

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Final Appraisal Determination

Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours

1 Guidance

- 1.1 Imatinib treatment at 400 mg/day is recommended as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic gastro-intestinal stromal tumours (GISTs).
- 1.2 Continuation with imatinib therapy is recommended only if a response to initial treatment (as defined in Section 1.5) is achieved within 12 weeks.
- 1.3 Responders should be assessed at intervals of approximately 12 weeks thereafter. Continuation of treatment in responders to imatinib therapy is recommended at 400 mg/day until the tumour ceases to respond, as defined in Section 1.5.
- 1.4 An increase in the dose of imatinib is not recommended for people receiving imatinib who develop progressive disease after initially responding (see Section 1.5).
- 1.5 For the purpose of this guidance, response to imatinib treatment should be assessed on the basis of the results of diagnostic imaging to assess size and density of the tumour(s), patients' symptoms and other factors, in accordance with the Southwest Oncology Group (SWOG) criteria detailed in Appendix D. For the purpose of this guidance, response to therapy is defined as the SWOG classifications of complete response, partial response or stable disease.

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

2 Clinical need and practice

- 2.1 Gastro-intestinal stromal tumours (GISTs) are rare connective tissue tumours that show a differentiation profile similar to the interstitial cells of Cajal. They represent less than 1% of the tumours arising in the gastro-intestinal (GI) tract. Although GISTs can occur along the length of the GI tract, the majority arise in the stomach (60–70%), small bowel (25–35%), colon and rectum (5%) and, to a lesser extent, the oesophagus. Presenting features of these tumours depend on the size and location of the tumour and include abdominal discomfort or pain, a feeling of abdominal fullness and the presence of a palpable mass. However, many people with GISTs are asymptomatic during early stages of the disease until tumours reach a large size, at which time the tumours rupture and bleed or obstruct the GI tract.
- 2.2 Most GISTs express the tyrosine kinase growth factor receptor c-KIT, which is detected by immunostaining with the antibody for the cell-surface marker CD117. Under normal conditions, this receptor is activated by stem-cell factor, which stimulates signal transduction pathways such as cell growth, differentiation and apoptosis (cell death). Most GISTs express a form of the tyrosine kinase receptor that is permanently 'switched on' (constitutively activated), leading to unregulated cell proliferation.
- 2.3 Until recently, there has been no appropriate test for the diagnosis of GIST. An immunohistochemical test for the presence of the cell-surface marker CD117 (present in 80–100% of GISTs) is now considered to be an appropriate diagnostic marker for the diagnosis of GIST. A diagnosis of GIST is made on the basis of histological characteristics of the tumour biopsy, clinical presentation and immunohistochemical profile, including a positive test for the CD117 marker.

- 2.4 As a result of difficulties in the diagnosis of GIST, estimates of its incidence vary widely, from 4 to 40 cases per million population, which corresponds to between 200 and 2000 new cases per year in England and Wales. Recent epidemiological data from Sweden suggest that the incidence of GIST is in the region of 15 per million per year. Approximately half of new cases of GIST are likely to be metastatic and/or unresectable on first presentation. Although GIST can occur at any age, the mean age of presentation is between 50 and 70 years.
- 2.5 The prognosis of people with GIST depends primarily on whether the tumour is resectable, although the size and location of the tumour and the stage of the tumour at initial diagnosis are also important prognostic indicators. A recent study suggested that the prognosis for unresectable and/or metastatic GIST is poor with few, if any, people surviving beyond 5 years.
- 2.6 Complete surgical resection is the treatment of choice for people presenting with GISTs amenable to surgery, but there is currently no effective treatment for people with unresectable and/or metastatic tumours. As GISTs are particularly resistant to conventional cytotoxic chemotherapy and radiotherapy, current treatment normally comprises symptom relief and best supportive care. This includes palliative care for the management of pain, fever, GI obstruction, and anaemia caused by GI haemorrhage.

3 The technology

- 3.1 Imatinib (Glivec, Novartis) is a signal-transduction inhibitor designed to selectively inhibit certain classes of tyrosine kinase that include the c-KIT receptor expressed in GIST. Imatinib binds to activated c-KIT receptors and blocks the cell signalling pathway to prevent uncontrolled cell proliferation. Imatinib was first licensed for the treatment of chronic myeloid leukaemia, for which NICE guidance exists (NICE Technology Appraisal Guidance No. 70).
- 3.2 Imatinib received European marketing authorisation in May 2002 for the treatment of adult patients with KIT (CD117)-positive unresectable and/or

metastatic malignant GIST. Licensing approval was based largely on a single, uncontrolled phase II study in 147 patients. Recent developments in pathology suggest that a small minority of GISTs that test negative for the c-KIT receptor may also respond to imatinib. However, the evidence to support this is currently limited and the UK marketing authorisation for imatinib does not include the treatment of this group of tumours.

- 3.3 The manufacturer's summary of product characteristics recommends oral imatinib at a dose of 400 mg/day for the treatment of unresectable and/or metastatic GIST, to be taken with a large glass of water at meal times. The licence also states that there are limited data on the effect of dose increases from 400 mg/day to 600 mg/day in patients whose disease progresses at the lower dose.
- 3.4 Imatinib costs £12.98 per 100 mg (excluding VAT; *British National Formulary [BNF]* 47, March 2004). The approximate annual acquisition cost of imatinib is between £19,000 (400 mg/day) and £28,500 (600 mg/day). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (see Appendix A) considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

- 4.1.1 No randomised controlled trials (RCTs) were identified that compared imatinib treatment with best supportive care in patients with unresectable and/or metastatic GIST. In the absence of controlled studies, historical controls were identified to provide information on the natural history of advanced GIST. Many patients in these studies had received other treatments (such as chemotherapy or radiotherapy). These studies provide the most appropriate data for comparison with studies of imatinib treatment.

- 4.1.2 The Assessment Group identified 15 studies of imatinib treatment of c-KIT-positive GIST, which included six ongoing uncontrolled trials (four of which were only available in abstract form), eight single case studies and one case series. In the absence of any controlled trials, the Assessment Group also identified 14 uncontrolled case series and cohort studies, that is, comparator studies (one of which is currently unpublished).
- 4.1.3 Key study outcomes included: survival; tumour status (tumour mass measured by computerised tomography [CT] or magnetic resonance imaging [MRI] and classified by response evaluation criteria in solid tumours [RECIST] or SWOG criteria); and Eastern Cooperative Oncology Group (ECOG) performance status (which measures functional status in everyday tasks, and which are also reported in quality-of-life measurement scales). Positron emission tomography (PET) imaging, reported in one study, provided information on the effect of imatinib on tumour metabolism.

4.1.4 Imatinib treatment

- 4.1.4.1 Study CSTI571-B2222 is a published ongoing phase II uncontrolled trial of imatinib treatment in 147 patients (91% of which were c-KIT-positive) with unresectable and metastatic GIST, which formed the basis of the licence application. The manufacturer also provided updated results of this study, which are not yet fully published. Patients were randomly assigned to receive a single dose of 400 mg (n = 73) or 600 mg (n = 74) of imatinib. Patients received imatinib treatment for a median of 21 months (range 7 to 783 days). The study was not powered to distinguish statistically significant differences in the efficacy of imatinib treatment between the two study arms (400 and 600 mg/day). The combined survival rate from the start of treatment was 88% at 1-year follow-up and 78% at 2-year follow-up. Median survival had not been reached after 31 months of follow-up.
- 4.1.4.2 Tumour response (based on SWOG criteria, Appendix D) evaluated at 21-month follow-up showed that 66% of patients achieved a partial response, 17% stable disease and 12% progressive disease (with 5% of patients

being unevaluable). No patients achieved a complete response. The manufacturer's submission reported resistance to imatinib in 16 patients; 3 patients exhibited primary resistance (no response to imatinib) and a further 13 exhibited secondary resistance to imatinib (loss of response to imatinib).

- 4.1.4.3 There were substantial improvements in patients' ECOG performance status. At the 4-month follow-up, the proportion of patients with normal functional status (grade 0) had increased from 42% at baseline to 64%, and the number of patients with impaired functional status of grade 2 (capable of self-care but unable to work) had decreased from 18% at baseline to 5%. These improvements were maintained in the 21% of patients who were followed up to 25 months.
- 4.1.4.4 The other published study was an ongoing phase I study, which evaluated imatinib treatment at licensed doses of 400 and 600 mg/day and unlicensed higher doses in 40 patients with advanced GIST (35 of whom were c-KIT-positive). After 9 to 12 months of follow-up, survival from start of treatment was 90%. Tumour response was evaluated using RECIST criteria in the 35 patients who were c-KIT-positive: 51% achieved a partial response; 31% stable disease; and 8.5% progressive disease. Tumour function evaluated in 14 patients using PET imaging after 8 days of treatment showed that eight patients had achieved a complete response, two patients a partial response and one patient no change. The remaining three patients showed disease progression after 28 days.
- 4.1.4.5 Of the four unpublished randomised trials, two were based on large patient samples and reported estimates of progression-free survival. An ongoing European study comparing 400 mg/day with (the unlicensed dose of) 800 mg/day in 946 patients reported progression-free survival at 2 years to be approximately 40% (400 mg/day) and 55% (800 mg/day). A study based in the USA, comparing the same daily doses in 746 patients,

reported progression-free survival at 6 months to be 80% (400 mg/day) and 82% (800 mg/day).

- 4.1.4.6 Study CSTI571-B2222 (registration study) reported that at least one adverse event had been experienced by all 147 patients by 21 months' follow-up. Of these, 37% were 'severe and undesirable' (grade 3) and 15% were 'life threatening and disabling' (grade 4). A total of 15 (10%) patients withdrew from the study because of adverse events; one third of these events were classed as drug-related. The most commonly reported side effects of imatinib include nausea, diarrhoea, periorbital oedema, muscle cramps, fatigue, rash and headache. The most common serious adverse events were unspecified haemorrhage and neutropenia, each event occurring in approximately 5% of patients. Overall, imatinib was well tolerated.
- 4.1.4.7 Patient group submissions commented on the dramatic effect of imatinib, with the majority of patients experiencing improvements in disease-related symptoms (such as abdominal distension and pain) and reporting improved appetite and a feeling of well-being. Some patients were able to resume normal daily activities, which included a return to full-time employment.
- 4.1.4.8 Expert testimony at the committee meeting provided evidence on the issue of resistance to imatinib. The clinical expert informed the Committee that, although data from the clinical trials are too premature to give definitive answers regarding resistance, they expect that approximately 40% of patients may become resistant to imatinib.

4.1.5 Case series and cohort studies on the natural history of disease progression

- 4.1.5.1 Fourteen primary studies of alternative treatments (surgical resection, chemotherapy, radiotherapy and chemoembolisation) for patients with advanced GIST provided information on the natural history of disease.

- 4.1.5.2 Median survival reported in 12 papers (983 patients) ranged from 2 to 39 months, with survival rates of 37–80% at 1-year follow-up, 6–45% at 3-year follow-up and 0–45% at 5-year follow-up. However, 12 out of 14 studies did not have the GIST diagnosis confirmed by c-KIT testing.
- 4.1.5.3 Data from an unpublished cohort study were used to represent the natural history of patients with GIST. A total of 143 c-KIT-positive patients (132 patients with recurrent or metastatic GIST) were included in the retrospective analysis. Of these, 91% had previously undergone surgical resection of the tumour, and all patients had received chemotherapy for a median duration of 55 weeks. Patients surviving to the time when imatinib treatment became available were transferred to the treatment (n = 67). Survival outcomes were presented for all patients (irrespective of whether they received imatinib) and for patients who never received imatinib.

4.2 **Cost effectiveness**

- 4.2.1 No published cost-effectiveness analyses or quality-of-life studies for patients with advanced GIST were identified in the literature. The manufacturer submitted an economic model, and the Assessment Group re-analysed this model to overcome identified shortcomings. The Assessment Group also developed its own economic model, which was revised after discussion at the committee meeting to answer questions raised about some of the assumptions underpinning all the models.
- 4.2.2 The manufacturer's model estimated the incremental cost effectiveness of imatinib treatment compared with best supportive care. Patients in the control arm were assumed to start in a state of progressive disease, where they remained until death, on the basis of survival estimates extrapolated from the cohort study (using selected patients who never received imatinib only). All patients in the imatinib treatment arm were assumed to respond to imatinib treatment immediately. The probability of developing progressive disease after initial response was based on the results of the CSTI571-B2222 study. The data from both the trial and the cohort study were extrapolated to 10

years using exponential curves. Estimates of health-related utility were derived by using clinical judgement to map ECOG performance status to a generic measure of health status (the EuroQol EQ-5D). The results of the model showed the incremental cost-effectiveness ratio (ICER) estimates to be £59,000 at 2 years, £24,000 at 5 years and £14,000 at 10 years.

4.2.3 The Assessment Group modified the manufacturer's model to overcome some concerns that the Group considered would overestimate the cost effectiveness of imatinib. The first of two key amendments was to the model structure; it sought to rectify the overestimation of benefit of imatinib by using both the survival and time-to-treatment-failure curves from the registration study to estimate the proportion of patients in the imatinib health state. The second key change was to estimate survival with progressive disease from all patients included in the cohort study, including those who later went on to receive imatinib. The ICER estimates following all the modifications were £41,000 at 2 years and £30,000 at 10 years.

4.2.4 At the instruction of the Appraisal Committee, the Assessment Group, in conjunction with the NICE Decision Support Unit (DSU), was commissioned to develop its own economic model. Additional data from the cohort study (survival estimates, censored at the time imatinib became available) were sourced to improve the estimates of survival with progressive disease. One of the key differences between the DSU model and the other economic models was that the DSU model was structured so that all patients started in the same health state of progressive disease. Also, all the relevant censored data from the cohort study were used to estimate survival following progressive disease – that is, not just patients who died before they could be prescribed imatinib, but also survivors up to the point at which they were transferred to imatinib treatment. Another key difference was that the extrapolations of both the trial data and the censored cohort study data were based on all the data available and did not assume a constant hazard ratio. The estimates of utility were the same as those included in the manufacturer's economic model. The

model was also structured to estimate the cost effectiveness of different policies regarding dose escalation.

- 4.2.5 The results of the DSU model suggest that the incremental cost per additional quality-adjusted life year (QALY) is approximately £32,000 for patients on 400 mg/day estimated over 10 years. The incremental cost effectiveness of a policy allowing dose escalation to 600 mg/day after failure of 400 mg/day is approximately £39,000 at 10 years compared with a policy of treatment with 400 mg/day and no dose escalation.

4.3 *Consideration of the evidence*

- 4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of imatinib for the treatment of GIST, having considered evidence on the nature of the condition and the value placed by users on the benefits of imatinib from people with GIST, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.
- 4.3.2 The Committee heard evidence from experts on the current treatment of patients with GIST, and it was aware that imatinib is the only effective treatment for metastatic and/or unresectable GIST. Experts advised that about half of all patients with GIST have unresectable and/or metastatic disease at presentation. Experts also advised that tumour response is most commonly assessed by CT scan (tumour size and density) or MRI scan (tumour size). The Committee also heard that although PET assessment of tumour metabolism at 1 week post-treatment could provide early information on patients' responses to imatinib treatment, the PET technology is not currently routinely available. The Committee therefore considered that assessment of tumour response should be based principally on the SWOG criteria (Appendix D) because this classification of tumour response was reported in the published clinical study and formed the basis of all of the economic models. The Committee understood that estimates of SWOG response criteria are assessed by CT/MRI and that these include an element

of assessment of symptoms and the need to take note that tumour enlargement may be related to swelling associated with tissue necrosis. It was also persuaded that changes in the density of the tumour deposits as assessed by CT scanning may also indicate response to therapy and that these changes should be included as part of the overall assessment of the response to imatinib. The Committee also concluded that further research into the use of PET for assessing tumour response would be beneficial.

- 4.3.3 The experts informed the Committee that patients with multiple lesions may experience tumour growth in some sites while the bulk of the tumour remains under control. The Committee carefully considered the SWOG criteria in relation to these situations. It acknowledged that the criteria would allow for an increase in tumour size of up to 50% or 10 cm (whichever is smaller) in the sum of products of all measurable lesions over the smallest sum observed. The Committee also noted that lesions that appear to increase in size because of the presence of necrotic tissue are not considered to have progressed using the SWOG criteria. For these reasons, the Committee concluded that the use of SWOG criteria to assess response is appropriate.
- 4.3.4 The experts advised the Committee on the difficulties involved in diagnosing metastatic and/or unresectable GISTs, the assessment of response to treatment and determining the appropriate mix and timing of treatments (surgery or drug therapy) for these patients. The Committee therefore concluded that imatinib therapy should be used only under the supervision of an expert with experience in the treatment of these patients. It is understood that this may also include shared care of the management of these patients between experts in GIST with other cancer centres.
- 4.3.5 The Committee heard evidence that mutational analysis to determine whether patients have a mutation in *KIT* may enable clinicians to predict the patients who are most likely to respond to imatinib treatment, as patients with no mutations in *KIT* have a poorer prognosis. Although these tests are not widely available in the UK, the Committee believed that further research into their

use to identify patients for whom imatinib may be particularly appropriate would be important.

- 4.3.6 The Committee carefully considered the appropriate length of time for which patients should receive imatinib after initiation of treatment before first assessment of response and at what stage treatment should be considered to have failed. Experts advised that patients are usually evaluated (by an assessment of diagnostic imaging and clinical symptoms) at about 12 weeks from the initiation of treatment, at which stage the disease is classified as complete response, partial response, stable disease or progressive disease. The experts also advised the Committee that a tumour response to imatinib, including stabilisation of disease, is usually seen within 12 weeks of initiation of treatment. The Committee also considered evidence from various sources that the maximum response of GIST to imatinib may not be reached for up to 6 to 12 months from initiation of treatment. The Committee was, however, persuaded that the time taken to achieve an initial response would be significantly less than that taken to achieve a maximum response, as is evidenced from the PET scanning studies, which show that response to imatinib can be achieved within the first 2 weeks of treatment. Additionally, the Committee noted that all of the clinical trials included early review of patients as part of the assessment of response to treatment. The Committee considered, therefore, that patients should initially receive imatinib treatment for up to 12 weeks before tumour response is evaluated, but that only patients responding to treatment (as defined in Section 1.5) by 12 weeks should continue to be treated with imatinib until there is further evidence of disease progression. In making this judgment, the Committee took into account the fact that the definition of tumour response allows for an increase in the size of tumour(s) due to necrosis and swelling, and for stabilisation (that is, no change) of disease within the SWOG criteria.
- 4.3.7 The Committee also considered the evidence on the effectiveness of the higher initial dose of imatinib of 600 mg/day from the CSTI571-B2222 study and the evidence published in abstract form on the daily dose of 800 mg. The

Committee concluded from the evidence reviewed that there was no difference in the effectiveness between initial doses of 400 mg/day and 600 mg/day. The Committee considered the early results from the two trials comparing initial doses of 400 mg/day and 800 mg/day. They acknowledged that the interim results from one of these trials showed a non-significant benefit in progression-free survival from 800 mg/day compared with 400 mg/day and that the other trial showed very little difference between the two daily dosages. The Committee concluded that the data from these studies were too premature to draw firm conclusions. The Committee was also aware that the safety and tolerability of a daily dose of imatinib of 800 mg has not yet been assessed by the Medicines and Healthcare products Regulatory Agency. The Committee concluded that it was unable to issue guidance on a dose of 800 mg/day because this dosage has not yet received a UK marketing authorisation, and it was persuaded that the licensed dosage of 400 mg/day was the most appropriate initial dose of imatinib.

- 4.3.8 The Committee considered evidence from the trials, and new information provided by the manufacturer, regarding dose escalation in patients with progressive disease. The Committee considered that the data on dose escalation were limited because the number of patients involved was small, the length of follow-up for these patients was short, and patients were not allocated to dose escalation by randomisation, possibly leading to bias in the results. The Committee considered all the evidence on dose escalation in relation to the economic models and concluded that dose escalation is not cost effective.
- 4.3.9 The Committee also considered views of the experts regarding dose escalation in patients with progressive disease following initial treatment. The experts advised that there is a lack of evidence supporting the effectiveness of dose escalation to 600 mg/day. The Committee acknowledged that studies were ongoing to evaluate the effectiveness of an 800 mg dose of imatinib, and it concluded that there is currently no robust evidence to suggest that

continued treatment with imatinib (including dose escalation) in patients with progressive disease is cost effective.

4.3.10 The Committee carefully considered the most appropriate estimates of survival for a control group for imatinib treatment in the cost-effectiveness modelling. All the models used data from the same unpublished historical control study to represent the natural history of GIST, but differed in the selection of patients and whether the data were censored for when imatinib treatment became available. The Committee considered this data to be the most appropriate because all patients' tumours were diagnosed as CD117-positive. The Committee concluded that data on the survival of the control group, censored for when imatinib became available, was the least prone to bias and the best estimate of prognosis of untreated GIST.

4.3.11 The Committee considered the different methods of extrapolating the trial and cohort study data to a 10-year time horizon in the cost-effectiveness models. The DSU model, which did not assume constant hazard and used all of the available data for both the treatment and control groups, was considered to be the most appropriate method of extrapolation. The Committee concluded that the cost-effectiveness estimates based on a 10-year time horizon were the most appropriate, because this time horizon was likely to encompass the key costs and benefits. The Committee considered the results from extrapolating the data in relation to new information (at 152 weeks' follow-up) provided by the manufacturer. The Committee acknowledged that the extrapolated time to progression in the DSU model was shorter, and that the extrapolated time to progression in the manufacturer's model was longer, than the time to progression shown by the new data supplied by the manufacturer. However, the Committee also noted that overall survival predicted using the DSU model was longer than suggested by the new data provided by the manufacturer. Thus, the Committee concluded that the ICER produced using the DSU model was likely to be an underestimate when considering this new data.

4.3.12 The Committee considered that the assumption that all patients would respond to imatinib immediately (as presented in the manufacturer's and Assessment Group model) was unlikely. The Committee concluded that the estimates of cost effectiveness based on the DSU model (in which all patients begin in the progressive phase) used the most appropriate available data and assumptions.

4.3.13 The Committee heard evidence from experts regarding likely tumour response rate in the event of dose escalation. The DSU model assumed that patients who are escalated to 600 mg/day after disease progression on 400 mg/day have the same response as when they initially responded to the lower dose. The experts advised the Committee that the time to treatment failure following dose escalation is likely to be substantially shorter than the initial response at 400 mg/day. The Committee therefore considered that this assumption (of an equivalent length of response following dose escalation) used in the DSU economic model was more optimistic than suggested by the experts. The Committee also considered new evidence on response following dose escalation provided by the manufacturer. The Committee considered that the assumption about the proportion of patients responding to dose escalation in the economic model was more optimistic than supported by the evidence provided by the manufacturer. These conclusions supported their view on the inappropriateness of dose escalation in progressive disease, as in Sections 4.3.8 and 4.3.9.

4.3.14 The Committee heard testimony from the representative for patients with GIST and the clinical experts about the dramatic improvement in health-related quality of life associated with successful imatinib treatment. In addition, the Committee considered advice from a clinical expert that, in a minority of patients, imatinib treatment may be given until unresectable tumours shrink to a size at which they can be surgically resected. The expected survival of these patients is better than the expected survival of patients whose tumours remain unresectable. The Committee considered that both of these factors may not have been fully represented in the economic

modelling. The Committee concluded that if data were available to model these issues more robustly, the ICERs would be slightly lower. However, it concluded that these factors did not alter its overall view of the cost effectiveness of imatinib therapy for GIST.

4.3.15 Experts commented that current practice sometimes includes the continuation of imatinib treatment in patients with progressive disease (as assessed by CT/MRI), provided that they report a symptomatic benefit without objective evidence of response. However, the Committee considered that, because there is a lack of robust evidence on the effectiveness of extended treatment in these patients, and because a decrease in the overall rate of response to imatinib treatment would increase the ICERs to an unacceptable level, the use of imatinib in this context should be undertaken only in the context of clinical studies.

4.3.16 The Committee was aware of the continuing research in this area and the emergence of new data published in abstract form during the consultation process. This new information included evidence relating to updated results from trials, dose escalation, assessment of response and discontinuation of imatinib therapy. The manufacturer also provided updated results for the CSTI571-B2222 study. The Committee considered that this evidence has not yet been fully peer reviewed and that much of the evidence relates to the unlicensed dose of imatinib of 800 mg/day. The Committee considered this evidence and its relation to the results of the economic models when making its recommendations. The Committee concluded that it would be important to re-evaluate the recommendations when new evidence becomes fully available or if substantial changes are made to the marketing authorisation of imatinib.

5 Recommendations for further research

5.1 A national register of all patients receiving imatinib treatment for GIST should be maintained. Details could include patient characteristics, dose and duration

of treatment, mutational analysis, tumour response rates and survival both with and after discontinuation of imatinib treatment. The response rates of patients who have received escalated doses of imatinib treatment in the context of clinical trials could also be included.

- 5.2 The key dose-response trials for imatinib for metastatic and/or unresectable GIST are still in progress. There are also studies assessing the use of imatinib in patients with metastatic and/or unresectable GIST that have been published in abstract form, and many report interim results.
- 5.3 The Institute recommends that further trials be undertaken to evaluate the benefit of maintenance therapy at 400 mg/day for patients with progressive disease, and the response rate of patients after switching to higher doses of imatinib treatment. The effectiveness of dose escalation should be evaluated for patients who do not respond to imatinib treatment at 400 mg/day, and for patients who initially respond to the lower dose but later develop progressive disease. These trials should incorporate measures of health-related quality of life. Information on survival following withdrawal of imatinib treatment should also be collected.
- 5.4 The Institute considered that studies should be conducted to assess:
- the effectiveness of PET assessment for the measurement of tumour response
 - the use of mutational analysis to predict individual responses to imatinib treatment.

6 Implications for the NHS

- 6.1 The cost impact of this guidance will depend on: the number of patients with unresectable and/or metastatic GIST; the proportion of patients who receive imatinib; the proportion of patients who respond to imatinib treatment; the duration of treatment; the price of imatinib; and the number of patients already prescribed imatinib for GIST.

- 6.2 Estimates of the annual incidence of GIST vary considerably. The manufacturer of imatinib estimated the number of new cases of unresectable and/or metastatic GIST to be between 80 and 240 people each year. It has also been suggested that current estimates of the incidence of GIST are underestimates, and these figures may increase as more tumours of patients with GIST are tested for c-KIT. The annual drug cost of imatinib is just under £19,000. Assuming that there will be 240 new patients eligible for imatinib treatment for GIST and that patients will be monitored by an average of four CT scans per year, the total cost of treating new patients in accordance with the guidance will be approximately £4.7 million in the first year. Assuming that the incidence rate does not change and that patients remain on imatinib treatment for an average of 1.44 years (as predicted by the DSU economic model), the total cost of treating patients with imatinib for GIST will be approximately £6.8 million when the number of patients receiving imatinib has reached a steady state.
- 6.3 The resource impact of this guidance on the NHS will depend on the number of patients currently receiving NHS prescriptions for imatinib for the treatment of GIST. Using the assumptions set out in Section 6.2, if 25% of eligible patients currently receive NHS prescriptions for imatinib for GIST, the additional cost of implementing this guidance will be approximately £5.1 million. If 75% of eligible patients are currently being treated with imatinib, the impact of the guidance will be less, at about £1.7 million. These estimates are based on a number of assumptions and could be much less if switching to higher doses of imatinib is reduced. The estimates may also be reduced further if GIST patients receive imatinib treatment as a result of the guidance rather than receiving inappropriate surgery or chemotherapy treatment.

7 Implementation and audit

- 7.1 All clinicians who treat people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST should review their current policies and practice to take account of the guidance set out in Section 1.
- 7.2 Local guidelines or care pathways for the care of patients with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
- 7.3.1 For a person with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST, imatinib treatment at 400 mg/day is provided as first-line management for up to 12 weeks.
- 7.3.2 Imatinib therapy at 400 mg/day is continued beyond the first 12 weeks only if a person's GIST responds to treatment within 12 weeks. (Response to treatment is defined in Section 1.5 and Appendix D.)
- 7.3.3 A person whose GIST has responded to imatinib therapy is assessed at intervals of approximately 12 weeks and imatinib therapy at 400 mg/day is continued until the GIST ceases to respond. (Response to treatment is defined in Section 1.5 and Appendix D.)
- 7.3.4 If progressive disease develops in a person whose GIST initially responded to imatinib therapy, the dose of imatinib is not increased.
- 7.3.5 A cancer specialist with experience in the management of people with metastatic and/or unresectable GISTs supervises the use of imatinib.

8 Related guidance

National Institute for Clinical Excellence (2003) Guidance on the use of imatinib for chronic myeloid leukaemia. *NICE Technology Appraisal Guidance* No. 70. London: National Institute for Clinical Excellence.

9 Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.
- 9.2 The guidance on this technology will be reviewed in September 2007.

David Barnett
Chair, Appraisal Committee
July 2004

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its 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. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into three branches, with the chair, vice-chair and a number of other members between them attending meetings of all branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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 Anthony Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, University of Bristol

Dr Tom Aslan

General Practitioner, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Professor Sheila M Bird

MRC Biostatistics Unit, Cambridge

Professor Rosamund Bryar

Professor of Community and Primary Care Nursing, St Bartholomew's School of Nursing and Midwifery, London

Dr Rodney Burnham

Consultant Physician and Gastroenterologist, Oldchurch Hospital, Romford

Dr Gary Butler

Consultant Paediatrician/Endocrinologist, Leeds General Infirmary

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer, Health Economics, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich

Dr Christopher Eccleston

Director Pain Management Unit, University of Bath

Professor Gary A Ford

Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

Ms Bethan George

Interface Liaison Pharmacist, Tower Hamlets PCT and Royal London Hospital, Whitechapel

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Dr Trevor Gibbs

Head, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, Greenford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin

Health Outcomes Manager, Johnson & Johnson Medical Ltd, Ascot

Dr Elizabeth Haxby

Lead Clinician in Clinical Risk Management, Royal Brompton Hospital, London

Professor Philip Home

Professor of Diabetes Medicine, University of Newcastle upon Tyne

Dr Catherine Jackson

Clinical Lecturer in Primary Care Medicine, Alyth Health Centre, Angus

Dr Terry John

General Practitioner, The Firs, London

Mr Muntzer Mughal

Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust, Chorley

Judith Paget

Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne

Health Economics, Nowgen: The North West Genetics Knowledge Park, Manchester

Mr James Partridge

Chief Executive, Changing Faces, London

Mrs Kathryn Roberts

Nurse Practitioner, Hyde, Cheshire

Professor Philip Routledge

Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Ms Anne Smith

Trustee, Long-Term Medical Conditions Alliance

Dr Debbie Stephenson

Head of HTA Strategy, Eli Lilly and Company, Hampshire

Professor Andrew Stevens (Vice-Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner, and Senior Lecturer, Department of Primary Care and General Practice, University of Birmingham

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Dr Paul Watson

Medical Director, Essex Strategic Health Authority

Dr David Winfield

Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

B. NICE Project Team

Each appraisal of a technology is assigned to one or more Health Technology Analyst(s) and a Technology Appraisal Project Manager within the Institute.

Eleanor Donegan and Louise Longworth

Technical Leads, NICE project team

Kathleen Dalby

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

A The Assessment Report for this appraisal was prepared by the West Midlands Health Technology Collaboration.

Wilson J, Connock M, Song F, Yao G, et al. *Imatinib for gastro-intestinal tumours*. October 2003.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:

- Novartis

II Professional/specialist and patient/carer groups:

- Association of Upper GI Surgeons
- Barking and Dagenham Primary Care Trust
- British Association of Surgical Oncology
- British Oncological Association
- British Oncology Pharmacy Association
- British Society of Gastroenterology
- CancerBACUP
- Department of Health
- Digestive Disorders Foundation
- Long-Term Medical Conditions Alliance
- Macmillan Cancer Relief
- Marie Curie Cancer Care
- National Cancer Alliance

- National Council for Hospice and Specialist Palliative Care Services
- Newark and Sherwood Primary Care Trust
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Surgeons
- Royal Pharmaceutical Society
- Tenovus Cancer Information Centre
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- British Medical Association
- British National Formulary
- Cancer Research UK
- Institute of Cancer Research
- MRC Clinical Trials Unit, Cancer Division
- National Cancer Research Institute
- NHS Confederation
- NHS Information Authority
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Sarcoma UK

- C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. 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 for the treatment of GIST by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.
- Dr David B Cook, Patient Representative, Life Raft, nominated by CancerBACUP
 - Professor Ian Judson, Professor of Cancer Pharmacology, Institute of Cancer Research, nominated by The Institute of Cancer Research and The Royal College of Physicians
 - Professor PJ O'Dwyer, Professor of Gastrointestinal Surgery, Western Infirmary, Glasgow, nominated by British Association of Surgical Oncology and The Institute of Cancer Research
 - Ms Sue Green, Senior Cancer Information Nurse, CancerBACUP, nominated by CancerBACUP

Appendix C. Detail on criteria for audit of the use of imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours

Possible objectives for an audit

An audit on the appropriateness and effectiveness of use of imatinib for the treatment of unresectable and/or metastatic GIST could be carried out to ensure the following.

- Imatinib is used appropriately for the treatment of unresectable and/or metastatic GISTs.
- The use of imatinib for the treatment of unresectable and/or metastatic GISTs is supervised by an appropriate cancer specialist.

Possible patients to be included in the audit

An audit could be carried out on patients diagnosed with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST over a reasonable time period for audit. In view of the small number of patients who may be eligible for inclusion in the audit, all patients should be included in the audit and it may be desirable to collect data for the audit concurrent with treatment.

Measures that could be used as a basis for an audit

The measures that could be used in an audit on the use of imatinib for the treatment of unresectable and/or metastatic GISTs are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. For a person with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST, imatinib therapy is provided as first-line management as follows:</p> <p>a. at 400 mg/day and</p> <p>b. for up to 12 weeks</p>	<p>100% of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST</p>	<p>None</p>	
<p>2. Imatinib therapy at 400 mg/day is continued beyond the first 12 weeks only if the person's GIST has responded to treatment within 12 weeks</p>	<p>100% of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST who have been provided imatinib</p>	<p>None</p>	<p>'GIST response to treatment' is assessed by a scan or MRI scan to assess the size and density of the tumour(s), patients' symptoms and other factors, and is classified as complete response, partial response or stable disease as defined by the SWOG criteria (see Appendix D).</p>
<p>3. A person whose GIST has responded to imatinib therapy is treated as follows:</p> <p>a. the person is assessed at intervals of approximately 12 weeks and</p> <p>b. imatinib therapy at 400 mg/day is continued until the GIST ceases to respond</p>	<p>100% of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST who have been provided imatinib and whose GIST has responded to imatinib</p>	<p>None</p>	<p>See above for definition of GIST response to treatment. 'Assessment' includes review of the findings of diagnostic imaging and clinical symptoms.</p>

	therapy		
4. If progressive disease develops in a person whose GIST initially responded to imatinib therapy, the dose of imatinib is not increased	100% of people in whom progressive disease develops when the GIST responded initially to imatinib therapy	A. In cases for which initial tumour flare reaction is possible, either symptoms must persist beyond 4 weeks or there must be additional evidence of progression B. Lesions that appear to increase in size due to presence of necrotic tissue are not considered to have progressed	See above for definition of progressive disease.
5. A cancer specialist with experience in the management of people with metastatic and/or unresectable GISTs supervises the use of imatinib	100% of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST who have been provided imatinib	None	Clinicians will need to agree locally on what constitutes supervision of the use of imatinib for people with KIT (CD117)-positive unresectable and/or KIT (CD 117) positive metastatic GIST, for audit purposes.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **crit**erion **plus** number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.

Appendix D. Southwest Oncology Group (SWOG) criteria for assessing tumour response

SWOG criteria	Definition
Complete response (CR)	Complete disappearance of all measurable and evaluable disease. No new lesions. No disease-related symptoms. No evidence of non-evaluable disease, including normalisation of markers and other relevant abnormal lab values. All measurable, evaluable and non-evaluable lesions and sites must be assessed using the same technique as baseline.
Partial response (PR)	Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline.
Stable disease (SD)	Does not qualify for CR, PR, progression or unknown. All measurable and evaluable sites must be assessed using the same technique used at baseline.
Progressive disease (PD)	<p>50% increase or an increase of 10 cm² (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, or clear worsening from previous assessment of any evaluable disease, or reappearance of any lesion which had disappeared, or appearance of any new lesion/site, or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). For 'scan-only' bone disease, increased uptake does not constitute clear worsening. Worsening of existing non-evaluable disease does not constitute progression.</p> <p>Exceptions: (1) In cases for which initial tumour flare reaction is possible (hypercalcaemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond 4 weeks or there must be additional</p>

	evidence of progression. (2) Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
Unknown	Progression has not been documented and one or more measurable or evaluable sites have not been assessed.