

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Final appraisal determination**

**Imatinib for the adjuvant treatment of  
gastrointestinal stromal tumours (review of  
NICE technology appraisal guidance 196)**

This guidance was developed using the single technology appraisal (STA) process.

**1 Guidance**

- 1.1 Imatinib is recommended as an option as adjuvant treatment for up to 3 years for adults who are at high risk of relapse after surgery for KIT (CD117)-positive gastrointestinal stromal tumours, as defined by the Miettinen 2006 criteria<sup>1</sup> (based on tumour size, location and mitotic rate).
- 1.2 People currently receiving treatment initiated within the NHS with imatinib that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

**2 The technology**

- 2.1 Imatinib (Glivec, Novartis Pharmaceuticals) is a selective kinase inhibitor which binds to activated c-KIT receptors and blocks the cell signalling pathway, preventing uncontrolled cell proliferation. It is administered orally. Imatinib has a UK marketing authorisation for the 'adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive gastrointestinal stromal tumours (GISTs). Patients who have a low or very low risk of recurrence should not receive adjuvant treatment'.

---

<sup>1</sup> Miettinen M, Lasota J (2006) Gastrointestinal stromal tumours: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Archives of Pathology & Laboratory Medicine* 130: 1466–78

- 2.2 The summary of product characteristics lists the following adverse reactions for imatinib: gastrointestinal effects, oedema, rash and neutropenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 The summary of product characteristics recommends a dose of 400 mg per day of imatinib as an adjuvant treatment after surgery for GISTs. It states that optimal treatment duration is not yet established but that length of treatment in a supporting clinical trial was 36 months. Imatinib is available in doses of 100 mg (60-tab pack) and 400 mg (30-tab pack) at net prices per pack of £862.19 and £1724.39 respectively (excluding VAT; 'British national formulary' [BNF] edition 67). At a dose of 400 mg per day, drug costs for a course of treatment would be approximately £20,700 for 1 year and £62,100 for 3 years. The net price of imatinib has risen since the original appraisal of [Imatinib for the adjuvant treatment of gastrointestinal stromal tumours](#) (NICE technology appraisal guidance 196). At that time, drug costs for a 1-year course of treatment (400 mg per day) would have been approximately £19,500. Costs may vary in different settings because of negotiated procurement discounts.

### 3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Novartis Pharmaceuticals and a review of this submission by the Evidence Review Group (ERG; section 9).

#### ***Clinical effectiveness***

- 3.1 The company's systematic review identified 3 phase III randomised controlled trials that evaluated imatinib as adjuvant treatment for gastrointestinal stromal tumours (GISTs): ACOSOG Z9001, the SSGXVIII/AIO study and EORTC 62024. The company identified 12 non-randomised trials and stated that their results generally supported those from the randomised controlled trials.

- 3.2 ACOSOG Z9001 was a randomised, double-blind, placebo-controlled phase III trial of adjuvant imatinib in adults at any level of risk of recurrence after complete surgical removal of KIT (CD117)-positive GISTs. The trial compared imatinib 400 mg per day for 1 year (n=359) with placebo for 1 year (n=354). The primary outcome was recurrence-free survival (changed from overall survival). Secondary outcomes included safety. The company provided intention-to-treat analyses for recurrence-free survival and overall survival in ACOSOG Z9001, for both the full population and a high-risk population identified retrospectively using the Miettinen 2006 criteria (Miettinen and Lasota, 2006; these criteria are based on tumour size, location and mitotic rate). At the time of the primary analysis, the study was unblinded and patients randomised to placebo who had not experienced disease recurrence (n=79) were allowed to crossover to treatment with imatinib for 1 year. Of these patients, 72 opted to crossover to receive 1 year of treatment with imatinib. The company also provided data from a 5-year follow-up analysis of ACOSOG Z9001 but noted that because these data were analysed according to intention to treat, they did not take into account the impact of treatment switching.
- 3.3 The SSGXVIII/AIO study was a randomised, open-label, prospective phase III trial of adjuvant imatinib in adults with KIT (CD117)-positive GISTs that had been removed during open surgery, and were classified as being at high risk of recurrence (based on modified US National Institutes of Health consensus criteria). It compared imatinib 400 mg per day for 1 year (n=199) with imatinib 400 mg per day for 3 years (n=198). The primary outcome was recurrence-free survival and secondary outcomes included safety and overall survival. The company presented results from the SSGXVIII/AIO study based on an analysis of 397 of the 400 randomised patients. Patients in the study were considered to be at high risk of recurrence in line with the modified version of the National Institutes of Health consensus criteria, but the company was also able to present post-hoc results for people at high risk using the Miettinen 2006

criteria (n=281). The company considered the baseline patient and disease characteristics in ACOSOG Z9001 and the SSGXVIII/AIO study to be well balanced between treatment groups. Neither study recorded health-related quality of life.

- 3.4 EORTC 62024 is an ongoing randomised, controlled, open-label, observational phase III study of adjuvant imatinib in adults with resected localised KIT (CD117)-positive GISTs who were at intermediate or high risk of recurrence, as defined by the National Institutes of Health consensus criteria. The study is comparing imatinib 400 mg per day for 2 years (n=454) with no other therapy after surgery (n=454). The primary outcome was originally overall survival, but this was later changed to imatinib failure-free survival (defined as the time at which patients had to change to a different tyrosine kinase inhibitor because of disease relapse or recurrence). Results for EORTC 62024 were presented from an interim analysis but the company stated that it was not possible to determine patients at high risk of recurrence in line with the Miettinen 2006 criteria. The company also stated that imatinib failure-free survival as a surrogate outcome for overall survival was different from other GIST trials. The company emphasised that robust conclusions on the effect of adjuvant therapy for 2 years on survival cannot be drawn from this interim analysis.

### ***Results for the full trial populations***

#### **ACOSOG Z9001**

- 3.5 At the primary outcome analysis of ACOSOG Z9001 (median follow-up 19.7 months), 1-year recurrence-free survival was estimated to be 98% (95% confidence interval [CI] 96 to 100) in the imatinib group and 83% (95% CI 78 to 88) in the placebo group, which was a statistically significant difference (hazard ratio [HR] 0.35 [0.22 to 0.53],  $p < 0.0001$ ). Overall survival at 2 years was estimated to be 98.8% in the imatinib group and 97.6% in the placebo group with a hazard ratio of 0.66 (95% CI 0.22 to 2.03), which was not a statistically significant difference.

- 3.6 At the 5-year follow-up analysis of ACOSOG Z9001, approximately 75% of patients in both groups remained on study. The 5-year follow-up data showed that estimated 5-year recurrence-free survival (median follow-up 46.3 months) was 72.8% (95% CI 67.1 to 78.4) in the imatinib group and 68.4% (95% CI 63.0 to 73.8) in the placebo group. Recurrence-free survival for imatinib was statistically significantly greater in the imatinib group compared with the placebo group during follow-up (HR 0.718 [95% CI 0.531 to 0.971],  $p=0.0305$ ). The company advised that the follow-up analysis was confounded by patients who had been randomised to placebo and were recurrence-free at the time of study unblinding and had then opted to crossover to active treatment for 1 year. The company reported that a supporting analysis which removed these patients had a hazard ratio of 0.671 (95% CI 0.491 to 0.919,  $p=0.0123$ ), but did not provide any further details about the methodology.
- 3.7 The 5-year follow-up analysis showed that 5-year overall survival (median follow-up of 60.2 months) in ACOSOG Z9001 was 91.3% for the imatinib group and 91.1% for the placebo group. There was no statistically significant difference in overall survival between treatment groups during follow-up (HR 0.816 [95% CI 0.488 to 1.365],  $p=0.4385$ ). A sensitivity analysis that censored for patients eligible for crossover to 1 year of imatinib treatment gave a hazard ratio of 0.746 (95% CI 0.441 to 1.262,  $p=0.2725$ ).

### **SSGXVIII/AIO study**

- 3.8 Median duration of follow-up was 54 months for the full population. The median time to recurrence was 53.2 months for the 1-year imatinib group, but it was not reached for the 3-year imatinib group. Overall, recurrence-free survival was statistically significantly longer in the 3-year group than the 1-year group (HR 0.46 [95% CI 0.32 to 0.65],  $p<0.0001$ ; 5-year recurrence-free survival 65.6% and 47.9% respectively). There was no statistically significant difference in the risk of recurrence or death between the 1-year and 3-year treatment groups during the first 1 year of

treatment or after 3 years. However, a difference was evident from 1 to 2 years (HR 0.26 [95% CI 0.13 to 0.53]) and from 2 to 3 years (HR 0.17 [95% CI 0.07 to 0.39]) after randomisation.

- 3.9 Overall survival was statistically significantly greater in the 3-year imatinib group than in the 1-year group (HR 0.45 [95% CI 0.22 to 0.89],  $p=0.019$ ; 5-year overall survival 92.0% and 81.7% respectively). However, there was no statistically significant difference in 5-year GIST-specific survival between the 2 groups (88.5% in the 3-year group compared with 95.1% in the 1-year group; HR 0.46 [95% CI 0.19 to 1.14],  $p=0.09$ ).

### **EORTC 62024**

- 3.10 The EORTC 62024 interim analysis was for a median follow-up of 4.7 years. Of the 908 patients who had been randomised to treatment, 835 were eligible for assessment. Recurrence-free survival for the total study population was statistically significantly greater in the imatinib group than in the observation group at 3 years (84% compared with 66%,  $p<0.001$ ) and 5 years (69% compared with 63%,  $p<0.001$ ). There were no statistically significant differences in 5-year imatinib failure-free survival between the imatinib and observation groups (87% compared with 84%; HR 0.80 [98.5% CI 0.51 to 1.26],  $p=0.23$ ). Overall survival at 5 years was similar in the imatinib and observation groups (100% and 99% respectively).

### ***Results for high-risk subgroups (Miettinen 2006 criteria)***

#### **ACOSOG Z9001**

- 3.11 Using the ACOSOG Z9001 primary analysis, the company identified 165 patients at high risk of disease recurrence according to the Miettinen 2006 criteria. For these patients, 1-year recurrence-free survival was 98.7% in the imatinib group and 56.1% in the placebo group. An analysis of overall survival showed no statistically significant difference between treatment groups overall ( $p=0.0764$ ). Overall survival at 2 years was 100%

in the imatinib group and 94.7% in the placebo group; at 4 years it was 100% and 90.9% respectively.

3.12 At the 5-year follow-up analysis, 103 high-risk patients had been identified in the imatinib group and 98 high-risk patients in the placebo group. An improvement in recurrence-free survival was observed in the imatinib group compared with the placebo group (HR 0.608 [95% CI 0.417 to 0.886],  $p=0.009$ ). The difference between the imatinib and placebo groups was at its greatest 18 months after randomisation (86.7% [95% CI 79.6 to 93.7] compared with 49.9% [95% CI 39.7 to 60.2] respectively), and then decreased over time (reaching 37.9% [95% CI 25.9 to 49.9] and 32.1% [95% CI 21.6 to 42.6] respectively at 5 years). The company noted that, unlike the primary analysis, the 5-year follow-up analysis was confounded by placebo patients who were recurrence-free at the time of study unblinding opting to crossover to active treatment for 1 year.

3.13 At the clarification stage, the company provided a report that used different methods of adjusting for treatment crossover in ACOSOG Z9001. The methods were: a rank-preserving structural failure time model, the iterative parameter estimation algorithm, inverse probability of censoring weights (IPCW) and per-protocol analyses that censored crossovers at the time of switching or excluded them altogether. The report concluded that the IPCW method was the most reliable for recurrence-free survival and overall survival. In patients at high risk of disease recurrence, the IPCW hazard ratio for recurrence-free survival was 0.50 (95% CI 0.3 to 0.78), which was similar to the simple, unweighted, per-protocol censoring approach (HR 0.52 [95% CI 0.35 to 0.77]). Both provide a numerically lower hazard ratio for recurrence-free survival than the intention-to-treat analysis (HR 0.61 [95% CI 0.42 to 0.89]). For overall survival, the IPCW hazard ratio in the high-risk group was 0.76 (95% CI 0.36 to 1.62), which was similar to the simple, unweighted per-protocol censoring approach (HR 0.79 [95% CI 0.40 to 1.55]). The report stated that these were

numerically lower than the hazard ratio for the intention-to-treat analysis (0.93 [95% CI 0.47 to 1.83]).

### **SSGXVIII/AIO study**

- 3.14 Overall, 70% of patients were at high risk of recurrence according to the Miettinen 2006 criteria (142 in the 1-year imatinib group and 139 in the 3-year imatinib group). At the 5-year follow-up, recurrence-free survival was longer in the 3-year group than in the 1-year group (HR 0.43 [95% CI 0.30 to 0.62],  $p < 0.0001$ ). Median time to recurrence was 35.9 months in the 1-year adjuvant imatinib group and 71.8 months in the 3-year adjuvant imatinib group.
- 3.15 Overall survival was greater in the 3-year imatinib group compared with the 1-year imatinib group (HR 0.39 [95% CI 0.19 to 0.79],  $p = 0.007$ ). Overall survival rates were higher with 3-year imatinib than 1-year imatinib at 4 years (94.5% [95% CI 88.6 to 97.3] compared with 83.0% [95% CI 73.8 to 89.1] respectively) and at 5 years (89.5% compared with 74.2%).

### **EORTC 62024**

- 3.16 The EORTC 62024 interim analysis showed that for a subgroup of patients with high-risk disease according to the National Institutes of Health consensus criteria, there was no statistically significant difference in 5-year imatinib failure-free survival between the imatinib and observation groups (77% and 73% respectively,  $p = 0.44$ ).

### ***Indirect comparison***

- 3.17 The company noted the absence of a head-to-head trial comparing no adjuvant treatment with 3 years of adjuvant imatinib, and considered the feasibility of an indirect comparison using a log hazard ratio with pairwise treatment comparisons, which assumes constant proportional hazards. However, after inspecting the Kaplan–Meier curves for recurrence-free survival in ACOSOG Z9001 and the SSGXVIII/AIO study, the company considered the shapes of the curves to be different for each treatment arm



and decided that the assumption of proportional hazards did not hold. From this, it concluded that a simple parametric proportional hazards model fitted to these curves would not accurately estimate mean survival and so did not conduct an indirect comparison using this method. For the purpose of the economic model, an indirect comparison using non-standard methodology was presented (see section 3.30).

### **Adverse events**

- 3.18 In ACOSOG Z9001, grade 3 or 4 adverse events occurred in 104 patients (31%) in the imatinib group and 63 patients (18%) in the placebo group. The most common of these were neutropenia (3% in the imatinib group and 1% in the placebo group), abdominal pain (3.6% compared with 1.7%), dermatitis (3% compared with 0%), nausea (2.4% compared with 1.2%) and elevated alanine aminotransferase levels (2.7% compared with 0%). The company reported that the adverse event rate was consistent with imatinib use in chronic myeloid leukaemia and metastatic GISTs.
- 3.19 In the SSGVXIII/AIO study, the incidence of adverse events was similar in patients receiving imatinib for 3 years (198/198, 100%) and for 1 year (192/194, 99.0%). The incidence of grade 3 or 4 events was 20.1% in the 1-year group and 32.8% in the 3-year group, with leukopenia and diarrhoea being the most common. More patients in the 3-year group (51 patients, 25.8%) discontinued imatinib than in the 1-year group (25 patients, 12.9%).
- 3.20 No safety data from EORTC 62024 had been reported before the company provided its evidence submission.

### **ERG's comments**

- 3.21 The ERG stated that the company's submission contained a generally unbiased estimate of imatinib's treatment effect, and noted that the randomised controlled trials had been well conducted (although 2 trials were open label and 2 had experienced a change in the primary

outcome). It indicated that the main limitation of the clinical evidence was that the treatment effect for high-risk patients was based on retrospective subgroup analyses that varied in the proportion of total number of randomised patients (the lowest being 28%), meaning that these are most likely underpowered.

- 3.22 The ERG stated that differences in baseline patient characteristics between the treatment arms were more pronounced in the Miettinen high-risk subgroups in than the full trial populations, indicating selection bias. However, the ERG was unclear if the imbalances were statistically significant. Although results were similar for the full population and high-risk subgroups (in terms of statistically significant recurrence-free and overall survival differences between trial arms), the ERG concluded that caution was necessary when interpreting the subgroup results.
- 3.23 The ERG highlighted that there were differences in the results for overall survival between ACOSOG Z9001 and the SSGXVIII/AIO study, and that neither of these trials was statistically powered to detect a difference in this outcome. In ACOSOG Z9001, there were few deaths overall and there was no statistically significant difference in overall survival for imatinib for 1 year compared with placebo at 2 years and 5 years. It further noted that even in the additional analyses that removed patients who had crossed over to active treatment, the difference between trial arms generally remained non-statistically significant. In the SSGXVIII/AIO study, there were comparatively more deaths and at 5 years there was statistically significantly longer overall survival associated with 3-year imatinib treatment compared with 1-year treatment. The ERG stated that although the differences in the overall death rates could potentially be explained by differences in patient characteristics (or other variables) between the 2 trials, the available evidence suggested that extending imatinib treatment to 3 years was associated with longer overall survival than 1-year treatment.

- 3.24 The ERG was concerned that the high degree of crossover at study unblinding in ACOSOG Z9001 may have confounded the results and was aware that the company had presented analyses in which patients were censored at the time of crossover. The ERG also reviewed the supplemental report that used various statistical methods to adjust for patient crossover in ACOSOG Z9001, which was provided as part of the company's response to clarification. The ERG agreed that all the methods had advantages and limitations in the assumptions made and their applicability to ACOSOG Z9001, but that the IPCW method appeared to be appropriate. The ERG noted that all methods produced hazard ratios that were lower than the intention-to-treat analysis and therefore more favourable to imatinib. It also noted that the IPCW method produced hazard ratios that were similar to a per-protocol analysis that simply censors switchers at the time of crossover. The ERG considered this to be conservative because both of these approaches gave hazard ratios that were slightly lower (approximately 0.1 to 0.2) than the intention-to-treat analysis, compared with bigger differences for some of the other methods.
- 3.25 The ERG noted that although the company did not present subgroup analyses mentioned in the NICE scope, the SSGXVIII/AIO study reported recurrence-free survival for predefined exploratory subgroup analyses according to tumour site, tumour size and tumour mutation site for the full population discussed in the company's submission. The ERG noted, however, that no results for the high-risk group in the SSGXVIII/AIO study had been reported in the journal publication. The results of these subgroup analyses were similar to those of the full population. In the genetic mutational status subgroup, there was a statistically significant treatment effect favouring imatinib for 3 years for patients with the KIT exon 11 mutation, but not for other mutations or for patients with no mutation (but the numbers in these latter groups were smaller). The ERG advised that these analyses were exploratory and were likely to be underpowered.

### **Cost effectiveness**

3.26 The company's cost-effectiveness analysis included patients at high risk of recurrence based on the Miettinen criteria (that is, a subset of the licensed indication described in section 2.1). The economic model compared adjuvant imatinib (1 or 3 years) after surgery with no adjuvant treatment. The company advised that this model was based on that submitted for NICE technology appraisal guidance 196 (that is, the guidance under review).

3.27 The company's model used a Markov state-transition approach. During each monthly cycle of the model, patients could:

- remain recurrence-free
- have a recurrent GIST (first or second recurrence)
- have progressive disease (and be treated with best supportive care)
- die (from GISTs or other causes).

Transition probabilities between the health states were based on the treatment-associated probabilities of recurrence or discontinuation. The model had a lifetime time horizon of 50 years, a 1-month cycle length, and a discount rate of 3.5% was applied to costs and health effects. The analysis was conducted from an NHS and personal social services perspective.

3.28 All patients entering the model were recurrence-free after surgery. They received either observation or adjuvant imatinib (for 1 or 3 years), and progressed through the model as follows:

- Patients who experienced a first recurrence while taking adjuvant imatinib therapy were assumed to then receive sunitinib (90%) or best supportive care (10%).
- Patients who experienced a first recurrence after receiving surgery only, or after discontinuing or completing planned adjuvant imatinib treatment, received first-line imatinib (400 mg per day treatment).

Patients who discontinued adjuvant imatinib because of adverse events were assumed to have the same rate of recurrence as patients remaining on adjuvant imatinib because they were not censored when calculating recurrence-free survival. The company assumed that 15% of patients had further surgery but this was not explicitly modelled (only costs were included, not effectiveness).

- After a second progression or recurrence, or discontinuation because of adverse events, most patients (90%) received sunitinib then best supportive care after further progression.
- Patients receiving best supportive care were assumed to have progressive disease and remained in this health state until death.

Moving between the different health states was dependent on the probabilities of events (recurrences, adverse events and death), which were taken from the SSGXVIII/AIO study, ACOSOG Z9001 and published sources. Before recurrence, it was assumed that death would be from non-GIST causes only. After recurrence, the monthly probability of death was 0.043 during or after best supportive care, 0.013 during or after imatinib and 0.040 during or after sunitinib (this was assumed to be independent of adjuvant treatment). Death due to non-GIST causes was based on published government life tables for England.

- 3.29 Because there was no head-to-head trial directly comparing surgery alone with 3 years of adjuvant imatinib, the company conducted an indirect comparison using data from the SSGXVIII/AIO study and ACOSOG Z9001. It considered that the assumption of constant proportional hazards was not met and so did not use the log hazard ratio with pairwise treatment comparisons. Instead, the baseline risk of recurrence for patients treated with surgical resection only was taken from ACOSOG Z9001. A parametric survival model was fitted to patient-level data from the placebo arm of the trial using data from the primary analysis (at study unblinding and before cross-over was allowed) and restricted to patients classified at high risk of recurrence according to the Miettinen

criteria. The Miettinen risk group for patients in this trial was derived from the 5-year follow-up analysis. The company examined goodness-of-fit (visually and using statistical methods), and assessed the extrapolation beyond the trial's duration for validity compared with the published results of other trials.

3.30 The company calculated a treatment effect for imatinib then applied it to the baseline risk of recurrence after surgery, only to estimate the risk of recurrence for patients treated with adjuvant imatinib therapy after surgery. The treatment effect was estimated for 2 distinct periods: during treatment and immediately after stopping treatment, to capture the differences in events rates observed in each period:

- During treatment, the same effect for imatinib was assumed regardless of treatment duration (1 or 3 years), with an estimated hazard ratio of 0.111 (95% CI 0.043 to 0.281) for risk of recurrence compared with placebo. This was calculated from the hazard ratio for recurrence from ACOSOG Z9001 using the Cox proportional hazards model with the data truncated at 12 months.
- After stopping treatment, when compared with placebo the estimated hazard ratios were 0.519 (95% CI 0.297 to 0.906) for 1 year of adjuvant imatinib and 0.344 (95% CI 0.160 to 0.741) for 3 years of adjuvant imatinib. These were estimated using datasets of patients who had not experienced disease recurrence during adjuvant treatment. The modified dataset from ACOSOG Z9001 was used to calculate the hazard ratio for recurrence for 1-year adjuvant imatinib compared with surgery only. The modified dataset from SSGXVII/AIO was used to calculate the hazard ratio for recurrence for 3-year adjuvant imatinib compared with 1-year adjuvant imatinib. These estimates of treatment effect were then combined using a frequentist indirect comparison using a fixed effects model to estimate the hazard ratio for recurrence for 3-year adjuvant imatinib compared with surgery only.

To estimate the risk of recurrence for patients treated with surgical resection followed by 1 and 3 years of adjuvant imatinib, the company then applied the estimated treatment effect for imatinib (during and after stopping treatment) to the baseline risk of recurrence for patients treated with surgery only. In its clarification response, the company advised that resistance to imatinib was implicitly included in the economic model through the response rates obtained in the clinical trials (in the adjuvant and advanced settings).

3.31 Health-related quality of life was not recorded in ACOSOG Z9001 and the SSGXVIII/AIO study. The company did a systematic review, which identified 3 potentially relevant health-related quality of life publications, to derive the utility values for its economic model:

- The company assumed that patients with GISTs who had undergone successful surgery and were recurrence-free had the same utility as healthy individuals of the same age (0.822).
- Patients receiving adjuvant imatinib treatment had a utility value of 0.741 (a utility decrement of 0.081 was applied to all patients in the base case to reflect adverse effects).
- Patients receiving first-line treatment with imatinib or sunitinib (that is, after first recurrence) had a utility value of 0.739.
- A utility value of 0.739 was also used for patients taking sunitinib after a second recurrence.
- The utility value for the best supportive care health state was 0.577.

3.32 The company's literature review did not identify any primary studies estimating the resource use associated with treating GISTs in the UK. Health state costs were derived from NHS reference costs, UK clinical guidelines and assumptions. The 1-time onset cost of recurrence was £1430.69 and was assumed to include 1 GP visit, 1 specialist outpatient visit, 1 CT scan and, where appropriate, surgical resection (assumed to be 15% of patients). Annual costs of continuing phase of cancer (defined

as the period between the first year after diagnosis and the last year of life) were estimated at £793.50 (an average of 2 GP visits, 5 outpatient visits and 0.5 CT scans). Costs for the last year of life were estimated to be £17,380. Drug costs for imatinib and sunitinib were taken from the British national formulary (October 2013), and the company incorporated the patient access scheme for the second-line use of sunitinib. Costs for treating adverse events with imatinib were based on the most frequent grade 3 and 4 adverse events in SSGXVIII/AIO (neutropenia, fatigue, nausea and vomiting, and diarrhoea). No costs were assumed for treating adverse effects in patients who received surgical resection only.

- 3.33 The company's base-case results showed that adjuvant imatinib treatment (1 year and 3 years) was associated with greater quality-adjusted life year (QALY) gains and higher costs than no adjuvant treatment. In the company's fully incremental analysis, the incremental cost-effectiveness ratio (ICER) for 1 year's treatment with imatinib compared with no adjuvant treatment was £3509 per QALY gained (incremental costs £7844; incremental QALYs 2.24). The ICER for 3 years' treatment with imatinib compared with 1 year was £16,006 per QALY gained (incremental costs £22,931; incremental QALYs 1.43).
- 3.34 At the clarification stage, the company reproduced the base-case analysis using the 5-year follow-up data for recurrence-free survival for the placebo arm of ACOSOG Z9001, which did not adjust for the crossover of patients from placebo to imatinib. In the company's fully incremental analysis, the ICER for 1 year's treatment with imatinib compared with no adjuvant treatment was £8556 per QALY gained. The ICER for 3 years' treatment with imatinib compared with 1 year was £17,057 per QALY gained (incremental costs and QALYs not provided).
- 3.35 The company carried out a range of deterministic sensitivity analyses to test the model's structural assumptions and confirmed that the ICERs were insensitive to changes in costs, utility values and most transition



probabilities. It reported that varying the 'on-treatment' and 'off-treatment' hazard ratios according to their upper and lower confidence limits caused changes in the ICERs, with all except 1 remaining below £30,000 per QALY gained. It confirmed that when the upper limits for both were included, the ICERs increased from £3509 per QALY gained to £30,058 per QALY gained for 1 year's treatment with imatinib compared with no adjuvant treatment, and from £16,006 per QALY gained to £29,162 per QALY gained for 3 years' treatment with imatinib compared with 1 year.

3.36 The company undertook probabilistic sensitivity analyses using 1000 iterations. Like the deterministic base-case analysis, these showed that adjuvant treatment with imatinib (1 year and 3 years) was associated with greater QALY gains and higher costs than no adjuvant treatment. For the pairwise comparisons with no adjuvant treatment, the ICER for 1 year's treatment with imatinib was £3635 per QALY gained (incremental costs £8375; incremental QALYs 2.30) and the ICER for 3 years' treatment with imatinib was £7950 per QALY gained (incremental costs £30,958; incremental QALYs 3.89). The company also provided a fully incremental analysis. The ICER for 1 year's treatment with imatinib compared with no adjuvant treatment remained at £3635 per QALY gained, and the ICER for 3 years' treatment with imatinib compared with 1 year was £14,205 per QALY gained (incremental costs £22,583; incremental QALYs 1.59). At a maximum acceptable ICER of £20,000 per QALY gained, the probability of imatinib being cost effective was 41.7% for 1 year's treatment and 58.3% for 3 years' treatment. When the maximum acceptable ICER was increased to £30,000 per QALY gained, the probability of 1 year's treatment with imatinib being cost effective decreased to 30.9%, whereas the probability of 3 years' imatinib treatment being cost effective rose to 69.1%.

3.37 The company conducted scenario analyses to further explore uncertainty. It found that there was little impact on the ICERs for any of the following scenarios:

- using different parametric distributions for the survival curves
- allowing dose escalation of imatinib in the metastatic setting
- varying the proportion of patients receiving best supportive care (instead of active treatment) after recurrence
- extending survival in the post-recurrence health states.

The company stated that its sensitivity analyses showed the ICERs were fairly insensitive to changes in parameters and assumptions, with the ICERs generally remaining below £20,000 per QALY gained. It noted that key drivers of the model were treatment effect over time and the time horizon of the analysis, and that changes in these parameters caused some ICERs to exceed £20,000 per QALY gained.

- 3.38 In response to a request made at the clarification stage, the company provided scenario analyses that assumed imatinib's treatment effect declined over time during the off-treatment period. The company's ICERs for adjuvant imatinib (1 or 3 years) compared with no adjuvant treatment, and for adjuvant imatinib for 3 years compared with 1 year, increased when the off-treatment hazard ratio was reduced to 75%, 50% or 25% after 5 years. The ICERs ranged from £4569 per QALY gained to £34,683 per QALY gained.

### ERG's comments

- 3.39 The ERG stated that the model structure and methodology used by the company was a reasonable approach to modelling the cost effectiveness of imatinib as adjuvant treatment for GISTs. It observed that the company had made some amendments to the model in response to comments during the original appraisal of [Imatinib for the adjuvant treatment of gastrointestinal stromal tumours](#) (NICE technology appraisal guidance 196). However, the ERG raised several concerns with the estimates and assumptions in the current model.
- 3.40 The ERG noted that the company's model did not explicitly model disease progression and instead defined the health states based on treatment. As

a result, the ERG considered that some of the later progressions in the model did not seem appropriate (for example, patients discontinuing treatment because of adverse events may transition to best supportive care without experiencing disease recurrence).

- 3.41 The ERG had reservations about the validity of some utility values. It stated that although the majority of these were based on the only published set of values for patients with advanced GISTs, insufficient methodological detail had been reported and there was a lack of information about respondents such as baseline characteristics of respondents, sample size, response rate or the valuation method adopted.
- 3.42 The ERG stated that there was substantial uncertainty over the company's methods used to derive the baseline risk of recurrence and relative treatment effects for adjuvant imatinib in its economic model. The ERG was aware that that the company had adopted these methods to avoid confounding by crossover in the placebo arm of ACOSOG Z9001. The ERG agreed that the Kaplan–Meier curves indicated changes in the shape of the survival curves after stopping adjuvant imatinib treatment, but stated that these trends might have been more apparent, and the cut-points more easily identified and justified, by plotting the hazard function rather than the Kaplan–Meier curves. Regarding the approach to estimating 'on-treatment' treatment effect, the ERG was concerned that the company had derived the treatment effects using a semi-parametric model (Cox proportional hazards) then applied these to fully parametric survival functions used to derive baseline risk of recurrence (that is, with surgery alone). The ERG noted that the on-treatment recurrence-free hazard ratio for the high-risk population, using the Cox proportional hazards model with the data truncated at 12 months, was 0.111 (95% CI 0.043 to 0.281). The ERG noted that this was lower than the hazard ratio of 0.265 (95% CI 0.148 to 0.477) that was reported in the clinical-effectiveness section of the company's submission, and was unclear

whether the difference was caused by truncating the data at 12 months or the retrospective reclassification of additional high-risk patients. The ERG noted that the company's submission does not state clearly the maximum follow-up for placebo patients before cross-over (censoring), so it was unable to judge the duration over which the baseline survival function was modelled. The ERG noted that the company's overall approach had required considerable post-hoc reorganisation of the trial data and was uncertain if this had introduced biases into the estimated effects. The ERG concluded that it may be more appropriate to use the crossover-adjusted recurrence-free survival estimates to derive clinical effectiveness parameters from ACOSOG Z9001.

3.43 The ERG also expressed substantial uncertainty about the most appropriate assumptions for extrapolating the effectiveness of adjuvant imatinib beyond the follow-up period of the randomised controlled trials providing baseline and relative treatment effects for adjuvant imatinib. The maximum follow-up in the randomised controlled clinical trials was around 9 years, and these effects were extrapolated over a lifetime (40-year) time horizon in the model. In particular, the ERG was concerned about the face validity of these survival extrapolations based on the Gompertz function, which suggested a long-term maintenance of recurrence-free survival in around 30% of patients who received 3 years' adjuvant imatinib treatment. The ERG was concerned that this may not be appropriate in a population initially identified as being at high risk of recurrence. This compares with approximately 20% recurrence-free survival at 20 years using the log-logistic model or approximately 5% using the other functions.

3.44 The ERG assessed the validity of the results generated using the company's model compared with the clinical trials. The ERG considered that there was a reasonable fit for recurrence-free survival compared with the clinical trials at 5 years for patients who had received adjuvant imatinib (for 1 year or 3 years) and at 2 years for patients who had received no adjuvant treatment. However, the ERG considered the fit for overall

survival to be poorer and noted that the company's model underestimated overall survival at 5 years for patients who had received 1- or 3-year adjuvant imatinib treatment, and at 2 years for patients who had received no adjuvant treatment. The ERG added that there was uncertainty around estimated long-term extrapolation of recurrence-free survival, and noted that long-term recurrence-free survival differed widely according to the parametric distribution chosen. The ERG noted that the parametric distribution chosen by the company produced the most favourable ICER for adjuvant imatinib treatment.

- 3.45 The ERG expressed uncertainty over the company's approach to incorporating costs for sunitinib in the model. It noted that the company estimated sunitinib use by allowing for a 21% probability of discontinuation per month, which resulted in an estimated mean duration of treatment of 3.48 cycles. The ERG considered that the company had over-estimated sunitinib use because the 2 clinical trials for sunitinib reported a median of 2 cycles of treatment. Based on the clinical trial results, the ERG calculated that 2.89 cycles would be a more appropriate mean estimate for use in the model. Using the ERG's estimate instead of the company's reduced the monthly cost of sunitinib (with a patient access scheme) from £1615.34 to £1231.17.
- 3.46 The ERG reviewed how the company had explored uncertainty in its economic model. It considered that both the parameters that were varied and the ranges used in the one-way sensitivity analyses were appropriate and comprehensive. The ERG indicated that the company's probabilistic sensitivity analyses included most of the variables within the model, that the probability distributions had been correctly applied and that the methods used to assess parameter uncertainty were appropriate. Nevertheless, the ERG noted that the sensitivity analyses in the company's submission did not include varying either the cost of imatinib, or the proportion receiving sunitinib or best supportive care after recurrence.

### ERG exploratory analyses

3.47 The ERG identified some errors in the utility values and management costs used in the company's submission and provided corrected base-case results. In a fully incremental analysis, the ERG's ICER for 1-year imatinib treatment compared with no adjuvant treatment was £3612 per QALY gained (incremental costs £7819; incremental QALYs 2.16). The ERG's ICER for 3 years' treatment with imatinib compared with 1 year was £16,663 per QALY gained (incremental costs £22,928; incremental QALYs 1.38). These corrected base-case ICERs were similar to the original base-case results provided by the company (see section 3.33).

3.48 The ERG explored issues and uncertainties that it had identified in the company's submission, including the assumption of a continuing off-treatment effect of adjuvant imatinib, the parametric distribution used for modelling recurrence-free survival, resistance to imatinib and the mortality estimates used for the recurrence health states. The ERG did the following analyses:

- It assumed no long-term off-treatment benefit after the reported follow-up, and reported that changing this assumption did not markedly alter the cost-effectiveness results.
- It used the exponential distribution to model recurrence-free survival and found that the ICERs increased to £9386 per QALY gained for 1-year adjuvant imatinib treatment compared with no treatment and to £18,741 per QALY gained for 3-year compared with 1-year imatinib treatment.
- It investigated the effect of varying the off-treatment hazard ratio for 1-year imatinib treatment compared with no adjuvant treatment, but maintaining the hazard ratio for 3-year compared 1-year imatinib treatment. The ERG reported that the ICERs were very sensitive to changes in the off-treatment hazard ratio for 1-year adjuvant imatinib treatment compared no adjuvant treatment:

- The ERG ran the analysis using the 95% upper confidence interval of the 5-year update unadjusted hazard ratio estimate of 0.727 (provided by the company at the clarification stage).
- It found that the ICER for 1-year adjuvant imatinib treatment compared with no adjuvant treatment increased to £10,489 per QALY gained.
- The ERG investigated the effect of assuming resistance to imatinib developing at recurrence in 15% of patients who were initially treated with adjuvant imatinib. Patients who were assumed not to respond to retreatment progressed to sunitinib. This assumption produced marginal changes to the ICERs.
- It varied the mortality rate by using the lower confidence interval estimates for GIST mortality in the post-recurrence health states, which slightly reduced the ICER for 1-year adjuvant imatinib compared with no treatment (from £3612 to £1595 to per QALY gained). There was little effect on the ICER for 3-year adjuvant imatinib compared with 1-year adjuvant imatinib (which decreased from £16,663 to £16,112 per QALY gained).
- It assumed that 15% of patients initially treated with adjuvant imatinib and re-challenged upon recurrence would not respond (based upon SSGXVIII/AIO data), and would then receive sunitinib. This produced marginal changes in the ICERs.

The ERG then ran an analysis that combined several of these factors (no treatment benefit after the end of trial, exponential distribution for recurrence-free survival and lower mortality rates). This increased the ICERs to £12,122 per QALY gained for 1-year adjuvant treatment compared with no treatment and £29,966 per QALY gained for 3-year treatment compared with 1-year treatment.

3.49 Full details of all the evidence are in the committee papers, which can be found on the web page for imatinib.

## 4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of imatinib as an adjuvant treatment, having considered evidence on the nature of gastrointestinal stromal tumours (GISTs) and the value placed on the benefits of imatinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

- 4.1 The Committee discussed the clinical treatment pathway for KIT (CD117)-positive GISTs in England, noting that [NICE technology appraisal guidance 196](#) had not recommended imatinib for the adjuvant treatment of GISTs. It heard from the clinical experts that people at high risk of recurrence had the greatest clinical need for adjuvant treatment after complete resection of KIT (CD117)-positive GISTs. It heard that these patients were eligible to receive adjuvant imatinib for up to 3 years via the Cancer Drugs Fund and that the remaining people with GISTs would be monitored for signs of recurrence ('watchful waiting', when the person's condition is monitored but they are not given any treatment). The Committee heard from patient experts that people place a high value on the psychological impact of taking a drug after surgery to increase their chances of remaining cancer free, as well as the physical and social advantages that this can bring (such as being able to take part in physical exercise and social activities). The clinical experts explained that later in the treatment pathway, imatinib was standard care at disease recurrence ([NICE technology appraisal guidance 86](#)), and that most patients would subsequently receive sunitinib ([NICE technology appraisal guidance 179](#)). The Committee heard that regorafenib was now available via the Cancer Drugs Fund at the end of the treatment pathway for certain patients with advanced GISTs who had previously received imatinib and sunitinib.
- 4.2 The Committee noted the changes in the evidence base since the publication of [NICE technology appraisal guidance 196](#) (that is, the



guidance under review). The Committee was aware that the clinical data in the company's submission for the original appraisal had focused on the primary analysis data from ACOSOG Z9001. It recalled that in the original appraisal, the Committee had concluded that these data were too immature to enable conclusions to be drawn about key aspects of imatinib's clinical effectiveness, and observed that the company's current submission included 3 phase III studies: ACOSOG Z9001, SSGXVIII/AIO and EORTC 62024. It further noted that the company's current submission described analyses with median follow-up of 4–5 years, and that outcomes included overall survival. The Committee noted the ERG's opinion that the studies were generally well designed and executed. The Committee concluded that the clinical-effectiveness evidence was suitable for its decision-making.

- 4.3 The Committee discussed how risk of recurrence after complete resection of GIST had been classified in the clinical trials and whether this was generalisable to clinical practice in England. It noted that 2 of the trials had stratified patients according to risk of recurrence using National Institutes of Health or modified National Institutes of Health criteria and that the third had enrolled patients at any risk of recurrence. It heard from the clinical experts that the Miettinen 2006 criteria (Miettinen and Lasota, 2006<sup>2</sup>) are the most commonly used tool in clinical practice in England to predict risk of recurrence, and that these had largely superseded the National Institutes of Health criteria. It heard from the clinical experts that patients at high risk of recurrence according to the Miettinen criteria are mostly likely to be considered for adjuvant treatment, based on tumour size, location and mitotic rate. The Committee was aware of concerns raised in response to consultation that although adopting the Miettinen 2006 criteria to identify patients at high risk is currently appropriate, research is underway that could at some point in the future inform a more accurate way of assessing risk of recurrence. However, the Committee

---

<sup>2</sup> Miettinen M, Lasota J (2006) Gastrointestinal stromal tumours: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Archives of Pathology & Laboratory Medicine* 130: 1466–78

agreed that it had to make recommendations on the basis of currently available information. It noted that technology appraisal review guidance may be reviewed when there is significant new evidence that is likely to change the recommendations, as described in [‘Guide to the processes of technology appraisal’](#), and concluded no changes to its recommendations were necessary at present. The Committee was aware that the marketing authorisation for imatinib as an adjuvant treatment for KIT (CD117)-positive GISTs was for people who were at ‘significant’ risk of relapse after complete resection, but observed that this group had not been defined by the regulatory agency.

- 4.4 The Committee considered the company’s subgroup analyses according to risk of recurrence, and noted that these were for patients at high risk of recurrence according to the Miettinen criteria (and this subgroup had been included in the company’s base case in the economic model). The Committee heard from the clinical experts that this subgroup was appropriate because it consisted of patients who had the greatest clinical need and whose risk had been classified according to criteria that were commonly used in England. The Committee also heard from the company that evidence for patients at only moderate risk of recurrence was limited and that there was no evidence for 3-year imatinib treatment in this group. The Committee did have some concerns about selection bias because the differences in baseline characteristics between treatment groups were more pronounced in the high-risk subgroups than the full patient population. However, it concluded that the evidence relating to the subgroup at high risk of recurrence according to the Miettinen criteria was the most appropriate for its decision-making.
- 4.5 The Committee reviewed the clinical-effectiveness evidence for adjuvant imatinib compared with placebo in people with resected KIT (CD117)-positive GISTs at high risk of recurrence according to the Miettinen criteria. It observed it was difficult to draw any conclusions about an overall survival benefit using the primary analysis of ACOSOG Z9001

because the data were immature (that is, there had been few deaths). It noted, however, that there was a statistically significant benefit for recurrence-free survival with 1-year imatinib in the 5-year follow-up analysis (HR 0.608 [95% CI 0.417 to 0.886],  $p=0.009$ ) and that the treatment effect could have been underestimated because of confounding factors (see section 3.2). The Committee acknowledged that crossing over from placebo to active treatment after the ACOSOG Z9001 primary analysis could confound subsequent analyses of recurrence-free survival and overall survival, causing imatinib's treatment effect to be underestimated. It was aware that statistical methods could be used to adjust for this crossover effect. It agreed with the company and the ERG that the inverse probability of censoring weights (IPCW) method was an appropriate way to adjust for the crossover effect in the high-risk group in ACOSOG Z9001. It noted that adjusting the 5-year analyses using the IPCW method lowered the hazard ratios for recurrence-free survival and overall survival compared with the unadjusted hazard ratios (that is, the treatment effect of imatinib appeared greater once the crossover effect had been removed; see section 3.13). The Committee noted that after adjusting for crossover, there was still no statistically significant difference in overall survival between the imatinib and placebo high-risk groups (HR 0.76, 95% CI 0.36 to 1.62). The Committee concluded that the clinical trial evidence showed that 1-year adjuvant imatinib increased recurrence-free survival compared with placebo. However, it was unclear if the increase in recurrence-free survival resulted in longer overall survival, even after the analyses had been adjusted using statistical methods to correct the crossover effect.

- 4.6 The Committee reviewed the clinical-effectiveness evidence for 3-year adjuvant imatinib compared with 1-year adjuvant imatinib in people with resected KIT (CD117)-positive GISTs at high risk of recurrence according to the Miettinen criteria. It observed that recurrence-free survival and overall survival at 5 years was statistically significantly longer in the 3-year arm compared with the 1-year arm. However, the Committee noted that

there were very small patient numbers towards the end of follow-up, with fewer than 10 patients per arm from 30 months onwards. It considered that this added uncertainty to the results, and it was unclear if this treatment benefit would persist over time after stopping treatment. The Committee concluded that adjuvant treatment with imatinib for 3 years was more clinically effective than giving it for 1 year during clinical trial follow-up, but that there was uncertainty whether this benefit would continue over the longer term.

- 4.7 The Committee discussed the role of genetic mutational analysis in identifying patients who would be more or less likely to benefit from adjuvant imatinib treatment. It heard from the clinical experts that it would be useful to perform mutational analysis before starting treatment because some GISTs were likely to be resistant to treatment with imatinib and sunitinib, such as those with a PDGFRA exon 18 D842V mutation. However, the Committee also heard that this patient population with the PDGFRA exon 18 D842V mutation is relatively small and that data on statistically significant differences in treatment effect for the high-risk population were not currently available. The Committee therefore concluded that it was currently unable to specify any patient subgroups with differential treatment benefits.
- 4.8 The Committee considered the adverse events associated with adjuvant imatinib. It heard from the clinical and patient experts that adverse events associated with imatinib treatment were predictable and manageable. The Committee concluded that adjuvant imatinib had an acceptable safety profile.
- 4.9 The Committee considered the company's approach to modelling the cost effectiveness of adjuvant imatinib. It noted that the Markov model structure was similar to that used in the original appraisal of adjuvant imatinib ([NICE technology appraisal guidance 196](#)). It was aware that progression through the model was based on treatment, rather than

disease progression, and noted that this was a potential source of bias. However, it heard from the ERG that the modelled health states were, in this instance, a reasonable approximation. The Committee concluded that the structure of the company's economic model was acceptable for assessing the cost effectiveness of adjuvant imatinib.

- 4.10 The Committee discussed the duration of adjuvant imatinib therapy used by the company in the model. It noted that the summary of product characteristics for imatinib states that, for this indication, 'optimal treatment duration is not yet established', but that imatinib had been given for a maximum of 3 years in the trials supporting the marketing authorisation. Consequently, the Committee agreed that it was appropriate to consider adjuvant treatment with imatinib for up to 3 years. It concluded that the company's approach of using 1-year or 3-year adjuvant imatinib in the economic model was acceptable as this reflected the clinical trial evidence available for people at high risk of recurrence after resection of KIT (CG117)-positive GISTs.
- 4.11 The Committee discussed how the company had estimated the baseline risk of recurrence (that is, with no adjuvant treatment). It noted that in the base case, the company had used data from the primary analysis of ACOSOG Z9001, rather than the 5-year follow-up analysis, to estimate the baseline risk of recurrence in people at high risk according to the Miettinen criteria. The Committee agreed with the ERG that it might have been more appropriate to use the hazard ratio for recurrence-free survival using 5-year follow-up data that had been adjusted for crossover using the IPCW method. However, the Committee was reassured by the company's incremental cost-effectiveness ratios (ICERs) using the 5-year follow-up data for recurrence-free survival for the placebo arm of ACOSOG Z9001 (unadjusted for crossover), which were similar to the base-case ICERs (see section 3.34). The Committee accepted the company's estimate of baseline risk of recurrence.

- 4.12 The Committee discussed how the company had incorporated the relative treatment effect into its economic model and accepted the company's assumption that imatinib's treatment effect was different during treatment compared with after treatment. The Committee initially focused on the on-treatment hazard ratio for recurrence-free survival for imatinib (1 and 3 years) compared with no adjuvant treatment. It noted the ERG's concern that the hazard ratio used in the company's model (0.111) was lower than the hazard ratio for the primary analysis of ACOSOG Z9001 (0.265). The company explained that this discrepancy was because the data used in the model had been truncated at 12 months (in line with the duration of imatinib treatment in the trial), and that additional patients, who had been identified as being at high risk of recurrence at the 5-year follow-up analysis, had been included. The Committee also heard from the clinical experts that a hazard ratio of 0.111 was plausible. The Committee noted that the company's deterministic sensitivity analyses showed that reducing the modelled clinical effectiveness of imatinib during treatment by using the upper confidence interval of the on-treatment hazard ratio (0.281) did not increase the ICERs above the range that is typically considered to be cost effective (£20,000–30,000 per QALY gained). The Committee concluded that the on-treatment hazard ratio of 0.111 in the company's economic model was associated with an acceptable level of uncertainty.
- 4.13 The Committee then looked at how the company had incorporated relative treatment effect after adjuvant imatinib treatment had finished (the off-treatment period). The Committee was concerned that there was a continuing differential off-treatment effect whereas it would intuitively be expected to taper off. It questioned whether the hazard ratios of 0.519 for 1-year adjuvant imatinib compared with placebo and 0.344 for 3-year imatinib compared with 1-year imatinib were too low, and discussed the sensitivity of the ICERs to the off-treatment hazard ratio. The Committee noted that the company's sensitivity analyses and the ERG's exploratory analyses indicated that the ICERs were sensitive to changes in the off-

treatment hazard ratio, but noted that the ICERs generally remained within the range that is typically considered to be cost effective. It noted that the ERG's exploratory analyses showed that assuming no long-term treatment benefit (that is, no benefit after the end of trial follow-up) did not markedly increase the ICERs. The Committee concluded that the off-treatment hazard ratios used in the company's model were sufficiently robust for generating cost-effectiveness estimates.

- 4.14 The Committee discussed how the company had extrapolated the clinical trial data to predict longer-term outcomes using a parametric survival model. The Committee understood the company's rationale for rejecting the Weibull, exponential and gamma distributions. The Committee noted the ERG's exploratory analysis using the exponential model, and considered that this was likely to underestimate imatinib's long-term treatment benefit and therefore produce ICERs that were higher than the true value. The Committee was concerned, however, that the company's Gompertz distribution could overestimate imatinib's long-term benefit. It noted that no justification had been given by the company for rejecting the log-logistic model, which was less optimistic for imatinib than the Gompertz distribution. The Committee concluded that there was some uncertainty in using the Gompertz model for the long-term extrapolation of imatinib's treatment benefit, and that this could cause the cost-effectiveness estimates generated using the company's model to be too optimistic.
- 4.15 The Committee reviewed the utility values used in the company's model. It acknowledged the ERG's concern about the lack of detail describing these in the company's submission but heard from the clinical experts that most of them seemed to be plausible. However, the Committee heard from the clinical experts that sunitinib had a poorer adverse-event profile than imatinib and it was not appropriate to assume the same treatment disutility for the 2 treatments. The Committee understood that if the utility values for people taking imatinib had been underestimated, then changing

this assumption would favour imatinib. However, the Committee noted that this would have only a limited impact on the ICER and concluded that the utility values in the company's model were generally acceptable.

- 4.16 The Committee considered the risks for mortality that had been used in the company's model. It heard from the company that mortality rates for the post-recurrence health states were taken from imatinib and sunitinib clinical trials (see section 3.28). However, because of a lack of data for recurrence after adjuvant treatment, patients in the model were assumed to have the same mortality risk following recurrence, regardless of whether they had received adjuvant imatinib treatment or not. Together with the issues related to the extrapolation of recurrence-free survival discussed in section 4.14, the Committee was particularly concerned about the large life-year gains predicted by the model at 3 years, but a clinical expert emphasised that this was consistent with the 5-year survival in the trial. The Committee noted that the ERG's exploratory analysis, which used lower mortality rates after recurrence to better fit the trial results, caused the ICERs to decrease slightly (see section 3.48). The Committee concluded that the mortality rates used by the company in its model were appropriate for the pre-recurrence health states, but that it preferred the ERG's values for the post-recurrence health states.
- 4.17 The Committee had some concerns about the validity of the total and incremental costs for the cost-effectiveness estimates generated using the company's model. It recalled that the estimated drug cost was £20,700 and £62,100 for 1 year and 3 years of adjuvant imatinib treatment respectively, producing incremental drug costs of £41,400. However, it noted that the company's base-case results reported incremental costs for 1-year adjuvant imatinib compared with no adjuvant treatment of less than £8000. Similarly, the incremental costs for 3-year adjuvant imatinib compared with 1-year adjuvant imatinib were around £23,000. The ERG explained that, regardless of any previous adjuvant treatment, health state costs after recurrence were high and that the greater proportion of people



who remained recurrence-free in the active treatment groups accounted for this apparent anomaly. The Committee concluded that it was satisfied with the way the company had incorporated total costs, including drug acquisition costs, into its economic model.

4.18 The Committee deliberated over the most plausible ICERs presented by the company and the ERG for adjuvant imatinib compared with no adjuvant treatment. The Committee considered that the company's base-case results (including a minor correction by the ERG) could underestimate the true value of the ICER because they used the Gompertz distribution for extrapolating recurrence-free survival, which possibly overestimated imatinib's long-term treatment effect (£3610 per QALY gained for 1-year adjuvant imatinib compared with no adjuvant treatment; £16,700 per QALY gained for 3-year adjuvant imatinib compared with 1-year adjuvant imatinib). However, the Committee considered that the ICERs from the ERG's combined exploratory analyses were too high because they used the exponential distribution to extrapolate long-term recurrence-free survival, which gave results that were not clinically plausible because recurrence-free survival rates were too low for no adjuvant treatment (£12,100 per QALY gained for 1-year adjuvant imatinib compared with no adjuvant treatment; £30,000 per QALY gained for 3-year adjuvant imatinib compared with 1-year adjuvant imatinib). The Committee concluded that the true value of the ICERs was between £3610 and £12,100 per QALY gained for 1-year adjuvant imatinib compared with no adjuvant treatment, and between £16,700 and £30,000 per QALY gained for 3-year adjuvant imatinib compared with 1-year adjuvant imatinib.

4.19 The Committee discussed whether imatinib could be considered an innovative treatment. Although it believed that the introduction of adjuvant treatment for GISTs could potentially be considered a step change in health-related benefits, it noted that imatinib has been available as a treatment elsewhere in the GIST treatment pathway for many years and

consequently the move to adjuvant treatment could not in itself be considered innovative. The Committee concluded that there were no additional health benefits that had not been included in the company's economic model.

- 4.20 The Committee discussed whether using imatinib as an adjuvant treatment for GISTs represented cost-effective use of NHS resources. It had noted concerns around the plausibility of the extent of life years gained and small increase in incremental costs predicted by the company's model for adjuvant imatinib treatment (see section 4.17). However, it was satisfied that, after a step-by-step examination, the assumptions and approaches used in the model were defensible. Moreover, it noted that the ICERs were insensitive to changes in many of the parameters in the company's sensitivity analyses and the ERG's exploratory analyses, and noted that they generally remained below £30,000 per QALY gained. The Committee also acknowledged the similarity between the deterministic ICER and the probabilistic ICER. Taking all of these factors into account, the Committee considered that the fully incremental ICER for the comparison of 3-year adjuvant imatinib with 1-year adjuvant imatinib, which was between £16,663 and £29,966 per QALY gained, was within the range normally considered to represent cost-effective use of NHS resources (£20,000–30,000 per QALY gained) and was associated with an acceptable level of uncertainty. Therefore, the Committee recommended adjuvant treatment with imatinib for up to 3 years as an option for KIT (CD117)-positive GISTs in people considered at high risk of recurrence as defined by the Miettinen 2006 criteria (based on tumour size, location and mitotic rate).

**Summary of Appraisal Committee’s key conclusions**

TAXXX	<b>Appraisal title:</b> Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (review of NICE technology appraisal guidance 196)	<b>Section</b>
<b>Key conclusion</b>		
<p>Imatinib is recommended as an option as adjuvant treatment for up to 3 years for adults who are at high risk of relapse after surgery for KIT (CD117)-positive gastrointestinal stromal tumours, as defined by the Miettinen 2006 criteria (based on tumour size, location and mitotic rate). The Committee decided that the evidence relating to the subgroup at high risk of recurrence according to the Miettinen criteria was the most appropriate for its decision-making. It concluded that the clinical trial evidence showed that 1-year adjuvant imatinib increased recurrence-free survival compared with placebo, although it was unclear if this resulted in longer overall survival. It further concluded that adjuvant treatment with imatinib for 3 years was more clinically effective than giving it for 1 year during clinical trial follow-up, as shown by statistically significantly longer recurrence-free survival and overall survival.</p> <p>The Committee considered that, based on the survival distributions used to estimate long-term recurrence-free survival, the company’s base-case results could underestimate the true value of the ICER, whereas the ERG’s combined exploratory analyses could overestimate it. The Committee concluded that the true value of the ICERs was:</p> <ul style="list-style-type: none"> <li>• between £3610 and £12,100 per QALY gained for 1-year adjuvant imatinib compared with no adjuvant treatment, and</li> <li>• between £16,700 and £30,000 per QALY gained for 3-year adjuvant imatinib compared with 1-year adjuvant imatinib.</li> </ul> <p>The Committee recommended adjuvant treatment with imatinib for up to 3 years as an option for KIT (CD117)-positive GISTs in people considered at high risk of recurrence as defined by the Miettinen criteria.</p>		1.1, 4.4, 4.5, 4.6, 4.18, 4.20
<b>Current practice</b>		
Clinical need of patients, including the availability of alternative treatments	The Committee noted that <a href="#">NICE technology appraisal guidance 196</a> had not recommended imatinib for the adjuvant treatment of GISTs and heard from the clinical experts that people at high risk of recurrence had the greatest clinical need for adjuvant treatment to prevent recurrence. The Committee also heard from patient experts that people place a high value on the psychological impact of taking a medicine after surgery to increase their chances of remaining cancer free.	4.1

<b>The technology</b>		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Imatinib is a selective kinase inhibitor which binds to activated c-KIT receptors and blocks the cell signalling pathway, preventing uncontrolled cell proliferation.  Although the Committee believed that the introduction of adjuvant treatment for GISTs could potentially be considered a step change in health-related benefits, it noted that imatinib has been available as a treatment for GISTs for many years and consequently the move to adjuvant treatment could not be considered innovative.	2.1, 4.19
What is the position of the treatment in the pathway of care for the condition?	The Committee noted that NICE technology appraisal guidance 196 had not recommended imatinib for the adjuvant treatment of GISTs. It was aware that people at high risk of recurrence were eligible to receive adjuvant imatinib for up to 3 years via the Cancer Drugs Fund.	4.1
Adverse reactions	Imatinib's summary of product characteristics lists gastrointestinal effects, oedema, rash and neutropenia as adverse reactions for imatinib. The Committee concluded that adjuvant imatinib had an acceptable safety profile.	2.2, 4.8
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The Committee observed that the company's submission included 3 phase III studies: ACOSOG Z9001, SSGXVIII/AIO and EORTC 62024 and presented analyses with median follow-up of 4–5 years. It noted the ERG's opinion that the studies were generally well designed and executed. The Committee concluded that the clinical-effectiveness evidence was suitable for its decision-making.	4.2
Relevance to general clinical practice in the NHS	The Committee heard from the clinical experts that the Miettinen 2006 criteria (Miettinen and Lasota, 2006) are the most commonly used tool in clinical practice in England to predict risk of recurrence. The Committee concluded that the evidence relating to the subgroup at high risk of recurrence according to the Miettinen criteria was the most appropriate for its decision-making.	4.4

<p>Uncertainties generated by the evidence</p>	<p>The Committee was aware that the marketing authorisation for imatinib as an adjuvant treatment for KIT (CD117)-positive GISTs was for people who were at ‘significant’ risk of relapse after complete resection, but observed that this group had not been defined by the regulatory agency. It concluded that the evidence relating to the subgroup at high risk of recurrence according to the Miettinen criteria was the most appropriate for its decision-making.</p>	<p>4.3, 4.4</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>Not applicable.</p>	
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee concluded that the clinical trial evidence showed that 1-year adjuvant imatinib increased recurrence-free survival compared with placebo, but was unclear if this resulted in longer overall survival. The Committee concluded that adjuvant treatment with imatinib for 3 years was more clinically effective than giving it for 1 year during clinical trial follow-up.</p>	<p>4.5, 4.6</p>
<p>How has the new clinical evidence that has emerged since the original appraisal (TA196) influenced the current (preliminary) recommendations?</p>	<p>The Committee noted that NICE technology appraisal guidance 196 had not recommended imatinib for the adjuvant treatment of GISTs.</p> <p>The Committee was aware that the company’s submission for the original appraisal had focused on the primary analysis data from ACOSOG Z9001. It recalled that in the original appraisal, the Committee had concluded that these data were too immature to enable conclusions to be drawn about key aspects of imatinib’s clinical effectiveness. It observed that the company’s current submission included 3 phase III studies and that it contained analyses with median follow-up of 4–5 years, and that outcomes included overall survival.</p> <p>The Committee concluded that the clinical-effectiveness evidence was suitable for its decision-making and, after a step-by-step examination of the company’s economic model, recommended adjuvant treatment with imatinib for up to 3 years as an option for KIT (CD117)-positive GISTs in people considered at high risk of recurrence as defined by the Miettinen criteria.</p>	<p>4.2, 4.20</p>

Evidence for cost effectiveness		
Availability and nature of evidence	The Committee concluded that the structure of the company's economic model was acceptable for assessing the cost effectiveness of adjuvant imatinib.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee discussed how the company had incorporated the relative treatment effect into its economic model and accepted the company's assumption that imatinib's treatment effect was different during treatment compared with after treatment. The Committee concluded that the on-treatment and off-treatment hazard ratios were sufficiently robust for generating cost-effectiveness estimates.	4.12, 4.13
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee concluded that there were no additional health benefits that had not been included in the company's economic model.	4.19
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable.	
What are the key drivers of cost effectiveness?	The Committee concluded that there was some uncertainty in using the Gompertz model for the long-term extrapolation of imatinib's treatment benefit, and that this could cause the cost-effectiveness estimates generated using the company's model to be too optimistic.	4.14
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the true value of the ICERs was between £3610 and £12,100 per QALY gained for 1-year adjuvant imatinib compared with no adjuvant treatment, and between £16,700 and £30,000 per QALY gained for 3-year adjuvant imatinib compared with 1-year adjuvant imatinib.	4.18

<p>How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA196) influenced the current (preliminary) recommendations?</p>	<p>The Committee noted that NICE technology appraisal guidance 196 had not recommended imatinib for the adjuvant treatment of GISTs and recalled that the original appraisal had concluded that the data were too immature to inform conclusions about imatinib’s clinical effectiveness. Having discussed the clinical-effectiveness evidence in the company’s current submission, which contained analyses with median follow-up of 4–5 years for outcomes including overall survival, it concluded that the evidence was suitable for decision-making. The Committee discussed how the company had incorporated the clinical data in its economic model and accepted the company’s estimates of baseline risk of recurrence, on-treatment hazard ratio and off-treatment hazard ratio.</p> <p>After a step-by-step examination of the company’s economic model, the Committee recommended adjuvant treatment with imatinib for up to 3 years as an option for KIT (CD117)-positive GISTs in people considered at high risk of recurrence as defined by the Miettinen criteria.</p>	<p>4.2, 4.12, 4.13, 4.20</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>Not applicable.</p>	
<p>End-of-life considerations</p>	<p>Not applicable.</p>	
<p>Equalities considerations and social value judgements</p>	<p>No potential equality issues were identified during the scoping process, in any of the submissions or during the Committee meeting. None had been previously identified in NICE technology appraisal guidance 196.</p>	

## 5 Implementation

5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has a gastrointestinal stromal tumour and the doctor responsible for their care thinks that adjuvant imatinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools [[link to www.nice.org.uk/guidance/TAXXX](http://www.nice.org.uk/guidance/TAXXX)] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

## 6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

### Published

- [Imatinib for the adjuvant treatment of gastrointestinal stromal tumours](#). NICE technology appraisal guidance 196 (2010).
- [Improving outcomes for people with sarcoma](#). NICE cancer service guidance (2006).
- [Improving supportive and palliative care for adults with cancer](#). NICE cancer service guidance (2004).
- [Gastrointestinal cancers](#). NICE pathway (2010).



## **7 Review of guidance**

- 7.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Andrew Stevens

Chair, Appraisal Committee

October 2014

## **8 Appraisal Committee members, guideline representatives and NICE project team**

### ***Appraisal Committee members***

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Professor Andrew Stevens**

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

#### **Professor Eugene Milne**

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

#### **Professor Kathryn Abel**

Director of Centre for Women's Mental Health, University of Manchester

#### **David Chandler**

Lay member

#### **Gail Coster**

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

**Professor Peter Crome**

Honorary Professor, Dept of Primary Care and Population Health, University College London

**Professor Rachel A Elliott**

Lord Trent Professor of Medicines and Health, University of Nottingham

**Dr Greg Fell**

Consultant in Public Health, Bradford Metropolitan Borough Council

**Dr Alan Haycox**

Reader in Health Economics, University of Liverpool Management School

**Dr Janice Kohler**

Formerly Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospitals Trust

**Emily Lam**

Lay member

**Dr Nigel Langford**

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

**Dr Allyson Lipp**

Principal Lecturer, University of South Wales

**Dr Andrea Manca**

Health Economist and Senior Research Fellow, University of York

**Dr Claire McKenna**

Research Fellow in Health Economics, University of York

**Professor Gary McVeigh**

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

**Dr Paul Miller**

Director, Payer Evidence, AstraZeneca UK Ltd

**Dr Anna O'Neill**

Deputy Head of Nursing & Healthcare School / Senior Clinical University Teacher,  
University of Glasgow

**Alan Rigby**

Academic Reader, University of Hull

**Professor Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS Foundation  
Trust

**Professor Matt Stevenson**

Technical Director, School of Health and Related Research, University of Sheffield

**Dr Paul Tappenden**

Reader in Health Economic Modelling, School of Health and Related Research,  
University of Sheffield

**Professor Robert Walton**

Clinical Professor of Primary Medical Care, Barts and The London School of  
Medicine & Dentistry

**Dr Judith Wardle**

Lay member

***Guideline representatives***

The following individuals, representing the Guideline Development Group responsible for developing NICE's clinical guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

**Dr Stephen Falk**

Consultant in Clinical Oncology, Bristol Haematology and Oncology Centre

***NICE project team***

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Linda Landells**

Technical Lead

**Raisa Sidhu**

Technical Adviser

**Nicole Fisher**

Project Manager

## 9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessment Centre

- Jones J et al. (2014) Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (review of TA196).

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

### I. Company:

- Novartis Pharmaceuticals

### II. Professional/specialist and patient/carer groups:

- GIST Support UK
- Sarcoma UK
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

### III. Other consultees:

- Department of Health
- NHS Blackpool CCG
- NHS England

- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical and patient expert nominations from the consultees and commentators. They gave their expert personal view on imatinib for the adjuvant treatment of gastrointestinal stromal tumours by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Ian Judson, Consultant Medical Oncologist, nominated by GIST Support UK – clinical expert
- Dr Newton ACS Wong, Consultant Histopathologist – clinical expert
- Mr Nic Puntis, Trustee, nominated by GIST Support UK – patient expert
- Mrs Barbara Doré, Chair, nominated by GIST Support UK – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Novartis Pharmaceuticals