2009 |
| Population | 43 | 12 | 118 | 133 | 12 |
| Follow up length (months) | 63 (max 71 months) | 8 (1.4 – 22.3) | - | - | - |
| Number of people with partial response or who had stable disease after treatment | 11 (25.6%) | 5 (41.7%) | 3 (partial response)<br><br>33 (30.0%) – stable disease | 3 (partial response)<br><br>36 (27.1%) – stable disease | 4 (33.3%) achieved either a partial response or had stable disease after treatment |

The manufacturer reported treatment response rates of people receiving an escalated dose of imatinib, from a confidential trial in their submission. However the Assessment Group did not use these data in their review because of inconsistencies between this information and the results from the same studies available as published articles.

Three sources reported response data for people receiving an initial dosage of imatinib 400 mg/day that was increased to 800 mg/day after disease progression (Blanke et al. 2008 [S0033 trial], Zalcberg et al. 2005 [EORTC-ITG-AGITG trial], and Park et al. 2009) as shown in table 3.

In addition, a secondary analysis of the EORTC-ISG-AGITG trial reported by Debiec-Rychter et al. indicated (without stating the number of people involved) that response after crossover was significantly more likely to occur in people with wild-type GIST than KIT exon 11 mutation (p = 0.0012). Response after

crossover was also significantly more likely to occur in people with KIT exon 9 mutation compared with exon 11 mutation (p = 0.0017).

No response data were provided for treatment with sunitinib at a dosage of 50 mg/day (as part of a 6-week treatment cycle – 4 weeks of treatment followed by 2 weeks with no treatment), after disease progression on imatinib 400 mg/day.

### Overall survival

Blanke et al. 2008 (S0033) reported the median length of overall survival for people treated with an initial dosage of imatinib 400 mg/day that was increased to 800 mg/day after disease progression, as shown in table 4.

**Table 4 Overall survival for people treated with an initial dosage of imatinib 400 mg/day that was increased to 800 mg/day after disease progression**

| Parameter | Blanke et al. 2008 (S0033) |
|---|---|
| Population | 118 |
| Median follow-up (years) | 4.5 |
| Median overall survival (months) after crossover | 19<br>(95% CI 13 – 23) |

Interim data for the S0033 trial were also provided by Rankin et al. (2004), who reported that median overall survival was 19 months.

The manufacturer's submission reported that the

[redacted]

The manufacturer reported that

[redacted]

[redacted]

Overall survival data were reported for people receiving sunitinib 50 mg/day after treatment failure on imatinib ≤ 400 mg/day in two abstracts of the same trial with different follow-up periods, as presented in table 5.

**Table 5 Median length of overall survival in people receiving sunitinib 50 mg/day after treatment failure on imatinib ≤ 400 mg/day**

| Parameter | **Reichardt et al. 2008** | **Seddon et al. 2008** |
|---|---|---|
| Population | 339 | 351 |
| Median follow-up (weeks) | 24 (4 cycles) | 51<br>(0.1 – 159) |
| Median overall survival (weeks) | 93<br>(95% CI 72 – 100) | 90<br>(95% CI 73 - 106) |

Although the month of analysis is the same month as that reported by Reichardt et al. 2008 and Rutkowski et al. 2008 the median length of overall survival is reported to be 80.4 weeks (95% CI 60.3 to N/A weeks), while the number of people whose disease failed to respond to imatinib ≤ 400 mg/day was also less (307 patients).

The study by Zalcberg did not report information on overall survival.

[redacted] and data from the study by Seddon et al. on people receiving sunitinib are presented in table 6.

[redacted]

| | Seddon (N = 351) Sunitinib 50 mg/day | | | [redacted] | | |
|---|---|---|---|---|---|---|
| **Number of years since the beginning of treatment** | **Probability of survival** | **95% CI** | | **Probability of survival** | [redacted] | |
| 1 | 0.684 | 0.626 | 0.741 | [redacted] | [redacted] | [redacted] |
| 2 | 0.441 | 0.379 | 0.503 | [redacted] | [redacted] | [redacted] |
| 3 | 0.200 | 0.140 | 0.261 | [redacted] | [redacted] | [redacted] |
| 4 | Not reported | | | [redacted] | [redacted] | [redacted] |

CI: confidence interval

### Disease-free survival

The Assessment Group did not report on disease-free survival because no one in any of the included studies achieved a complete response to treatment.

### Progression-free survival

Progression-free survival data were not published for the B2222 trial for people receiving an initial dosage of imatinib 400 mg/day increased to 600 mg/day after disease progression.

Blancke et al. (S0033 trial) and Zalcberg et al. (EORTC-ISG-AGITG) reported progression-free survival data for people treated with an initial dosage of imatinib 400 mg/day escalated to 800 mg/day after disease progression. The results are summarised in table 7.

**Table 7 Progression-free survival data for people treated with an initial dosage of imatinib 400 mg/day escalated to 800 mg/day after disease progression**

| Parameter | Blanke et al. 2008 [S0033 trial] | Zalcberg et al. [EORTC-ITG-AGITG trial] |
|---|---|---|
| Population | 99 | 108 |
| Median follow-up (months) | 54 | 35 |
| Median progression-free survival | 5 months (95% CI 2 – 10) | 81 days |

[redacted]

No progression data were reported by Seddon et al. for people receiving an initial dose of imatinib ≤ 400 mg/day followed by sunitinib 50 mg/day after treatment failure.

**Time to treatment failure**

Park et al. reported data on the duration of response and time to treatment failure. Of the 12 people who had their dose escalated to 600 mg/day after disease progression, 1 person died of a cause unrelated to both disease and treatment, while the remaining 11 progressed after a median of 1.7 months (range 0.7–24.9 months).

Data from the EORTC-ISG-AGITG trial showed that of the people who showed a partial response or had stable disease after treatment crossover (initially receiving imatinib 400 mg/day increased to 800 mg/day after disease progression), the median duration of 'stabilisation' was 153 days (range 37–574 days).

For the sunitinib trial, the specific median treatment duration for people initially receiving imatinib ≤ 400 mg/day followed by sunitinib 50 mg/day after disease progression was not provided. However the interim median treatment duration for the whole cohort was reported as 126 days (range 1–618 days). At that

time (median follow-up not stated) it was noted that median treatment duration 'did not significantly differ based on the dose of prior imatinib therapy (≤ 400 compared with > 400 mg/day)'.

**Health-related quality of life**

None of the included studies reported health-related quality of life data.

**Adverse events**

Adverse events were not reported for people receiving an escalated dose of imatinib 600 mg/day after disease progression.

Data were reported by Zalcberg et al. (EORTC-ISG-AGITG trial) for people receiving imatinib 400 mg/day increased to 800 mg/day after disease progression. They do not explicitly state the number of discontinuations because of adverse events in the EORTC-ISG-AGITG trial, but they do report that the vast majority of discontinuations (88.4% or approximately 86 of 97 withdrawals) were because of disease progression. This suggests that the maximum number of withdrawals because of adverse events would be 11.6%, that is, 11 people.

Zalcberg et al. reported interim data for this trial showing that 31% of people (exact number not given) required a dose reduction (please note, this was stated as 'cumulative incidence'). No information was provided on the reduced dose given.

Interim data for the S0033 trial reported by Dileo et al. showed that of the 77 people who had crossed over from imatinib 400 mg/day to 800 mg/day at that time, 18 (23.3%) had at least one dose delay, and 12 (15.6%) had at least one dose reduction because of oedema and rash. No information was provided on the reduced dose given.

[redacted]

[redacted]

No adverse event data were available for people receiving an initial dose of imatinib ≤ 400 mg/day followed by sunitinib 50 mg/day after disease progression.

For more information on adverse event data please see table 7 (page 41), table 8 (page 42) and table 9 (page 43) in the assessment report.

## *3.2 Cost effectiveness*

**Manufacturer's submission**

The manufacturer did not submit a cost-effectiveness analysis of imatinib. The reasons for this were stated to be the lack of available comparative data. This was especially the case for studies comparing imatinib with sunitinib, making it difficult to conduct a robust and plausible indirect comparison of the two drugs.

[redacted]

**Assessment Report**

The Assessment Group carried out a systematic review of the literature to develop an economic model and to determine the cost effectiveness of using imatinib at an escalated dose of 600 or 800 mg/day to treat people with unresectable and/or metastatic GISTs (whose disease has progressed on treatment with imatinib 400 mg/day), compared with treatment with sunitinib (within its recommended dose range for people whose treatment with imatinib has failed because of resistance or intolerance) or best supportive care only.

The Assessment Group identified 250 papers from the initial literature search. Of these, 18 were selected as potentially relevant abstracts, and 13 were included for further screening. Nine were then selected for review and 7 of these were found to report a full economic evaluation that assessed both the costs and cost effectiveness of comparative treatments. The main features of the included studies are given in table 12 of the assessment report (page 49).

Treatment costs for different drugs are given in table 8. Also listed are the incremental cost-effectiveness ratios (ICERs) for the main outcomes (that is, life year saved, progression-free survival, QALYs). Although the Contreras-Hernandez et al. study considered three alternative treatments (sunitinib, imatinib and best supportive care), it did not report an ICER for imatinib compared with best supportive care.

**Table 8 Summary of results from studies reviewed (assessment report, page 54)**

| Study | Comparator | Mean treatment cost per person | ICER1 | ICER2 |
|---|---|---|---|---|
| Chabot et al. (2008)<br><br>(2005 prices) | Sunitinib | Can$46,125 | Sunitinib vs BSC Can$49,826 per life year saved | Sunitinib vs BSC Can$79,884 per QALY gained |
| | BSC | Can$11,632 | | |
| Contreras-Hernandez et al. (2008)<br><br>(2006 prices) | Sunitinib | US$17,806<br>(SD = US$695,<br>CI = US$15,377 to 19,816) | | Sunitinib vs BSC US$15,734 per person treated with sunitinib; US$56,612 per year of progression-free survival; US$46,108 per life year gained |
| | Imatinib | US$35,057<br>(SD = US$1253,<br>CI = US$31,381 to 38,705 | | |
| | BSC | US$2071<br>(SD = US$473,<br>CI = US$1543 to 2869) | | |
| Mabasa et al. (2008)<br><br>(2006 prices) | Imatinib | Can$79,839 | Imatinib vs BSC (control) Can$15,882 per life year | |
| | BSC | Can$1743 | | |
| Paz-Ares (2008)<br><br>(2007 prices) | Sunitinib | €23,259 | Sunitinib vs BSC €30,242 per life year | Sunitinib vs BSC €4090 per progression free month<br>€49,090 per QALY gained |
| | BSC | €1622 | | |
| Huse et al. (2007) | Imatinib | US $416,255 | | |

| Study | Comparator | Mean treatment cost per person | ICER1 | ICER2 |
|---|---|---|---|---|
| (2005 prices) | BSC | US$341,886 | | |
| Wilson et al. (2005)<br><br>(2004 prices) | Imatinib | £18,896 (400 mg/day)<br>£24,368 (600 mg/day)<br>Other treatment costs £1136 | | Cost per QALY gained<br>£70,206 (year 2),<br>£51,514 (year 3),<br>£36,479 (year 5) and<br>£25,859 (year 10) |
| | BSC | £562 | | |

BSC: best supportive care; CI: confidence interval; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; SD: standard deviation

**Summary of the review of published economic evaluation studies**

The Assessment Group found that most of the economic evaluation studies reviewed used modelling. Only two studies compared both imatinib and sunitinib with best supportive care for people whose condition failed to respond or became resistant to imatinib 400 mg/day. Of the five studies that used modelling, Contreras-Hernandez et al. did not use QALYs as health outcome measures.

The Assessment Group did not identify any published economic evaluation studies relevant for the UK comparing all the relevant interventions. The study that included an economic evaluation of higher dose imatinib in the UK (Wilson et al.) did not have as a comparator people whose disease failed to respond to imatinib 400 mg/day. The model allowed people whose condition failed to respond to imatinib 400 mg to cross over to imatinib 600 mg/day rather than 800 mg/day.

**Economic model**

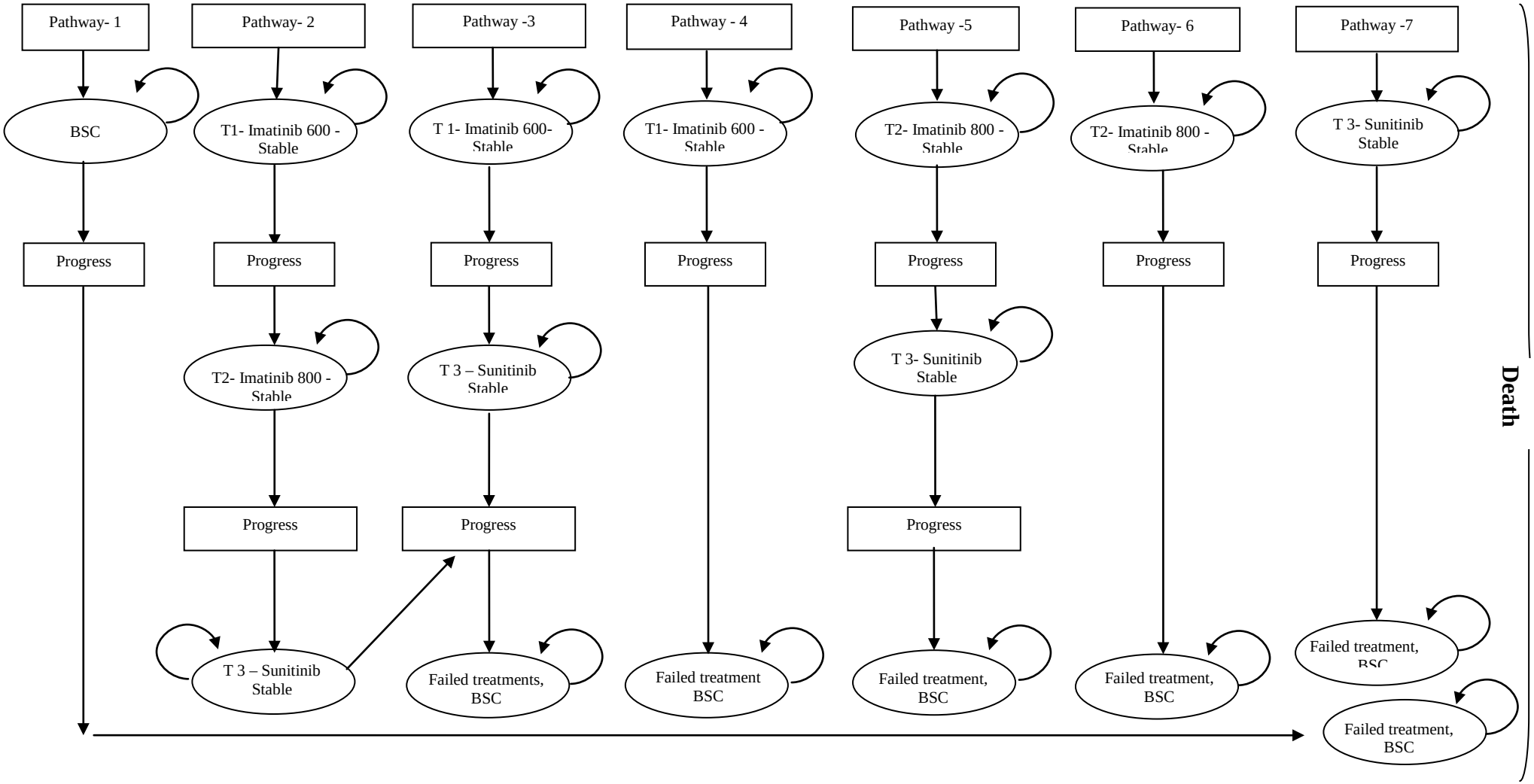
The Assessment Group developed a model to compare alternative treatment strategies for people with KIT (CD117)-positive unresectable and/or metastatic GISTs whose disease has progressed on treatment with imatinib 400 mg/day or whose treatment with imatinib has failed because of resistance or intolerance. The treatments to be compared in the models were:

- Treatment with an escalated dose of 600 mg/day, controlling symptoms with best supportive care

- Treatment with an escalated dose of 800 mg/day, controlling symptoms with best supportive care
- Sunitinib (within its recommended dose range), controlling symptoms with best supportive care
- Controlling symptoms with best supportive care only.

The Assessment Group considered a range of different alternative treatment pathways for people whose disease progressed on imatinib 400 mg/day. Based on advice from the Assessment Group's clinical advisers, the Assessment Group decided on seven clinically plausible pathways (figure 1) on which the model is based. In figure 1, circles represent health states that people may return to, rectangles represent health states while people receive treatment, and the arrows show the possible directions in which people could move at the end of each cycle, depending on the transition probabilities. The states considered in the model were those thought to reflect care pathways for people with GIST. People entering the pathways are those whose disease failed to respond on imatinib 400 mg/day. The alternative treatments considered were T1 = imatinib 600 mg/day, T2 = imatinib 800 mg/day, T3 = sunitinib (recommended dosage 50 mg/day), BSC = best supportive care.

**Figure 1. Markov model for GIST when treatment has failed with imatinib 400 mg/day (page 59 of the assessment report)**



The Assessment Group developed a Markov model to model these treatment pathways using Tree Age Pro 2009. In the model people whose disease progressed or whose treatment failed because of resistance or intolerance on imatinib 400 mg/day enter one of the seven care pathways.

**Key assumptions of the modelling exercise**

Data on the clinical effectiveness of interventions were based on the systematic review of clinical effectiveness described earlier. These data were combined within the model with health state utilities data to provide estimates of QALYs for the alternative treatment pathways for people with GIST.

**Probability of death**

As described in the systematic review, few data were available for any of the treatments, particularly for direct comparisons. Therefore, the data available are imprecise and potentially biased. The direction and magnitude of any bias is unknown. Therefore, the data used to derive probabilities of death for each treatment should therefore be considered with caution.

- Probability of death for best supportive care: the data were taken from three studies and pooled weighted estimates suggest that 87.9% (51 out of 58) died during the observation period of 60 months.
- Probability of death for imatinib 600 and 800 mg/day: the data for imatinib 600 mg/day were taken from the available trial data and 45% (5 of 11) of people who crossed over to imatinib 600 mg/day died during the trial period of 60 months. The data for imatinib 800 mg/day were taken from Blanke et al. The data suggest that 64.41% (76 of 118) died in this group. The monthly mortality rate was derived as an exponential rate.
- Probability of death for sunitinib: the data for sunitinib came from Seddon et al. In this study 54.99% (193 of 351) of people receiving sunitinib were still alive after a median survival period of 11.76 months. The monthly mortality rate was derived from this survival rate by assuming an exponential rate. In

the analysis it was assumed that the mortality rate for people receiving sunitinib is the same regardless of any previous treatment.

Using an exponential function, the proportions given above were inputted to derive the monthly rate for the probability of death, that is, the probability of dying in one given cycle within the Markov model. The probabilities in Table 9 refer to the probability of death per month. This is described in pages 62 and 63 of the Assessment Report.

**Response rate to treatment**

In the model, response to treatment included partial response, complete response and those reported to be in a stable condition.

The response rates for imatinib 600 and 800 mg/day were based on data from the B2222 trial. This trial reported that 25.58% (11 out of 43) of people had responded and remained stable on imatinib 600 mg/day during a median follow-up of 63 months. It also reported that 30% (75 out of 250) of people responded to imatinib 800 mg/day and showed a partial response or had remained stable after a median follow-up of 54 months.

For sunitinib the response rate was estimated from the weighted average response rate from two studies. In these studies a total of 266 of 382 people responded, and the simple weighted mean was used to derive the pooled response rate. This response rate was assumed to be unaffected by previous treatment. The non-response data for each treatment were converted into monthly transition probabilities by assuming an exponential rate.

**Costs**

The model included the costs of imatinib 400, 600 and 800 mg/day and sunitinib 50 mg/day. Because sunitinib treatment involved taking medication for 4 weeks and then no medication for 2 weeks, the medication costs of this drug per year were estimated and then equally proportioned to each month in that year. Data on drug costs were obtained from the British National Formulary 58. The Assessment Group assumed that people on best

supportive care remain on some medication and that the cost of this was equivalent to the cost of imatinib 400 mg/day.

Resource use in the treatments was based on the study by Wilson et al. 2005 and included GP visits (£40 per year), outpatient visits including tests (£440 per year), computed tomography (CT) scans (£656 per year) and the costs of managing adverse events (£159 per year). The estimates for these services used by Wilson et al. at 2003 prices were used for the Assessment Group's model after adjusting for inflation (using the Hospital and Community Health Services [HCHS] inflation index for the year 2008/09). Based on these estimates, the total monthly cost for these services for people receiving imatinib is £128.16. In the absence of other data this cost has been used for both imatinib 600 and 800 mg/day.

For the sunitinib group resource costs were based on the single technology appraisal submission from Pfizer (technology appraisal 179) for patient monitoring, outpatient and GP visits (£799.73 per year), CT scans (£336 per year) and the costs of managing adverse events (£159 per year). These costs were at 2008 prices and were inflated to 2009 prices using the HCHS index. Based on these data the estimated total monthly cost for these services for people receiving sunitinib is £185.

For best supportive care, data from the Pfizer submission were used for patient monitoring, outpatient and GP visits (£249 per year) and CT scans (£105 per year). The costs were at 2008 prices and were adjusted for inflation to 2009 prices using the HCHS Index.

**Utility data**

There were few data relating to health state utilities. The health state valuations were derived from the EQ-5D and the utility values were taken from Wilson et al. and Chabot et al. The utility for progression-free survival for people responding to imatinib (regardless of dose) was 0.935. The utility for people receiving best supportive care was taken from Chabot et al. and was

assumed to be 0.577. In the absence of alternative data it was assumed that the utility for people who have not progressed on sunitinib is the same as that assumed for imatinib (that is, 0.935).

Table 9 presents the parameter inputs for the model, the sources of data, and values and data used to inform the probabilistic sensitivity analysis (described below).

In the sensitivity analysis, the high value drug costs (imatinib and sunitinib) were assumed to be similar to the values used by the Assessment Group in their model for the base-case analysis (based on the BNF price). For the lower value, the Assessment Group took an average of the prices of the higher and lower doses, assuming that the dose may be lowered in the treatment pathways used in the model. For sunitinib, the price of the lower dose was assumed.

**Table 9 Model parameters, values and data sources (assessment report, pages 66–67)**

| Description | Value | Low | High | Values | Data source and assumptions |
|---|---|---|---|---|---|
| Cost of imatinib 600 mg/day | £2406 | £2005 | £2406 | | BNF58 (September 2009)<br>Low value is average of imatinib 400 and 600 mg |
| Cost of imatinib 800 mg/day | £3208 | £2807 | £3208 | | BNF58 (September 2009)<br>Low value is average of imatinib 600 and 800 mg |
| Cost of best supportive care | £1604 | £1283 | £1604 | | Include cost of imatinib 400mg (BNF58 September 2009 ) |
| Cost of sunitinib | £3139 | £2092.5 | £3138.8 | | BNF58 (September 2009)<br>Low value is average of reduced dose of sunitinib |
| Other costs and managing BSC treatment | £50.61 | | | | Resource use in the treatment were based on the study by Wilson et al. (2005) |
| Other costs and managing imatinib treatment | £128.16 | | | | Resource use in the treatment were based on the study by Wilson et al. (2005) assumed to be same for imatinib 600 and 800 mg/day |
| Other costs and managing sunitinib treatment | £185.11 | | | | Resource use in the treatment were based on the study by Wilson et al. (2005) and STA Pfizer |
| Probability of death: BSC | 0.014627 | | | α = 0.8448898<br>β = 57.775 | Pooled weighted rate |
| Probability of death: imatinib 600 mg/day | 0.007472 | | | α = 0.08162<br>β =10.91838 | B2222 study |
| Probability of death: imatinib 800 mg/day | 0.011857 | | | α = 1.39948<br>β =116.600 | S0033 study |
| Death due to GIST: | 0.026706 | | | α = 9.3284 | Seddon (2008) |

| | | | | | |
|---|---|---|---|---|---|
| sunitinib | | | | β =341.62 | |
| Transition probability of non-response to imatinib 600 mg/day | 0.011743 | | | α = 0.504949<br>β =42.495051 | B2222 study |
| Transition probability of non-response to imatinib 800 mg/day | 0.012879 | | | α = 3.21875<br>β =246.780 | S0033 study and Zalcberg et al. (2005) |
| Transition probability of non-response to sunitinib | 0.080959 | | | α = 12.30<br>β =139.6945 | Weighted average response rate |
| Utility with imatinib 600 mg/day | 0.935 | 0.712 | 0.939 | | Wilson et al. (2005) |
| Utility with imatinib 800 mg/day | 0.935 | 0.712 | 0.939 | | Wilson et al. (2005) |
| Utility for progression of disease | 0.577 | 0.52 | 0.712 | | Wilson et al. (2005) |
| Utility with sunitinib treatment | 0.935 | 0.712 | 0.939 | | Chabot et al. (2008) |
| Time period that utilities, costs and probabilities relate to | 1 month | | | | Assumption |
| Number of cycles model is run for | 120 (10 years) | 72 (6 years) | 144 (12 years) | | Assumption |
| Discount rate | 0.002917 | 0 | 0.005 | | NICE guideline |

**Time horizon for the model**

The model looked at the costs and outcomes for GIST treatments. The time horizon of the model was 10 years and the cycle length was 1 month to reflect the natural history of the disease.

## *Results of the cost-effectiveness analysis*

The results of the model are presented as incremental cost per QALY gained. The costs and outcomes were discounted at 3.5% in accordance with NICE policy. Both deterministic and probabilistic sensitivity analyses were conducted, as described below.

**Base case**

Table 10 shows the mean estimates of cost and effectiveness of the six treatment paths modelled. Path 4 (treatment with imatinib 600 mg/day) has an incremental cost per QALY gained of less than £30,000 compared with path 1 (best supportive care). The only other non-dominated or non-extendedly dominated strategy was path 2 (imatinib 600 mg/day to imatinib 800 mg/day to

sunitinib). However, the incremental cost per QALY gained (compared with the next more costly option – path 4) is above of £40,000.

In the base-case analysis for path 7 the finding that sunitinib was dominated by best supportive care when effectiveness was measured in life years but not dominated when effectiveness was measured in QALYs gained illustrates the importance of the utility estimates used in the model. Again these data were sparse, particularly for sunitinib, and do not reflect the potential side effects. This was because the survival estimates for sunitinib were based on limited non-randomised and non-comparative data (as was the case for all the other comparators). Therefore, any comparison should be considered with caution.

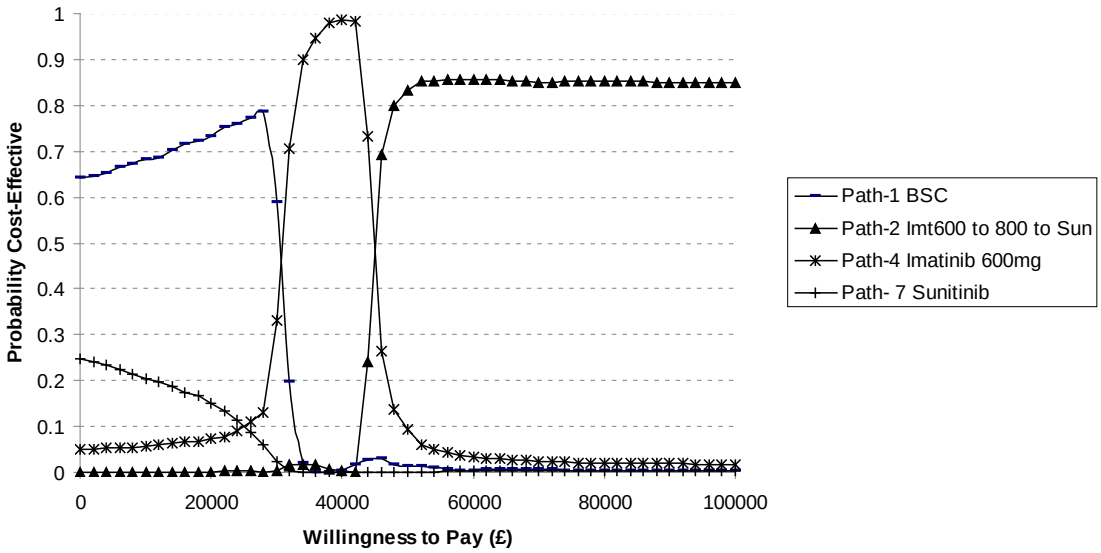
**Table 10 Base-case analysis and incremental cost–utility of the alternative treatment pathways (assessment report, page 70)**

| Strategies | Cost | Incremental cost | Life years | Incremental life years | QALYs | Incremental QALYs | Incremental cost per QALY |
|---|---|---|---|---|---|---|---|
| Path 1 – best supportive care | £92,811 | | 4.154 | | 2.397 | | |
| Path 7 – sunitinib | £96,688 | £3877 | 3.716 | Dominated | 2.411 | 0.014 | £272,365 |
| Path 4 – imatinib 600 mg/day | £147,060 | £50,372 | 5.211 | 1.057 | 4.256 | 1.845 | £27,304 |
| Path 3 – imatinib 600 mg/day to sunitinib | £149,200 | £2,139 | 5.032 | Dominated | 4.286 | 0.030 | £71,723 |
| Path 6 – imatinib 800 mg/day | £153,901 | £4702 | 4.506 | Dominated | 3.635 | -0.651 | Dominated |
| Path 5 – imatinib 800 mg/day to sunitinib | £155,828 | £6628 | 4.336 | Dominated | 3.659 | -0.627 | Dominated |
| Path 2 – imatinib 600 to 800 mg/day to sunitinib | £172,152 | £22,953 | 5.278 | 0.067 | 4.803 | 0.517 | £44,359 |
| **With dominated and extendedly dominated options removed** | | | | | | | |
| Path 1 – best supportive care | £92,812 | | 4.154 | | 2.397 | | |
| Path 4 – imatinib 600 mg/day | £189,484 | £54,249 | 5.211 | 1.057 | 4.256 | 1.859 | £29,181 |
| Path 2 – imatinib 600 to 800 mg/day to sunitinib | £212,595 | £25,092 | 5.278 | 0.067 | 4.803 | 0.547 | £45,850 |

QALY: quality-adjusted life year

The Assessment Group considered that the results reported in table 10 are imprecise, mainly because of the clinical-effectiveness data used. Therefore, the Assessment Group performed a partial probabilistic sensitivity analysis, with the uncertainty surrounding response rates and mortality rates being characterised by beta distributions.

**Figure 2 Cost-effectiveness acceptability curve for alternative treatments over the 10-year time horizon* (assessment report, page 71)**




*Pathways with a low probability of being cost effective over the payment threshold for the QALY values considered have not been shown.

## Sensitivity analysis

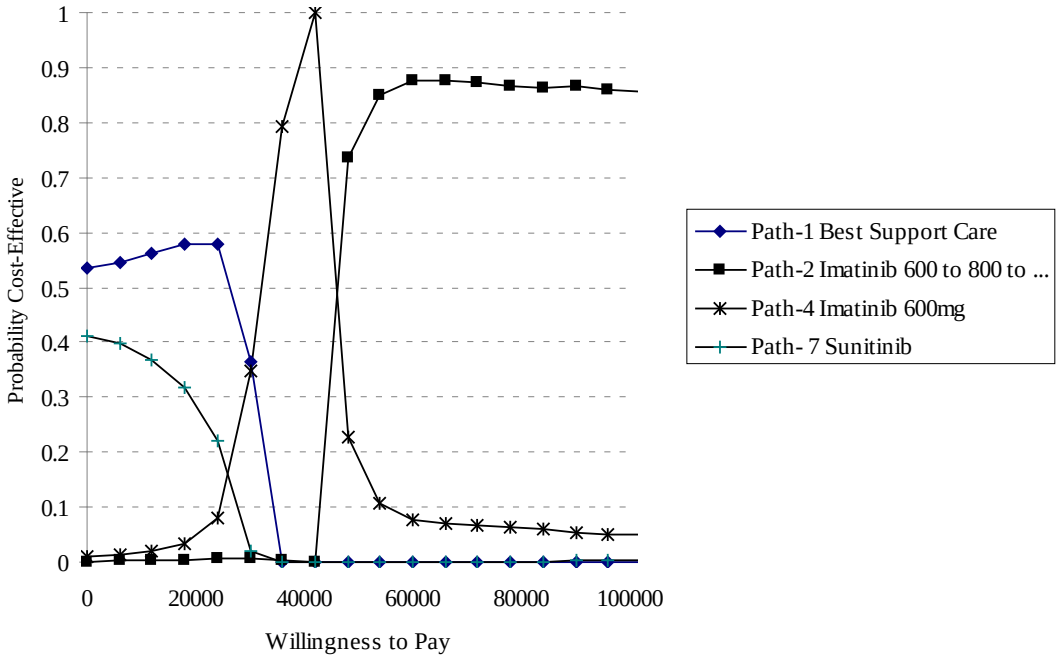
The Assessment Group performed sensitivity analyses to account for uncertainties in different parameters. The results are given below.

### Uncertainty around the distributions used for mortality and response rates

The beta distributions used to generate figure 2 do not fully characterise the extent of the uncertainty about the mortality and response rate estimates used in the model. As noted above, this is because the data essentially came from non-randomised, non-comparative sources, and therefore any comparisons drawn may be highly biased. For this reason, in this sensitivity analysis uniform distributions were used instead of beta distributions (figure 3). These

uniform distributions were assumed to be symmetrical around the point estimates used in the base-case analysis.

**Figure 3 Cost-effectiveness acceptability curve for alternative treatments over the 10-year time horizon assuming uniform distributions for mortality and response rates* (assessment report, page 72)**




* Pathways with a low probability of being cost effective over the payment threshold for the QALY values considered have not been shown.

## Uncertainty surrounding structure and methodological assumptions around distribution

Table 11 reports the results of the sensitivity analysis around the time horizon of the model.

**Table 11 Sensitivity around the time horizon of the model (assessment report, page 75)**

| | Strategy | Cost (£) | QALYs | Incremental cost per QALY (£) |
|---|---|---|---|---|
| Base case, for example, discount rates = 3.5% on cost | Path 1 – best supportive care | 92,811 | 2.397 | |
| | Path 7 – sunitinib | 96,688 | 2.411 | 272,365 |
| | Path 4 – imatinib 600 mg/day | 147,060 | 4.256 | 27,304 |

| | | | | |
|---|---|---|---|---|
| and benefit; time horizon = 10 years | Path 3 – imatinib 600 mg/day to sunitinib | 149,200 | 4.286 | 71,723 |
| | Path 6 – imatinib 800 mg/day | 153,901 | 3.635 | Dominated |
| | Path 5 – imatinib 800 mg/day to sunitinib | 155,828 | 3.659 | Dominated |
| | Path 2 – imatinib 600 to 800 mg/day to sunitinib | 172,152 | 4.803 | 44,359 |
| Sensitivity analysis 3, for example, discount rates = 3.5%; time horizon = 6 years | Path 1 – best supportive care | 73,246 | 1.960 | |
| | Path 7 – sunitinib | 79,720 | 2.032 | Ext Dom |
| | Path 4 – imatinib 600 mg/day | 114,433 | 3.402 | 28,560 |
| | Path 3 – imatinib 600 mg/day to sunitinib | 117,729 | 3.455 | Ext Dom |
| | Path 6 – imatinib 800 mg/day | 126,750 | 3.017 | Dominated |
| | Path 5 – imatinib 800 mg/day to sunitinib | 129,873 | 3.066 | Dominated |
| | Path 2 – imatinib 600 to 800 mg/day to sunitinib | 131,848 | 3.758 | 48,969 |
| Sensitivity analysis 4, for example, discount rates = 3.5%; time horizon = 12 years | Path 1 – best supportive care | 98,464 | 2.510 | |
| | Path 7 – sunitinib | 101,589 | 2.509 | Dominated |
| | Path 4 – imatinib 600 mg/day | 156,943 | 4.489 | 29,553 |
| | Path 3 – imatinib 600 mg/day to sunitinib | 158,421 | 4.507 | Ext Dom |
| | Path 6 – imatinib 800 mg/day | 161,295 | 3.790 | Dominated |
| | Path 5 – imatinib 800 mg/day to sunitinib | 162,637 | 3.803 | Dominated |
| | Path 2 – imatinib 600 to 800 mg/day to sunitinib | 183,961 | 5.093 | 44,736 |
| QALY: quality-adjusted life year; Ext Dom: extended dominance | | | | |

### Uncertainty surrounding transition probabilities of survival and response to treatment with imatinib 600 mg/day

The data available for imatinib 600 mg/day were sparse and suggested superior effectiveness compared with imatinib 800 mg/day. These data are potentially unreliable because they are based on non-randomised, non-comparative data, and are potentially counter intuitive (in a direct comparison imatinib 800 mg/day would not be expected to be less effective than imatinib 600 mg/day). Therefore, in this sensitivity analysis the mortality and response rates with imatinib 600 mg/day were the same as those for imatinib 800 mg/day. Table 12 shows the changes in mortality and response rates.

### Table 12 Changes to mortality and response rates (assessment report, page 76)

| | Strategy | Cost (£) | QALYs | Incremental cost per QALY (£) |
|---|---|---|---|---|
| Base case | Path 1 – best supportive care | 92,811 | 2.397 | |

| | | | | |
|---|---|---|---|---|
| | Path 7 – sunitinib | 96,688 | 2.411 | 272,365 |
| | Path 4 – imatinib 600 mg/day | 147,060 | 4.256 | 27,304 |
| | Path 3 – imatinib 600 mg/day to sunitinib | 149,200 | 4.286 | 71,723 |
| | Path 6 – imatinib 800 mg/day | 153,901 | 3.635 | Dominated |
| | Path 5 – imatinib 800 mg/day to sunitinib | 155,828 | 3.659 | Dominated |
| | Path 2 – imatinib 600 mg/day to 800 mg/day to sunitinib | 172,152 | 4.803 | 44,359 |
| Sensitivity analysis 5, survival and response rates to imatinib 600 mg/day same as imatinib 800 mg/day | Path 1 – best supportive care | 92,811 | 2.397 | |
| | Path 7 – sunitinib | 96,688 | 2.411 | 272,365 |
| | Path 4 – imatinib 600 mg/day | 126,074 | 3.635 | 24,019 |
| | Path 3 - imatinib 600 mg/day to sunitinib | 128,001 | 3.659 | 80,476 |
| | Path 2 – imatinib 600 mg/day to 800 mg/day to sunitinib | 149,703 | 4.145 | 44,603 |
| | Path 6 – imatinib 800 mg/day | 153,901 | 3.635 | Dominated |
| | Path 5 – imatinib 800 mg/day to sunitinib | 155,828 | 3.659 | Dominated |

QALY: quality-adjusted life year

### Uncertainty surrounding utility values

The sensitivity of a lower and higher utility value for disease progression was examined. The results are presented in table 13.

### Table 13 Sensitivity analysis around the utility assumed for disease progression (assessment report, page 78)

| | Strategy | Cost (£) | QALYs | Incremental cost per QALY (£) |
|---|---|---|---|---|
| Base case, for example, utility of progressive state = 0.577 | Path 1 – best supportive care | 92,811 | 2.397 | |
| | Path 7 – sunitinib | 96,688 | 2.411 | 272,365 |
| | Path 4 – imatinib 600 mg/day | 147,060 | 4.256 | 27,304 |
| | Path 3 – imatinib 600 mg/day to sunitinib | 149,200 | 4.286 | 71,723 |
| | Path 6 – imatinib 800 mg/day | 153,901 | 3.635 | Dominated |
| | Path 5 – imatinib 800 mg/day to sunitinib | 155,828 | 3.659 | Dominated |
| | Path 2 – imatinib 600 to 800 mg/day mg to sunitinib | 172,152 | 4.803 | 44,359 |
| Sensitivity analysis 6, utility of progressive state = 0.52 | Path 1 – best supportive care | 92,811 | 2.160 | |
| | Path 7 – sunitinib | 96,688 | 2.242 | Ext Dom |
| | Path 4 – imatinib 600 mg/day | 147,060 | 4.158 | 27,156 |
| | Path 3 – imatinib 600 mg/day to sunitinib | 149,200 | 4.219 | 34,911 |
| | Path 6 – imatinib 800 mg/day | 153,901 | 3.543 | Dominated |
| | Path 5 – imatinib 800 mg/day to sunitinib | 155,828 | 3.596 | Dominated |
| | Path 2 – imatinib 600 to 800 mg/day to sunitinib | 172,152 | 4.782 | 40,759 |
| Sensitivity analysis 7, | Path 1 – best supportive care | 92,811 | 2.958 | |

| | | | | |
|---|---|---|---|---|
| utility of progressive state = 0.712 | Path 7 – sunitinib | 96,688 | 2.812 | Dominated |
| | Path 4 – imatinib 600 mg/day | 147,060 | 4.488 | 35,440 |
| | Path 3 – imatinib 600 mg/day to sunitinib | 149,200 | 4.444 | Dominated |
| | Path 6 – imatinib 800 mg/day | 153,901 | 3.853 | Dominated |
| | Path 5 – imatinib 800 mg/day to sunitinib | 155,828 | 3.808 | Dominated |
| | Path 2 – imatinib 600 to 800 mg/day to sunitinib | 172,152 | 4.853 | 68,837 |
| QALY: quality-adjusted life year; Ext Dom: extended dominance | | | | |

### Uncertainty surrounding the cost of imatinib and sunitinib

The Assessment Group explored reducing the cost of imatinib 600 mg/day, imatinib 800 mg/day and sunitinib. The results are presented in table 14.

### Table 14 Sensitivity around the costs of imatinib and sunitinib (assessment report, pages 79–80)

| | Strategy | Cost (£) | QALYs | Incremental cost per QALY (£) |
|---|---|---|---|---|
| Base case, imatinib 600 mg £2406, imatinib 800 mg $3208.16, sunitinib £3138.8 | Path 1 – best supportive care | 92,811 | 2.397 | |
| | Path 7 – sunitinib | 96,688 | 2.411 | 272,365 |
| | Path 4 – imatinib 600 mg/day | 147,060 | 4.256 | 27,304 |
| | Path 3 – imatinib 600 mg/day to sunitinib | 149,200 | 4.286 | 71,723 |
| | Path 6 – imatinib 800 mg/day | 153,901 | 3.635 | Dominated |
| | Path 5 – imatinib 800 mg/day to sunitinib | 155,828 | 3.659 | Dominated |
| | Path 2 – imatinib 600 to 800 mg/day to sunitinib | 172,152 | 4.803 | 44,359 |
| Sensitivity analysis 8 (change in cost of imatinib 600 mg), imatinib 600 mg £2005, imatinib 800 mg $3208, sunitinib £3138.8 | Path 1 – best supportive care | 92,811 | 2.397 | |
| | Path 7 – sunitinib | 96,688 | 2.411 | Ext Dom |
| | Path 4 - imatinib 600 mg/day | 130,272 | 4.256 | 20,150 |
| | Path 3 - imatinib 600 mg/day to sunitinib | 132,412 | 4.286 | Ext Dom |
| | Path 6 – imatinib 800 mg/day | 153,901 | 3.635 | Dominated |
| | Path 2 – imatinib 600 to 800 mg/day to sunitinib | 155,364 | 4.803 | 45,850 |
| | Path 5 – imatinib 800 mg/day to sunitinib | 155,828 | 3.659 | Dominated |
| Sensitivity analysis 9 (change in cost of imatinib 800 mg), imatinib 600 mg £2406, imatinib 800 mg $2807, sunitinib £3138.8 | Path 1 – best supportive care | 92,811 | 2.397 | |
| | Path 7 – sunitinib | 96,688 | 2.411 | Ext Dom |
| | Path 6 – imatinib 800 mg/day | 139,988 | 3.635 | Ext Dom |
| | Path 5 – imatinib 800 mg/day to sunitinib | 141,915 | 3.659 | Ext Dom |
| | Path 4 – imatinib 600 mg/day | 147,060 | 4.256 | 29,181 |
| | Path 3 – imatinib 600 mg/day to sunitinib | 149,200 | 4.286 | Ext Dom |
| | Path 2 – imatinib 600 to 800 mg/day to sunitinib | 166,000 | 4.803 | 34,609 |
| Sensitivity analysis 10 (change in cost of | Path 7 – sunitinib | 87,533 | 2.411 | |
| | Path 1 – best supportive care | 92,811 | 2.397 | Dominated |

| | Strategy | Cost (£) | QALYs | Incremental cost per QALY (£) |
|---|---|---|---|---|
| sunitinib), imatinib 600 mg £2406, imatinib 800 mg $3208, sunitinib £2092 | Path 3 – imatinib 600 mg/day to sunitinib | 144,524 | 4.286 | 30,400 |
| | Path 4 – imatinib 600 mg/day | 147,060 | 4.256 | Dominated |
| | Path 5 – imatinib 800 mg/day to sunitinib | 151,560 | 3.659 | Dominated |
| | Path 6 – imatinib 800 mg/day | 153,901 | 3.635 | Dominated |
| | Path 2 – imatinib 600 to 800 mg/day to sunitinib | 170,364 | 4.803 | 49,940 |

QALY: quality-adjusted life year; Ext Dom: extended dominance

# 4 Issues for consideration

- Given the nature of the evidence base for this appraisal, how clinically effective does the Committee consider escalated doses of 600 mg/day or 800 mg/day imatinib to be?
- Does the Committee consider the methodology for estimating overall survival used by the manufacturer and Assessment Group appropriate?
- Does the Committee consider that subgroups with certain exon mutations should be considered separately?
- What is the Committee's view on the impact of withdrawing treatment with imatinib?
- Does the Committee consider that the adverse effect profile for imatinib at 600 mg/day or 800 mg/day following progression at 400 mg/day, or sunitinib is important for making decisions and for consideration in the economic model?
- Does the Committee consider that the treatment pathways modelled by the Assessment Group appropriately reflect clinical practice?
- What is the Committee's view on the following areas of uncertainty which were not considered due to lack of data in the economic analysis:
  - alternative assumptions about how probabilities of death and response change over time
    - disutility for sunitinib

- How does the uncertainty relating to the economic evaluation affect the Committee's conclusion of the cost effectiveness of 600mg/day and 800mg/day imatinib?

# 5 Authors

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# Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by Aberdeen Health Technology Assessment Group:

- Hislop J et al. Systematic review of the clinical and cost-effectiveness of imatinib at escalated doses of 600 mg/day or 800 mg/day for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours which have progressed on treatment at a dose of 400 mg/day. Aberdeen Health Technology Assessment Group, Institute of Applied Sciences, University of Aberdeen, March 2010.

B Submissions or statements were received from the following organisations:

I Manufacturers/sponsors

- Novartis Pharmaceuticals UK

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

- GIST Support UK
- Royal College of Physicians

# Appendix B

Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (NICE technology appraisal guidance 86)

## 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 the full guidance (see www.nice.org.uk/TA086guidance). 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.