NICE National Institute for Health and Care Excellence

NICE guidance

Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance partially replaces TA86.

1 Recommendations

This guidance should be read in conjunction with NICE's technology appraisal guidance on imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (TA86).

This guidance updates recommendation 1.5 of TA86. All other recommendations in TA86 still stand.

1.1 Imatinib at 600 or 800 mg/day is not recommended for people with unresectable and/or metastatic gastrointestinal stromal tumours whose disease has progressed after treatment with 400 mg/day imatinib.

1.2 People who are currently receiving 600 or 800 mg/day imatinib for unresectable and/or metastatic gastrointestinal stromal tumours should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 Clinical need and practice

2.1 Gastrointestinal stromal tumours (GISTs) are rare tumours of the gastrointestinal tract. Although GISTs can occur along the length of the gastrointestinal tract from the oesophagus to the anus, the majority (60% to 70%) arise in the stomach. Most GISTs are associated with overexpression of the tyrosine kinase receptor KIT (CD117), which is thought to promote tumour growth or to inhibit tumour cell death through a signal transduction pathway involving stem cell factor.

2.2 Approximately one-third of people with GISTs are asymptomatic during the early stages of the disease. Signs and 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.

2.3 Approximately 900 people are newly diagnosed with GISTs in the UK each year. Although GISTs can occur at any age, the usual age of presentation is between 50 and 70 years. Diagnosis of GIST is confirmed by clinical presentation and tissue biopsy to determine the histological characteristics of the tumour, including expression of the KIT (CD117) protein. Approximately 4% of GISTs have characteristic clinical and morphological features, but do not express the KIT (CD117) protein.

2.4 The size, growth rate and location of the tumour often influence prognosis. Without treatment GISTs progress and will eventually metastasise. Prognosis depends on whether the tumour can be resected, which is the primary treatment for GISTs. Only 50% of GISTs are resectable at presentation. Conventional cytotoxic chemotherapy and radiotherapy are ineffective in treating advanced or metastatic GISTs. Similarly, surgery to treat advanced or metastatic GISTs is not recommended unless there is an immediate clinical need, such as to remove an obstructing tumour.

3 The technology

3.1 Imatinib (Glivec, Novartis Pharmaceuticals UK) is a signal-transduction inhibitor that selectively inhibits tyrosine kinases, including the KIT (CD117) receptor that is expressed in GISTs. Imatinib binds to activated KIT (CD117) receptors and blocks the cell-signalling pathway to inhibit uncontrolled cell proliferation. Imatinib has a UK marketing authorisation for the treatment of adults with KIT (CD117)-positive unresectable and/or metastatic malignant GISTs.

3.2 The most commonly reported adverse events in trials of imatinib were oedema, fatigue, myalgia, muscle cramps, rash, abdominal pain, vomiting, diarrhoea and nausea. For full details of adverse effects and contraindications, see the summary of product characteristics.

3.3 Imatinib is administered orally. The summary of product characteristics recommends 400 mg/day imatinib for the treatment of unresectable and/or metastatic GISTs. It states that there are limited data on the effect of increasing the dose of imatinib from 400 mg/day to 600 or 800 mg/day in people whose disease has progressed at the lower imatinib dose.

3.4 Imatinib is available in strengths of 100 mg (60-tablet pack) and 400 mg (30-tablet pack) at a cost of £802.04 and £1,604.08 per pack respectively (excluding VAT; BNF, edition 59). The annual acquisition costs for treatment with imatinib are approximately £19,500 (400 mg/day), £29,300 (600 mg/day) and £39,100 (800 mg/day). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee considered evidence from a number of sources.

4.1 Clinical effectiveness

4.1.1 The Assessment Group considered the clinical effectiveness of increased doses of imatinib (600 or 800 mg/day) compared with sunitinib or best supportive care for the treatment of people with unresectable and/or metastatic GISTs whose disease had progressed on 400 mg/day imatinib. Studies reporting the clinical effectiveness of comparator treatments (sunitinib plus best supportive care or best supportive care alone) were also identified.

4.1.2 The Assessment Group did not identify any randomised controlled trials or non-randomised studies comparing the effectiveness of increased doses of imatinib (600 or 800 mg/day) with sunitinib or best supportive care. However, it identified 6 papers and ten abstracts reporting 4 separate clinical trials and 1 non-randomised retrospective cohort study that included a treatment arm of 400 mg/day imatinib and reported data separately for people who initially received 400 mg/day imatinib, then received an increased dose of imatinib when disease progressed ('crossover groups'). The outcomes for people who took increased doses of imatinib informed this appraisal.

4.1.3 The EORTC-ISG-AGITG randomised controlled trial (Zalcberg et al. 2005; Debiec-Rychter et al. 2006) compared 800 mg/day imatinib with 400 mg/day imatinib in people with advanced GISTs (473 people from total trial population of 946 participants). When disease progressed in people randomised to 400 mg/day imatinib the dose was increased to 800 mg/day imatinib (n=133 out of 473 people). Interim response data were reported for 97 people from this trial (Zalcberg et al. 2004). The S0033 randomised controlled trial (Blanke et al. 2008a) also compared 800 mg/day imatinib with 400 mg/day imatinib in people with advanced GISTs (345 people from total trial population of 746 participants). One hundred and seventeen people originally randomised to 400 mg/day who received an increased dose of 800 mg/day imatinib after disease progression were assessed for response. Interim response data (Rankin et al. 2004) were

reported for 68 people. The B2222 randomised controlled trial (Blanke et al. 2008) compared 400 mg/day imatinib (n=73) with 600 mg/day imatinib (n=74) in people with advanced GISTs. People with disease progression on 400 mg/day imatinib, but who could tolerate a higher imatinib dose, received an increased dose of 600 mg/day. Forty-three people originally randomised to 400 mg/day imatinib and 13 people originally randomised to 600 mg/day imatinib received increased doses of imatinib. A retrospective cohort study (n=24; Park et al. 2009) reported data for people with metastatic or unresectable GISTs. People in this study received an initial dose of 400 mg/day imatinib that was increased to 600 or 800 mg/day imatinib on disease progression.

4.1.4 The Assessment Group identified 7 abstracts that provided interim results for an ongoing, non-comparative open-label trial on the effectiveness of sunitinib in people whose condition had failed to respond to treatment with different doses of imatinib (including doses up to 400 mg/day). An abstract by Seddon et al. (2008; n=1,117) was considered by the Assessment Group to be the primary source for this trial. The Assessment Group also used data from Reichardt et al. (2008) to obtain overall survival rates for sunitinib and data from Prior et al. (2009) and Demetri et al. (2006) to obtain response rates for sunitinib.

4.1.5 Overall, 28.1% (EORTC-ISG-AGITG), 34.2% (S0033) and 58.9% (B2222) of people initially randomised to receive 400 mg/day imatinib had disease progression and received either 600 or 800 mg/day imatinib. All the people in the retrospective cohort study received an increased dose of imatinib. In the sunitinib study (Seddon et al. 2008), 31.4% of people received sunitinib after disease progression on 400 mg/day imatinib.

Overall response

4.1.6 The results for people treated with an increased dose of 600 mg/day imatinib after disease progression on 400 mg/day imatinib were reported in the B2222 trial and the retrospective cohort study. In the B2222 trial, the median length of follow-up was 63 months (maximum 71 months) from randomisation. After disease progression, 11 out of 43 people (25.6%) who increased to 600 mg/day imatinib either had a partial response or had stable disease. The Assessment Group noted that some of the people who received increased doses may have

had an initial response to 400 mg/day imatinib before disease progression. In the retrospective cohort study the median length of follow-up was 8 months (range 1.4 to 22.3 months). Of the 12 people who received 600 mg/day imatinib, 5 (41.7%) either had a partial response or had stable disease after treatment.

4.1.7 The results for people treated with an increased dose of 800 mg/day imatinib after disease progression on 400 mg/day imatinib were reported in the S0033 trial, the EORTC-ISG-AGITG trial, and the retrospective cohort study. Of the subgroups who received increased doses in the S0033 and EORTC-ISG-AGITG trials (117 out of 345, and 133 out of 473 people respectively), 3 people in each trial had a partial response to treatment, while 33 and 36 people respectively achieved stable disease as a best response. Out of a total of 250 people in the 2 studies combined, 75 (30%) met the criteria for a response to treatment after an increase in the dose of imatinib from 400 to 800 mg/day. The retrospective cohort study reported that 4 of the 12 people (33.3%) who received an increased dose of imatinib (800 mg/day) after disease progression either had a partial response or had stable disease.

4.1.8 The manufacturer of imatinib reported confidential data from a meta-analysis of the S0033 and EORTC-ISG-AGITG trials in their submission, which reported the response to treatment in people who received increased doses of imatinib. However, the Assessment Group did not review these data because of differences in the numbers of people who achieved stable disease or had a partial response after increased doses of imatinib compared with the results from the same studies available as published articles.

4.1.9 Interim data for the EORTC-ISG-AGITG trial reported that, of 97 people whose disease had progressed on 400 mg/day imatinib, 2 (2.1%) showed a partial response, 30 (30.9%) had stable disease, and 65 (67.0%) still had progressive disease after an increase in the dose of imatinib from 400 to 800 mg/day. Interim data from the S0033 trial showed that, of 68 people whose disease had progressed on 400 mg/day imatinib, 5 (7.4%) had a partial response and 20 (29.4%) had stable disease after an increase in the dose of imatinib from 400 to 800 mg/day.

4.1.10 In addition, a secondary analysis of the EORTC-ISG-AGITG trial (Debiec-Rychter et al. 2006) suggested (without stating the number of people involved) that

response to treatment after increasing the dose of imatinib from 400 to 800 mg/day was significantly more likely to occur in people with wild-type GISTs compared with the KIT exon 11 mutation (p=0.0012). Response after increasing the dose of imatinib was also significantly more likely to occur in people with the KIT exon 9 mutation compared with the exon 11 mutation (p=0.0017). The Assessment Group noted that it was outside the remit of this appraisal to consider outcomes for patients receiving escalated doses other than after disease progression on an initial dose of 400 mg/day imatinib. In the Debiec-Rychter et al. study, the dose of imatinib was increased to 800 mg/day shortly after starting on 400 mg/day imatinib, not necessarily after disease progression. Because of the lack of data available from the study, it was not possible for the Assessment Group to analyse the impact of increased doses of imatinib after disease progression on 400 mg/day imatinib for people with specific KIT exon mutations.

4.1.11 Response rates to treatment with 400 mg/day imatinib followed by 50 mg/day sunitinib on disease progression were not reported in the studies identified by the Assessment Group. The Assessment Group instead calculated a weighted average response rate from 2 studies (Demetri et al. 2002; Prior et al. 2009), but noted that there were differences between the patient groups in these 2 studies. The Prior et al. study did not report the dose of imatinib that people received before starting on sunitinib. In Demetri et al., people were randomised to receive sunitinib or placebo after treatment failure with a median dose of 800 mg/day imatinib (300 to 1,600 mg/day). Across these 2 studies 266 of a total of 382 people had a response to treatment, and a simple weighted mean was used to derive the pooled response rate (69.6%). This response rate was assumed to be unaffected by prior treatment received. The Assessment Group determined that there was no statistically significant difference in the response rates between these 2 studies.

Overall survival

4.1.12 The S0033 study reported the overall survival for people who were randomised to an initial dose of 400 mg/day imatinib which was increased to 800 mg/day after disease progression. The median follow-up for the study was 4.5 years (follow-up calculated from start of increased dose following disease progression

at 400 mg/day imatinib), during which time 76 of 118 people (64.4%) had died. The median overall survival was 19 months (95% confidence interval [CI] 13 to 23 months) from the point at which the dose of imatinib was increased. Interim data for the S0033 trial were also provided by Rankin et al. (2004), who reported that median overall survival after the increase in dose of imatinib was 19 months.

4.1.13 Two abstracts with different follow-up periods for the same study reported overall survival data for people receiving 50 mg/day sunitinib after disease progression or for people who could not tolerate imatinib at a dose of up to 400 mg/day. Reichardt et al. (2008) analysed data after a median of 24 weeks, at which point 231 of 339 people (68.1%) were still alive. Seddon et al. (2008) analysed data after a median of 51 weeks (range 0.1 to 159 weeks) and 193 of 351 people (55.0%) were still alive. The Assessment Group used data on the proportion of people still alive (Reichardt et al.) and the median follow-up (Seddon et al.) in its analysis.

Progression-free survival

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

4.1.15 The S0033 and the EORTC-ISG-AGITG trials reported data on progression-free survival for people randomised to an initial dose of 400 mg/day imatinib, which was increased to 800 mg/day after disease progression. For the S0033 trial, at a median follow-up of 54 months from randomisation, the disease had progressed in 99 of 118 people (83.9%) who received 800 mg/day imatinib. Median progression-free survival was estimated to be 5 months (95% CI 2 to 10 months). Using interim data from this trial for 68 people (Rankin et al. 2004), the authors estimated a median progression-free survival after crossover of 4 months. For the EORTC-ISG-AGITG trial, at a median follow-up of 25 months (maximum follow-up 35 months), the disease had progressed in 108 of 133 people (81.2%) who received 800 mg/day imatinib. Median progression-free survival was 2.7 months.

4.1.16 The sunitinib trial (Seddon et al. 2008) reported no data on disease progression

in people randomised to an initial dose of imatinib of up to 400 mg/day, followed by 50 mg/day sunitinib after disease progression.

Time to treatment failure

4.1.17 The retrospective cohort study reported data on the duration of response and time to treatment failure. Of the 12 people who received an increased dose of 600 mg/day imatinib after disease progression on 400 mg/day, 1 person died of a cause unrelated to both disease and treatment, while disease progressed in the remaining 11 people after a median of 1.7 months (range 0.7 to 24.9 months).

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

4.1.19 The sunitinib trial (Seddon et al. 2008) did not provide the specific median duration of treatment with sunitinib for people who initially received up to 400 mg/day imatinib, followed by 50 mg/day sunitinib after disease progression. However, the median duration of treatment for the whole cohort was reported as 126 days (range 1 to 618 days) and did not differ significantly between people based on the dose of imatinib they received before sunitinib treatment.

Health-related quality of life

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

Adverse events

4.1.21 Adverse events were not reported for people receiving an increased dose of 600 mg/day imatinib after disease progression on 400 mg/day imatinib.

4.1.22 No information on adverse events in people receiving an increased dose of 800 mg/day imatinib after disease progression on 400 mg/day was given by

Zalcberg et al. (EORTC-ISG-AGITG trial). The authors reported that the majority of people who stopped taking imatinib (88.4%) did so because of disease progression. The Assessment Group suggested that this indicates 11.6% (11 of 97) stopped treatment because of adverse events. Interim data from this study showed that 31% of people (absolute number not given) needed to reduce the dose from 800 mg/day imatinib to a dose that was not reported.

4.1.23 Interim data for the S0033 trial reported by Dileo et al. (2005) showed that of the 77 people who had increased their dose of imatinib from 400 to 800 mg/day, 18 (23.4%) had at least 1 delay in dose, and 14 (18%) had at least 1 dose reduction because of oedema or rash. No information was given on the reduced dose given.

4.1.24 No adverse event data were available for people in the sunitinib trial (Seddon et al. 2008).

4.2 Cost effectiveness

4.2.1 The Assessment Group carried out a systematic review of the literature. Seven studies that assessed both the costs and cost effectiveness of imatinib or alternative treatments for GISTs were identified.

4.2.2 Three studies compared imatinib (at 400 mg/day or at increased doses) with best supportive care (Wilson et al. 2005; Mabasa et al. 2008; Huse et al. 2007). Two studies included sunitinib, increased doses of imatinib, and best supportive care or palliative care as comparators (Contreras-Hernandez et al. 2008; Teich et al. 2009). Because the results of the Teich et al. study were available in abstract form only, its definition of best supportive care was not available. Studies by Chabot et al. (2008) and Paz-Ares et al. (2008) compared treatment with sunitinib and best supportive care for people with GISTs that were resistant to or intolerant of imatinib.

4.2.3 The study by Wilson et al. (2005) used a modified version of the model submitted by the manufacturer in NICE's technology appraisal guidance on imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (TA86). This appraisal evaluated the cost effectiveness of increased doses of

imatinib (to 600 mg/day) after disease progression on 400 mg/day in people with unresectable and/or metastatic GISTs from a UK NHS perspective. The estimates for the incremental cost per quality-adjusted life year (QALY) gained compared with best supportive care ranged from £51,515 to £98,889 at 2 years, and from £27,331 to £44,236 at 5 years.

4.2.4 The study by Contreras-Hernandez et al. (2008) suggested that 800 mg/day imatinib would deliver cost savings compared with best supportive care when best supportive care includes treatment with imatinib at a dose lower than 800 mg/day. Over a 5-year treatment horizon, Contreras-Hernandez et al. (2008) found that the mean life years gained was 1.40 for people receiving sunitinib, 1.31 for people receiving imatinib 800 mg/day and 1.08 for people receiving best supportive care. The study also suggested that receiving 800 mg/day imatinib incurred the highest mean treatment costs, indicating that 800 mg/day imatinib is dominated by sunitinib. Teich et al. (2009) found that 800 mg/day imatinib was less effective than sunitinib (0.02 life years gained and 0.47 progression-free life years gained) and less costly over 6 years, also indicating that 800 mg/day imatinib is dominated by sunitinib.

Manufacturer's submission

4.2.5 The manufacturer did not submit a cost-effectiveness analysis of imatinib for this appraisal. The manufacturer stated that major limitations with the available clinical data prevented it from developing a sufficiently robust health economics model.

Assessment Group economic assessment

4.2.6 The Assessment Group developed a Markov model to compare alternative treatments for people with KIT (CD117)-positive unresectable and/or metastatic GISTs whose disease had progressed on imatinib 400 mg/day or whose treatment with imatinib had failed because of resistance or intolerance. The Assessment Group specifically addressed the cost effectiveness of imatinib at doses of 600 or 800 mg/day compared with best supportive care or sunitinib.

4.2.7 The model looked at the costs and outcomes for GIST treatments. A time horizon of 10 years and a cycle length of 1 month were used to reflect the natural history of the disease. The costs and outcomes were discounted at 3.5% in accordance with the NICE reference case.

4.2.8 The Assessment Group considered a range of treatment pathways for people whose disease had progressed on 400 mg/day imatinib. Based on advice from its clinical advisers, the Assessment Group decided on 7 clinically plausible pathways on which to base the model:

- Pathway 1: people receive best supportive care plus 400 mg/day imatinib
- Pathway 2: people receive 600 mg/day imatinib, and on disease progression, they receive 800 mg/day imatinib. On further disease progression people then receive 50 mg/day sunitinib, followed by, on further disease progression, best supportive care plus 400 mg/day imatinib.
- Pathway 3: people receive 600 mg/day imatinib, and on disease progression, they receive 50 mg/day sunitinib. After further disease progression on sunitinib, people receive best supportive care plus 400 mg/day imatinib.
- Pathway 4: people receive 600 mg/day imatinib, and on disease progression, they receive best supportive care plus 400 mg/day imatinib.
- Pathway 5: people receive 800 mg/day imatinib, and on disease progression, they receive 50 mg/day sunitinib. After disease progression on sunitinib, people receive best supportive care plus 400 mg/day imatinib.
- Pathway 6: people receive 800 mg/day imatinib, and on disease progression, they receive best supportive care plus 400 mg/day imatinib.
- Pathway 7: people receive 50 mg/day sunitinib, and on disease progression, they receive best supportive care plus 400 mg/day imatinib.

The Assessment Group determined clinical effectiveness using results from the systematic review and other evidence. No data were available to estimate the effectiveness of any of the treatment pathways compared with each other.

4.2.9 In the model the Assessment Group combined the estimates of effectiveness

with data on health state utility to provide estimates of QALYs for the different treatment pathways. The Assessment Group obtained data on survival for best supportive care (which includes treatment with 400 mg/day imatinib for all patients) from 2 studies (McGrath et al. 1987; Pierie et al. 2001). Pooled weighted estimates from these studies suggested that 87.9% (51 of 58) of people died during the observation period of 60 months. Data on survival for people receiving 600 mg/day imatinib were obtained from the B2222 trial. Forty-five per cent (5 of 11) of people whose dose of imatinib was increased from 400 mg/day to 600 mg/day died during the trial period of 60 months. Data on survival for 800 mg/day imatinib came from the S0033 trial, and indicated that 64.4% (76 of 118) of people died in this group during a median follow-up period of 4.5 years. The data on survival for people receiving sunitinib came from Seddon et al. (2008) and showed that 55.0% (193 of 351) of people receiving sunitinib were still alive after a median survival period of 11.8 months. The Assessment Group derived a monthly mortality rate from these survival rates and assumed exponential rates. The Assessment Group also assumed that the monthly mortality rate for people receiving sunitinib did not depend on whether they had received previous treatment.

4.2.10 The Assessment Group took response rates for 600 mg/day imatinib from the B2222 trial. The trial reported that 25.5% (11 of 43) of people receiving 600 mg/day imatinib had a response to treatment and remained stable during a median follow-up of 63 months. Data from the S0033 and EORTC-ISG-AGITG trials provided the response rate to 800 mg/day imatinib. The trials reported that 30% (75 of 250) of people receiving 800 mg/day imatinib showed a partial response or remained stable after a median follow-up of 54 months. For response rates to sunitinib, the Assessment Group took data from 2 studies (Demetri et al. 2002; Prior et al. 2009). A simple weighted mean was used to derive a pooled response rate of 70% (266 of 382) at a median follow-up period of 3.6 months, which did not take into account previous treatment. The Assessment Group converted data reflecting no response for each treatment into monthly transition probabilities by assuming an exponential rate.

4.2.11 The costs of 400 mg/day, 600 mg/day and 800 mg/day imatinib and 50 mg/day sunitinib in the Assessment Group's model were calculated from costs listed in BNF 58. Because sunitinib treatment is given for 4 weeks followed by no treatment for 2 weeks, the Assessment Group calculated the costs per year, and

a proportional rate per month. The Assessment Group assumed that the cost for people receiving best supportive care was equivalent to the cost of 400 mg/day imatinib (which all people on best supportive care also received).

4.2.12 The Assessment Group based resource costs for 600 mg/day and 800 mg/day imatinib on those reported by Wilson et al. (2005). The resource costs included GP visits and outpatient visits, including tests, computed tomography scans and the costs of managing adverse events. For sunitinib and best supportive care, the Assessment Group based resource costs on the manufacturer's submission for NICE's technology appraisal guidance on sunitinib for the treatment of gastrointestinal stromal tumours. The Assessment Group adjusted the costs from 2008 to 2009 prices using the Hospital and Community Health Services Index.

4.2.13 The Assessment Group derived health state utility values from the EQ-5D and Chabot et al. (2008) in the absence of data from the available clinical studies. The utility value for progression-free survival for people whose disease responded to imatinib, regardless of dose, was assumed to be 0.935. The utility value for people receiving best supportive care was assumed to be 0.577 (Chabot et al. 2008). In the absence of alternative data, the utility value for people whose disease responded to sunitinib was assumed to be the same as that for imatinib, that is, 0.935.

4.2.14 The base-case results show that pathway 4 (600 mg/day imatinib followed by, on disease progression, best supportive care plus 400 mg/day imatinib) has an incremental cost-effectiveness ratio (ICER) of £27,304 per QALY gained compared with pathway 7 (50 mg/day sunitinib then best supportive care plus 400 mg/day imatinib). For pathway 2 (600 mg/day imatinib, increasing to 800 mg/day imatinib, then 50 mg/day sunitinib followed by best supportive care plus 400 mg/day imatinib) the ICER was £45,850 per QALY gained (compared with the next least costly option, pathway 4). For pathway 3 (600 mg/day imatinib, then 50 mg/day sunitinib followed by best supportive care plus 400 mg/day imatinib) the ICER was £71,723 per QALY gained (compared with the next more costly option, pathway 4). Both pathway 5 (800 mg/day imatinib, then 50 mg/day sunitinib, followed by best supportive care plus 400 mg/day imatinib) and pathway 6 (800 mg/day imatinib, then best supportive care plus 400 mg/day imatinib) were dominated by pathway 4 (that is, they were more costly and less effective). The estimated survival benefit of 800 mg/day imatinib compared with

best supportive care was 4.2 months.

4.2.15 The Assessment Group also performed sensitivity analyses to account for uncertainties in the model. The parameters varied included structure and methodological assumptions around distribution, transition probabilities of survival and response to treatment with 600 mg/day imatinib, utility values, and the costs of imatinib and sunitinib.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of increased doses of imatinib after disease progression on 400 mg/day imatinib, having considered evidence on the nature of unresectable and/or metastatic GISTs and the value placed on the benefits of imatinib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.3.2 The Committee discussed current clinical practice for the treatment of people with unresectable and/or metastatic GISTs. The Committee heard from the clinical specialists that, despite the recommendations in NICE's technology appraisal guidance TA86 on imatinib (recommendation 1.4 states that 'an increase in the dose of imatinib is not recommended for people receiving imatinib who develop progressive disease after initially responding'), people frequently receive 800 mg/day imatinib when their disease progresses on 400 mg/day imatinib if they have tolerated previous imatinib treatment. The clinical specialists reported that 600 mg/day imatinib is rarely prescribed after disease progression on 400 mg/day. The Committee was aware that NICE's technology appraisal guidance on sunitinib recommends that patients have the option to receive treatment with sunitinib after disease progression on 400 mg/day imatinib. However, the clinical specialists explained to the Committee that clinicians often consider increasing the dose of imatinib before offering treatment with sunitinib because imatinib is considered to have a more favourable adverse event profile, even at higher doses, than sunitinib. They also noted that if a person's disease progresses on 400 mg/day imatinib, it is common practice (in approximately 50% of people) to continue treatment with 400 mg/day imatinib in addition to best supportive care if the person tolerates imatinib, however this is inconsistent with

NICE's technology appraisal guidance TA86 on imatinib, which does not recommend continued treatment with imatinib after disease progression (recommendation 1.3). The Committee heard from patient experts that the limited data available suggest that imatinib at higher doses may be effective in prolonging survival and improving quality of life. Clinical specialists and patient experts also highlighted the importance of providing hope to people with metastatic GISTs by offering them additional treatment options after disease progression on 400 mg/day imatinib. Despite the lack of clinical trial evidence to demonstrate the effectiveness of increased doses of imatinib treatment after disease progression on 400 mg/day imatinib, the Committee acknowledged that there is a perception among both patient experts and clinical specialists that treatment with 800 mg/day imatinib after disease progression on 400 mg/day imatinib may offer some benefit.

Clinical effectiveness

4.3.3 The Committee considered the evidence provided by the Assessment Group and the manufacturer on the clinical effectiveness of 600 and 800 mg/day imatinib after disease progression on 400 mg/day imatinib. The Committee heard from the Assessment Group that no randomised controlled trials were identified on the effectiveness of an increased dose of imatinib after disease progression on 400 mg/day imatinib compared with sunitinib or best supportive care – the 2 comparator treatments identified in the scope for this appraisal. Uncontrolled observational data were available evaluating the effectiveness of increased doses of imatinib in people with unresectable and/or metastatic GISTs who had not received previous imatinib treatment. However, the Committee was concerned that the populations in these studies differed from the population covered by this appraisal (that is, people whose disease has progressed on 400 mg/day imatinib), and that the studies did not explore the comparisons defined in the scope. The Committee also noted that the populations in the studies varied substantially and that combining results may introduce more uncertainty. The Committee noted that this appraisal is a part review of NICE's technology appraisal guidance TA86 on imatinib, published in 2004, which was intended to only address whether increased doses of 600 or 800 mg/day imatinib could be recommended after disease progression on 400 mg/day imatinib. The Committee noted that consultees had requested the review based on the belief that a large amount of

clinical evidence about imatinib had been published since 2004. The Committee further noted that during the scoping process for this review consultees and commentators for this appraisal were given another opportunity to comment on the appropriateness of this review. The Committee was reminded that, at the time of the review proposal, the manufacturer of imatinib was seeking to extend the marketing authorisation for 800 mg/day imatinib for unresectable and/or metastatic GISTs and that the manufacturer supported the review going ahead. However, in their submission and during the Committee meeting, the manufacturer stated that no new evidence had emerged since 2004 on the effectiveness of increased doses of imatinib after disease progression on 400 mg/day imatinib. The Committee heard from the patient experts that they were disappointed that the available studies did not provide clear evidence about the effectiveness of higher doses of imatinib. The Committee agreed with the manufacturer and the Assessment Group that there is a lack of robust data available to demonstrate the effectiveness of increased doses of imatinib after disease progression on 400 mg/day imatinib, and that the available evidence is associated with uncertainty and potential bias.

4.3.4 The Committee noted that the majority of available data related to people who received an increased dose of 800 mg/day imatinib after disease progression on 400 mg/day imatinib. Only one phase 2 study (B2222) described the experience of 43 people who received an increased dose of 600 mg/day imatinib. The Committee heard that data from the Gastrointestinal Stromal Tumor Meta-Analysis Group (metaGIST) was published in March 2010. However, these data were not included in the Assessment Group's economic analyses because the population was randomised to higher doses of imatinib at baseline and had not received treatment with 400 mg/day imatinib first. Therefore, the population in the metaGIST study was different from the population for this appraisal. The Committee discussed the possible biases in the evidence for increased doses of imatinib from the uncontrolled observational data. The Committee recognised that if people with a better prognosis preferentially received increased doses of imatinib, then any improvement in outcome might not be because of the use of higher doses. For example, the Committee was aware that in the B2222 study, people with disease progression on 400 mg/day imatinib, received a higher dose of imatinib if they were described as having a good performance status (such as ECOG status <2). The Committee heard from the manufacturer that there are no ongoing trials that address the decision problem in this appraisal. The Committee

heard from the clinical specialists that a trial comparing high-dose imatinib with sunitinib had been stopped after it failed to recruit a sufficient number of people. The Committee concluded that the Assessment Group had made a good effort to include all available data relevant to this appraisal in its report but was concerned about the lack of data and the nature of the evidence available.

4.3.5 After receiving comments from consultees and commentators on the appraisal consultation document, the Committee considered the UK guideline for the management of GISTs that was published in May 2009. The Committee noted that the guideline contains the same evidence that was identified for this appraisal by the Assessment Group and the manufacturer, and that the development of the guideline had been sponsored by the manufacturer of imatinib. The Committee was aware that the guideline did not consider the cost effectiveness of any treatments and therefore the recommendations in this appraisal would likely be different from the guideline.

4.3.6 The Committee considered the effectiveness of imatinib in slowing disease progression in unresectable and/or metastatic GISTs. The Committee heard from the clinical specialists that comparable measures of disease progression had been used in the different clinical trials. The Committee heard that the 3 studies in which the dose of imatinib was increased from 400 mg/day to 800 mg/day showed that approximately one-third of people had either a partial response or had stable disease after receiving the increased dose. The Committee concluded that imatinib treatment at higher doses may offer some benefit to people whose disease progresses on 400 mg/day imatinib; however, because of the biases inherent to the clinical-effectiveness evidence available, it was aware that this conclusion was uncertain.

4.3.7 The Committee heard from the patient experts that measuring plasma concentrations of imatinib could be a major advantage, because it might allow an individualised approach to the dosing of imatinib. However, the clinical specialists noted that this does not happen in routine UK clinical practice, and the Committee noted that no data had been presented to demonstrate an association between plasma concentrations and outcomes. The Committee concluded that while measuring plasma concentrations of imatinib might potentially be of benefit in the future, it could not base any recommendations on this because of the current lack of evidence and because it was not done in routine clinical practice.

4.3.8 The Committee discussed whether benefits from increased doses of imatinib might be greater in certain subgroups of people. The Committee heard from the clinical specialists that there is some evidence suggesting that GISTs with certain mutations in the KIT gene are likely to be more or less sensitive to imatinib treatment. The clinical specialists suggested that the presence of an exon 9 mutation may be associated with a better outcome in people whose dose is increased to 800 mg/day imatinib. In addition, the clinical specialists explained that, although outside the current marketing authorisation, clinicians might choose to begin treatment with 800 mg/day imatinib without having tried lower doses in people with confirmed exon 9 mutations. However, they explained that the clinical evidence supporting this practice is based on the experience of a small number of people. The Committee also noted that data from a meta-analysis (metaGIST), in which people with exon 9 mutations started treatment on 800 mg/day imatinib, showed that there was no statistically significant difference in overall survival between people with exon 9 mutations treated with 400 mg/day imatinib compared with 800 mg/day imatinib. Furthermore, in light of the limited data available, the Committee noted that any economic analyses for this subgroup would not be considered more robust than for the entire population. The Committee also understood that mutational analysis in people with progressive disease had a limited role, if any, in clinical decision-making about increasing imatinib doses. Therefore, the Committee concluded that there was not sufficient evidence to justify a separate recommendation for the use of 600 or 800 mg/day imatinib for people with exon 9 mutations whose disease had progressed on imatinib 400 mg/day.

4.3.9 The Committee considered the data reported by the Assessment Group for the comparator treatment, sunitinib. The Committee noted that this evidence was mainly from an 'expanded access programme', in which regulators allow investigational drugs to be used to treat people with serious or immediately life-threatening diseases who cannot participate in clinical trials and who have no alternative therapy. The Committee was aware that people in this study were treated with sunitinib after receiving higher (600 or 800 mg/day) rather than lower (400 mg/day) doses of imatinib and did not necessarily reflect the population of interest in this appraisal – that is, people whose disease progresses on 400 mg/day imatinib.

Cost effectiveness

4.3.10 The Committee discussed the cost effectiveness of imatinib 600 and 800 mg/day after disease progression on 400 mg/day imatinib. The Committee noted the Assessment Group's view that it had great difficulty undertaking an assessment of cost effectiveness in the absence of robust comparative clinical evidence for increased doses of imatinib after disease progression on 400 mg/day imatinib. The Committee also noted that the manufacturer stated that they would not submit an economic model because of the lack of robust data comparing increased doses of imatinib with sunitinib and best supportive care.

4.3.11 The Committee then considered the monthly mortality rates used in the Assessment Group's economic evaluation and noted that they were key drivers of the outcomes in the model. The Committee noted that a higher monthly mortality rate for people receiving sunitinib treatment was used in the Assessment Group's model than for people receiving best supportive care, which the Committee considered was implausible. The Committee heard from the Assessment Group that the limited evidence available reported that the mortality rate for 600 mg/day imatinib was lower than the rate for 800 mg/day imatinib, and that treatment with 800 mg/day imatinib generated fewer life years and fewer QALYs than treatment with 600 mg/day imatinib. The Committee considered these data implausible and agreed that this difference was unlikely to reflect the true effect of 600 and 800 mg/day imatinib, but that this highlighted the limitations in the clinical evidence for the 2 doses. The Committee also noted that the monthly mortality rate applied for best supportive care appeared to be very low, despite these data being pooled from 2 studies that had been carried out before imatinib was introduced into clinical practice. The Committee also considered that when the studies were carried out, advanced diagnostic methods for GISTs did not exist, and that people may have had other tumours (for example, leiomyosarcoma) which were associated with a different mortality rate than for GISTs. The Committee was also aware that best supportive care was likely to have improved since the studies were carried out, leading to better outcomes, including lower mortality rates. The Committee concluded that, taking into account the limitations of the data used to derive the monthly mortality rates, the results presented by the Assessment Group may not reflect the true value of cost effectiveness of high doses of imatinib after disease progression on 400 mg/day imatinib and therefore should be interpreted with caution.

4.3.12 The Committee discussed the options for collecting data to establish outcomes in people receiving increased doses of imatinib or 1 of the comparator treatments defined in the scope. The Committee noted that despite the research recommendation in NICE's technology appraisal guidance TA86 on imatinib (published in 2004) suggesting that a national register for people receiving imatinib treatment for GISTs be maintained, such a register had not been established. The Committee heard from the manufacturer that a national register for people with GISTs is currently being set up, with pilot testing expected to begin by the end of 2010. The Committee heard from the clinical specialists that a small register has also been set up in Scotland to collect long-term treatment outcomes for people with GISTs, and that observational data from specialist cancer centres in the USA may also be available. The Committee welcomed the initiative of the manufacturer to establish a register for people with GISTs and suggested that it is important that the register collects data on outcomes specific to unresectable and metastatic GISTs.

4.3.13 The Committee discussed the health-related quality of life of people with unresectable and/or metastatic GISTs. It noted that the Assessment Group did not identify any data to use in its economic model that specifically measured the quality of life of people with GISTs who received imatinib treatment. The Committee heard from patient experts that the health measures defined in the NICE reference case, such as the EQ-5D, might not capture the benefits that people gain from imatinib treatment. The Committee considered the utility value used in the Assessment Group's economic model for imatinib and sunitinib (0.935). The Committee considered that this value was implausibly high and noted that this value had been derived from 3 out of 9 clinicians who had responded to a questionnaire. The Committee also noted that this utility value was higher than the value used in NICE's technology appraisal guidance on sunitinib, after disease progression on imatinib treatment. Although the Assessment Group carried out some sensitivity analyses that varied the utility value, the Committee was not convinced that the most plausible value had been used and considered that this added further uncertainty to the model. The Committee also considered that using a more appropriate utility value would probably increase the ICER because the difference between the utility values for active treatment and the comparator would be smaller. Therefore, the Committee concluded that collecting utility data is important for any future informed decision-making for this population.

4.3.14 The Committee considered comments from consultees and commentators on the appraisal consultation document. The Committee heard that recommendations in NICE's technology appraisal guidance TA86 on imatinib for stopping imatinib 400 mg/day were not supported by clinical specialists. The Committee heard that consultees noted that the lack of clinical evidence for this appraisal was directly attributable to the rarity of GISTs. The Committee acknowledged that, although the rarity of GISTs did contribute to the lack of evidence, more could have been done to describe the clinical experience that exists. The consultees and commentators repeated the Committee's concerns that a disease register had not been established since the publication of NICE's technology appraisal guidance TA86 on imatinib. The Committee also noted that the Assessment Group had highlighted issues contributing to the uncertainty about the clinical and cost effectiveness of imatinib at increased doses after disease progression on 400 mg/day. These issues include differing study populations, a lack of clinical evidence, and particularly sparse data on the clinical pathway of treatment with sunitinib after disease progression on 400 mg/day imatinib. The Committee appreciated the point made by consultees and commentators that, as this appraisal affected only a small group of people, giving clinicians the discretion to prescribe imatinib at doses higher than 400 mg/day would have little overall financial impact on the NHS. However, the Committee emphasised that (in line with NICE's guide to the methods of technology appraisal) the potential budget impact of the adoption of a new technology does not determine its decision.

4.3.15 The Committee explored whether it was possible to estimate a most plausible ICER. The Committee noted that the lowest ICER calculated by the Assessment Group was £27,300 per QALY gained for 600 mg/day imatinib after disease progression on 400 mg/day imatinib compared with sunitinib. However, in light of the inconsistencies in the model inputs and in the results, it recognised that this value was associated with considerable uncertainty, and should be interpreted with caution. The Committee discussed whether making any changes to the major assumptions made by the Assessment Group or further modelling might reduce the uncertainty in the estimates of cost effectiveness for high doses of imatinib. The Committee noted that any further modelling would need estimates of disease progression and mortality rates to be plausible as well as comparable across different treatment arms. The Committee agreed that all of the following changes in the assumptions would be likely to increase the ICER associated with imatinib treatment at increased doses:

- Decreasing the utility value for imatinib and sunitinib from 0.935 to a more plausible value.
- Assuming that only 50%, rather than 100%, of people receive 400 mg/day imatinib in addition to best supportive care after progression of disease at higher doses of imatinib, which is in line with current clinical practice.
- Assuming that no one receives 400 mg/day imatinib in addition to best supportive care after progression of disease at higher doses of imatinib, which is in line with current NICE recommendations.
- Using more up-to-date estimates of the effectiveness of best supportive care, which is assumed to be more effective now than when the data used in the modelling were collected.
- Accounting for utility values for additional adverse events associated with higher doses of imatinib.
- Using a more realistic effectiveness estimate for sunitinib treatment – this would be likely to increase the ICER for imatinib compared with sunitinib.

  Because these assumptions would increase rather than decrease the ICERs for increased doses of imatinib, the Committee concluded that it was highly likely that the ICERs for 600 or 800 mg/day imatinib after disease progression on 400 mg/day imatinib, compared with best supportive care or with sunitinib were above £30,000 per QALY gained.

4.3.16 Because of the lack of robust clinical effectiveness evidence available, the Committee explored if there were any other approaches for exploring a most plausible ICER. The Committee acknowledged that when imatinib was first appraised in 2004 in NICE's technology appraisal guidance TA86 on imatinib, the results of the model from the Decision Support Unit (DSU) suggested that 400 mg/day imatinib had an ICER of approximately £32,000 per QALY gained compared with best supportive care. In addition, the ICER for 600 mg/day imatinib after disease progression on 400 mg/day compared with best supportive care was estimated to be £39,000 per QALY gained. The Committee noted that at the time these results were considered to be uncertain and that since then no clinical evidence has been published that would improve the robustness of the modelling results or reduce the uncertainty of the cost effectiveness of imatinib

at increased doses. The Committee also considered that, given that the acquisition cost of 600 and 800 mg/day imatinib is obviously much higher than the cost of 400 mg/day imatinib, higher doses would need to be substantively more effective to be considered cost effective. The Committee concluded that the available evidence does not suggest that higher doses of imatinib lead to a substantive increase in effectiveness for the treatment of unresectable and/or metastatic GISTs after disease progression on 400 mg/day imatinib and that using this approach corroborates the conclusion that the most plausible ICER for 600 or 800 mg/day imatinib compared with best supportive care or with sunitinib was above £30,000 per QALY gained.

4.3.17 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

  In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.3.18 The Committee was aware that the number of people newly diagnosed with GISTs in England and Wales ranges from approximately 200 to 2000 per year. It noted that imatinib has a marketing authorisation for a number of other indications in addition to the treatment of unresectable and/or metastatic GISTs. The Committee noted that for people with unresectable GISTs, prognosis is poor, with survival generally less than 2 years without further treatment. The

Committee noted that in the economic model the survival benefit following treatment with imatinib 800 mg/day compared with best supportive care was 4.2 months. However, the Committee agreed that the evidence for this life extension could not be considered sufficiently robust, considering the uncertainty about the assumptions in the economic model, and the lack of comparative clinical effectiveness data. In addition, the Committee noted that the results of the meta-analysis (metaGIST) showed no overall survival benefit for people receiving 800 mg/day imatinib compared with people receiving 400 mg/day imatinib in people with exon 9 mutations. The Committee therefore concluded that increased doses of imatinib after disease progression on 400 mg/day imatinib did not meet the criteria for being a life-extending, end-of-life treatment.

4.3.19 The Committee considered whether its recommendation was associated with any potential issues related to equality, and noted comments made during consultation on the appraisal consultation document that not recommending 600 or 800mg/day of imatinib following disease progression with 400mg/day imatinib unfairly discriminates against people with rare diseases. The Committee also noted the respective consultees' acknowledgement that having a rare disease does not constitute 1 of the protected characteristics in the current equalities legislation or the Equality Act. However, the Committee was aware that it has general Public Law obligations of fairness and reasonableness in respect of the impact of its guidance on patients. The Committee was also aware that the Human Rights Act and article 14 of the European Convention on Human Rights (ECHR) can protect groups of people other than those covered by the UK equalities legislation. As regards article 14 ECHR, the Committee noted that it was not clear that patients affected by this appraisal or those with an exon 9 mutation would be regarded as a 'group' protected by article 14, nor that any of the substantive ECHR articles was engaged. In relation to both the ECHR obligations and public law requirements, the Committee considered that its recommendation did not unfairly disadvantage any groups within the remit of this appraisal. The Committee noted that its role was to appraise clinical and cost effectiveness and that in relation to each technology it is required to consider the robustness or otherwise of the available evidence. The Committee took into account the lack of robust clinical evidence for a survival benefit of higher doses of imatinib, specifically for the subgroup of people that have been reported to respond better, that is people with an exon 9 mutation. The Committee was also aware that an alternative treatment option is available for this group of people

because NICE's technology appraisal guidance on sunitinib recommends that patients have the option to receive treatment with sunitinib after disease progression on 400 mg/day imatinib. The Committee was satisfied that its recommendation was consistent with NICE's legislative obligations under the equalities legislation and the requirement for fairness.

4.3.20 In summary, the Committee agreed that clinical opinion suggests that increased doses of imatinib after disease progression on 400 mg/day imatinib may offer benefit to some people. However, since the previous appraisal of imatinib (NICE's technology appraisal guidance TA86), there are no new good-quality data on the clinical effectiveness of increasing the dose of imatinib. The Committee concluded that the current available clinical and cost-effectiveness evidence does not justify a positive recommendation for the use of imatinib at increased doses of 600 mg/day and 800 mg/day as an appropriate use of NHS resources for the treatment of people with unresectable and/or metastatic GISTs whose disease has progressed on 400 mg/day imatinib.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has unresectable and/or metastatic gastrointestinal stromal tumours and the healthcare professional responsible for their care thinks that imatinib is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

6.1 The Committee concluded that there were substantial gaps in the evidence and that research into the following areas should be considered:

- A national register should be maintained for all people with GISTs being treated with imatinib, sunitinib and best supportive care (to support future appraisals of treatments for this patient group). Details should include patient characteristics, dose and duration of treatment, tumour response rates and survival, both with and after discontinuation of treatment.
- The use of mutational analysis to predict individual response to imatinib treatment and long-term outcomes.
- The use of plasma level measurement to individualise imatinib treatment and to optimise long-term outcomes.

7 Appraisal Committee members 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.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Michael Boscoe
Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust

Professor John Cairns

Professor of Health Economics, Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty
External Relations Director – Pharmaceuticals and Personal Health, Oral Care Europe

Professor Jack Dowie
Health Economist, London School of Hygiene and Tropical Medicine

Dr Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Sally Gooch
Independent Nursing and Healthcare Consultant

Eleanor Grey
Lay member

Sanjay Gupta
YPD Service Case Manager, Southwark Health and Social Care, Southwark PCT

Dr Neil Iosson
General Practitioner

Dr Rosa Legood
Lecturer, London School of Hygiene and Tropical Medicine

Terence Lewis
Lay member

Dr Ruairidh Milne
Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Stephen Palmer
Senior Research Fellow, Centre for Health Economics, University of York

Dr Sanjeev Patel

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr John Rodriguez
Assistant Director of Public Health, NHS Eastern and Coastal Kent

Navin Sewak
Primary Care Pharmacist, NHS Hammersmith and Fulham

Roderick Smith
Finance Director, West Kent Primary Care Trust

Cliff Snelling
Lay member

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Nathalie Verin
Health Economics Manager, Boston Scientific UK and Ireland

Dr Colin Watts
Consultant Neurosurgeon, Addenbrookes Hospital

Tom Wilson
Director of Contracting and Performance, NHS Tameside and Glossop

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.

João Vieira, Sally Doss
Technical Leads

Fiona Rinaldi
Technical Adviser

Jeremy Powell
Project Manager

8 Sources of evidence considered by the Committee

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

- Hislop J, Quayyum Z 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, March 2010

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Manufacturers or sponsors, professional or specialist, patient or carer groups, and other consultees were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Novartis Pharmaceuticals UK

Professional or specialist, and patient or carer groups:

- Beating Bowel Cancer
- Bowel Cancer UK
- Cancer Research UK
- GIST Support UK
- Macmillan Cancer Support
- Rarer Cancers Forum
- Royal College of Nursing
- Royal College of Pathologists

- Royal College of Physicians, Medical Oncology Joint Special Committee
- Sarcoma UK
- United Kingdom Oncology Nursing Society

Other consultees:

- Department of Health
- Welsh Assembly Government

Commentator organisations (without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- National Cancer Research Institute
- National Collaborating Centre for Cancer
- NHS Quality Improvement Scotland
- Pfizer

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on imatinib by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Robin Reid, Consultant Pathologist, nominated by NHS Quality Improvement Scotland – clinical specialist
- Professor Ian Judson, Consultant, nominated by Royal College of Physicians – clinical specialist
- Dr David Cook, Retired, nominated by GIST Support UK – patient expert
- Judith Robinson, Chair of GIST Support UK, nominated by GIST Support UK – patient expert

Representatives from the following manufacturers or sponsors attended Committee

meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Novartis Pharmaceuticals UK

Update information

September 2013: Correction to show that recommendation 1.5 in NICE's technology appraisal guidance on imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours had been updated, rather than recommendation 1.4.

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