

# Guidance on the use of imatinib for chronic myeloid leukaemia

Technology appraisal guidance

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[www.nice.org.uk/guidance/ta70](http://www.nice.org.uk/guidance/ta70)

## 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.

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This guidance replaces TA50.

This guidance is partially replaced by TA425 and TA426.

# 1 Guidance

- 1.1 This recommendation has been updated and replaced by NICE technology appraisal guidance on [dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia](#).
- 1.2 Imatinib is recommended as an option for the treatment of people with Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) who initially present in the accelerated phase or with blast crisis. Additionally, imatinib is recommended as an option for people who present in the chronic phase and then progress to the accelerated phase or blast crisis if they have not received imatinib previously.
- 1.3 This recommendation has been updated and replaced by NICE technology appraisal guidance on [dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia](#).
- 1.4 For people in chronic-phase CML who are currently receiving interferon alpha (IFN- $\alpha$ ) as first-line treatment, the decision about whether to change to imatinib should be informed by the response of the disease to current treatment and by the tolerance of the person to IFN- $\alpha$ . This decision should be made after informed discussion between the person with CML and the clinician responsible for treatment, taking full account of the evidence on the risks and benefits of imatinib and the wishes of the person.

## 2 Clinical need and practice

- 2.1 CML is one of the most common types of leukaemia in England and Wales. In CML, the bone marrow produces an excessive number of abnormal stem cells. The abnormal cells eventually suppress the production of normal white blood cells, which act to protect the body against infection.
- 2.2 CML accounts for more than one in six leukaemias in adults, with around 600 new cases being registered in England and Wales each year; the annual case rates are 1.0 per 100,000 men and 0.8 per 100,000 women. In England and Wales, around 2660 people have CML.
- 2.3 Ninety-five percent of people with CML have a chromosomal abnormality caused by a reciprocal translocation between parts of the long arms of chromosome 22 and chromosome 9; this produces what is commonly known as the 'Philadelphia chromosome'. As a consequence of the translocation, a *bcr-abl* fusion gene is produced. The abnormal protein encoded by this fusion gene is a constitutively active tyrosine kinase, which influences cellular processes such as proliferation, differentiation and survival. Cells containing the abnormal gene and protein replicate quickly and may be protected from programmed cell death. They therefore become predominant, initially in the bone marrow and subsequently in the bloodstream, impairing the production of normal white cells.
- 2.4 CML is diagnosed by the presence of a characteristic blood and bone marrow cellular picture, together with cytogenetic and molecular diagnostic techniques (such as fluorescence in situ hybridisation, Southern and Western blotting techniques, reverse transcriptase polymerase chain reaction, and CRKL phosphorylation assay).
- 2.5 CML usually has three identifiable phases: the chronic phase, the accelerated phase and the blast-crisis phase. The chronic phase is the initial phase of CML; it is usually relatively stable and benign, and typically lasts around 3–5 years following diagnosis. The accelerated phase is seen in about two-thirds of people affected; others progress

directly to blast crisis. The accelerated phase typically lasts for 2–15 months before progression to the blast-crisis phase occurs. The blast-crisis phase lasts 3–6 months and inevitably leads to death. Typically, the annual progression from chronic to blast-crisis phase is 5–10% in the first 2 years, and 20% in subsequent years.

- 2.6 Current treatment options for CML include allogeneic stem cell transplant (SCT), IFN- $\alpha$ , imatinib (for the accelerated and blast-crisis phases, and second-line therapy in the chronic phase), and conventional chemotherapy (usually with hydroxyurea [HU; also known as hydroxycarbamide] or busulfan). Treatment depends on the general health and age of the person and, for transplantation, on the availability of a suitable matched stem cell donor.
- 2.7 SCT remains the only potentially curative option for CML. However, the shortage of donors, patient-related factors such as age, and risks associated with the procedure, limit the number of people for whom SCT is an option. SCT is generally thought to be more successful in young people and those who are at a relatively early stage of CML. Treatment-related mortality associated with SCT is estimated to be between 20% and 40%. Conventional chemotherapy and immunotherapy (with IFN- $\alpha$ ) do not offer a cure; they are used with the aim of maintaining the person in – or returning him or her to – the chronic phase.
- 2.8 Most people in the chronic phase who are not suitable candidates for SCT are offered IFN- $\alpha$ , which is regarded as superior to conventional chemotherapeutic agents in improving survival. However, 15–25% of people with CML discontinue IFN- $\alpha$  therapy because of intolerable side effects. The immediate side effects of IFN- $\alpha$  include fever, chills and anorexia; more serious chronic side effects are fatigue, depression, insomnia, weight loss, peripheral neuropathy, alopecia, stomatitis, diarrhoea and short-term memory loss. For those who are intolerant of IFN- $\alpha$ , or in whom IFN- $\alpha$  treatment has failed, imatinib is the treatment of choice, in line with the previous guidance issued by the Institute in September 2002 (*NICE Technology Appraisal Guidance No. 50*).
- 2.9 The treatment strategies for the accelerated and blast-crisis phases of CML are less well defined. Most people will have received prolonged

treatment in the chronic phase of the disease, usually with IFN- $\alpha$ , imatinib or HU, and in the accelerated phase disease control may be maintained in some people by increasing the doses of these drugs. High-dose combination chemotherapy is commonly used for people in blast crisis; the agents used include mercaptopurine, dexamethasone, prednisolone, idarubicin hydrochloride, etoposide, cytosine arabinoside, vincristine sulphate and daunorubicin.

## 3 The technology

- 3.1 Imatinib (Glivec) is the first in a new class of cancer drugs, the signal-transduction inhibitors, rationally designed to competitively inhibit BCR-ABL tyrosine kinase activity. By blocking specific signals in cells expressing the BCR-ABL protein, imatinib reduces the uncontrolled proliferation of white blood cells that is a characteristic feature of the disease.
- 3.2 Imatinib initially received marketing authorisation from the European Agency for the Evaluation of Medicinal Products (EMA) for the treatment of people with Philadelphia-chromosome-positive CML in the chronic phase after failure of IFN- $\alpha$ , or in the accelerated phase or blast crisis, despite the absence of evidence from randomised controlled trials (RCTs); this was in November 2001. The licence was granted "under exceptional circumstances" and on the basis of the data on surrogate measures such as overall haematological and cytogenetic response rates, and progression-free survival. The EMA stated that "the indications for which the medicinal product in question [imatinib] is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the quality, safety and efficacy of the medicinal product". Recently, the licence was extended, on the basis of new evidence from an RCT, to include the treatment of people with newly diagnosed Philadelphia-chromosome (*bcr-abl*)-positive CML for whom SCT is not considered as the first line of treatment.
- 3.3 The manufacturer's Summary of Product Characteristics (SmPC) states that there are no controlled trials demonstrating an increase in survival. It also states that the effect of imatinib on the outcome of SCT has not been determined, and that the experience with imatinib in children with CML is very limited.
- 3.4 The majority of people taking imatinib experience adverse reactions at some stage. The most frequently reported adverse effects of imatinib in clinical studies include nausea, vomiting, oedema (fluid retention), muscle cramps, skin rash, diarrhoea, abdominal pain, headache and



fatigue. Cytopenia, particularly neutropenia and thrombocytopenia, has been reported in all studies, with a higher incidence in people in blast crisis and in the accelerated phase compared with those in the chronic phase. In clinical studies, 1% of people in the chronic phase, 2% of those in the accelerated phase, and 5% of those in the blast-crisis phase were withdrawn because of adverse events. For full details of side effects and contraindications, see the SmPC.

- 3.5 The recommended dosages of imatinib in the SmPC are 400 mg/day in the chronic phase and 600 mg/day in the accelerated phase and blast crisis. The dose is taken orally, once daily, with a meal and a large glass of water. Dose escalation from 400 mg/day to 600 mg/day for people in the chronic phase, and from 600 mg/day to 800 mg/day (given as 400 mg twice daily) for people in the accelerated phase or blast-crisis phase is sometimes considered, provided that there is no severe adverse drug reaction or severe nonleukaemia-related neutropenia or thrombocytopenia.
- 3.6 Imatinib costs £12.98/100 mg (excluding VAT; *British National Formulary* 45, March 2003). The approximate annual cost of imatinib is between £19,000 and £28,500 for a person in the chronic phase, and between £28,500 and £38,000 for a person in the accelerated phase or in blast crisis, depending on the dose.

## 4 Evidence and interpretation

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

### 4.1 Clinical effectiveness

- 4.1.1 Haematological response (HR) and cytogenetic response (CR) have been used as surrogate measures of efficacy in imatinib studies. HR refers to the normalisation of blood cell counts, whereas CR refers to the reduction (partial CR) or elimination (complete CR) from the bone marrow of white blood cell precursors with the Philadelphia chromosome.
- 4.1.2 One RCT and three case series were identified in published literature; all were sponsored by the manufacturer of imatinib. All three case series were described as open-label, non-randomised, phase II studies. Of these, one investigated the efficacy of imatinib as a second-line treatment (after failure of IFN- $\alpha$ ) in 454 people with chronic-phase CML; one investigated the efficacy of imatinib in 181 people in the accelerated phase; and the third investigated imatinib in 229 people in blast crisis. These three case series were reviewed by the Institute when producing the previous NICE guidance on imatinib (*NICE Technology Appraisal Guidance No. 50*).
- 4.1.3 The RCT (known as the IRIS trial) compared imatinib with the combination of IFN- $\alpha$  and cytarabine (Ara-C) in 1106 people with newly diagnosed chronic-phase CML. Full details of the IRIS trial and a summary of the updated results from the case series were made available to the Institute as part of the manufacturer's submission for this appraisal. The major outcome measures in these studies were time to progression, CR, HR and survival. The IRIS trial also reported on measures of quality of life (QoL).

#### Chronic phase (first line)

- 4.1.4 In the IRIS trial, intention-to-treat analyses of the results at 18 months

indicated that the disease had not progressed in an estimated 92% of people in the imatinib group (n = 553) compared with 74% of people in the IFN- $\alpha$  and Ara-C combination group (n = 553). Additionally at 18 months, complete CR was achieved more often in people in the imatinib group compared with those in the IFN- $\alpha$  and Ara-C combination group (76% versus 15% of people, respectively).

- 4.1.5 The difference in overall survival between groups was not statistically significant at 18 months: 97% in the imatinib group versus 95% in the IFN- $\alpha$  and Ara-C combination group (p = 0.16).
- 4.1.6 Withdrawal because of side effects was 2.2% in the imatinib group compared with 6.0% in the IFN- $\alpha$  and Ara-C combination group at 18 months. Crossover as a result of intolerance was much higher in the IFN- $\alpha$  and Ara-C combination group (25%) compared with the imatinib group (less than 1%).
- 4.1.7 QoL was reported to be better in the imatinib group compared with the IFN- $\alpha$  and Ara-C combination group when assessed at 1, 3 and 6 months using the 'Functional Assessment of Cancer Therapy – Biological Response Modifier' (FACT-BRM) instrument. However, interpretation of the results may be difficult because of different completion rates of the groups (80% in the imatinib group versus 59% in the IFN- $\alpha$  and Ara-C group at 12 months) and the high withdrawal rates in the IFN- $\alpha$  and Ara-C combination group. In addition, only three of the five subscales of the FACT-BRM were used in this trial.
- 4.1.8 In the IRIS trial, the overall crossover rate (including crossover as a result of treatment failure) between groups was high, in particular for those who were initially treated with the IFN- $\alpha$  and Ara-C combination. At 18 months, 11 out of 553 (2%) people in the imatinib group and 318 out of 553 (58%) in the IFN- $\alpha$  and Ara-C group had crossed over treatments.

## **Chronic phase (after failure of or intolerance to IFN- $\alpha$ )**

- 4.1.9 In the case series that investigated the efficacy of imatinib in 454 people with late chronic-phase CML, for whom previous therapy with IFN- $\alpha$  had failed, complete HR was achieved in 95% of people, major CR (complete

or partial) in 60% of people, and complete CR in 41% of people, at 18 months. Overall survival was 95% at 18 months. Additional analysis of data reported in this study suggested that progression-free survival at 18 months was significantly longer in those who demonstrated major CR at 3 months compared with those who did not (97% versus 88%,  $p = 0.005$  by the log-rank test).

- 4.1.10 At the 31-month follow-up, 74% of the original study population remained on imatinib and 48% of these still demonstrated complete CR. The progression-free survival was estimated to be 87% at 24 months, with overall survival of 92% at 24 months.

## Accelerated phase

- 4.1.11 In the published accelerated-phase study, the results were reported at median follow-up times of 9.9 (400-mg group,  $n = 77$ ) and 11 months (600-mg group,  $n = 158$ ). Combining both groups and time points, 53% achieved complete HR and 19% returned to the chronic phase. Major CR was reported in 24% of the study population, whereas 17% had complete CR. Estimated overall survival rates at 12 months were 65% (95% confidence interval [CI], 53% to 77%) for the 400-mg group, and 78% (95% CI, 68% to 81%) for the 600-mg group. Median survival had not been reached in either group at the time the study results were published. The progression-free survival rates at 12 months were 44% (95% CI, 31% to 56%) for the 400-mg group, and 67% (95% CI, 59% to 76%) for the 600-mg group.

- 4.1.12 At the 36-month follow-up in the 600-mg group, the overall survival rate was 66%, with an expected time to progression of 23 months.

## Blast crisis

- 4.1.13 In the published blast-crisis study, sustained HR (lasting at least 4 weeks) was reported for 31% of people ( $n = 229$ ); 8% of people had complete HR and 18% had returned to the chronic phase. The median duration of treatment was 4.0 months (600 mg). At this time point, 16% of people achieved major CR, with 7% having complete CR. Among those who achieved a sustained response, the median duration of HR was

estimated to be 10 months. The overall 12-month survival rate was estimated to be 32%.

- 4.1.14 At the 36-month follow-up, 8% of the study population remained on imatinib, and the overall median survival was 6.9 months.

## 4.2 Cost effectiveness

- 4.2.1 Only one published abstract concerned with economic evaluation of second-line imatinib therapy (after IFN- $\alpha$  had failed) was identified in the literature. In addition, the manufacturer's submission presented an economic model, and the Assessment Group developed an independent economic model.
- 4.2.2 The published economic evaluation (abstract only) did not provide full details of methodology or sensitivity analyses. This study reported the incremental cost-effectiveness ratio (ICER) of imatinib as a second-line treatment over HU in the chronic phase to be £35,000 per quality-adjusted life year (QALY). The ICER for imatinib compared with combination chemotherapy or palliative care in the accelerated phase was around £22,000 per QALY and in the blast-crisis phase £43,500 per QALY. The year of costs was not stated but the abstract was presented in 2002.
- 4.2.3 The manufacturer's submission included an economic evaluation based on a new Markov model that compared the costs and QALYs in a hypothetical cohort of 1000 newly diagnosed people receiving imatinib as a first-line treatment with a similar cohort of 1000 people receiving IFN- $\alpha$ . The model runs for 30 years, using 1-month cycles. The key effectiveness data were based on the IRIS study. Using two different techniques to estimate the survival benefit, the manufacturer's model estimated that the ICERs for imatinib treatment when compared with IFN- $\alpha$  were £19,000 and £27,000 per QALY.
- 4.2.4 An independent economic model was developed by the Assessment Group to determine the ICER of imatinib compared with HU and IFN- $\alpha$ , and of IFN- $\alpha$  compared with HU in terms of cost per QALY. This is a Markov model that follows a cohort of 1000 people with CML from the

start of treatment until death, or for a maximum of 20 years. The cycle length for the model is 3 months and costs are calculated based on an NHS perspective. Key effectiveness data comes from published literature.

- 4.2.5 The independent model estimated the ICER of imatinib compared with IFN- $\alpha$  to be around £26,000 per QALY gained (ranging from £13,500 to £52,000). Results were relatively robust when subjected to a number of sensitivity analyses. The highest ICER estimate was obtained when higher doses of imatinib were assumed (that is, 600 mg for the chronic and accelerated phases and 800 mg for the blast-crisis phase). Imatinib was less cost effective when compared with HU, with an ICER of £87,000 per QALY. The ICER of IFN- $\alpha$  when compared with HU was considerably higher – in excess of £1 million per QALY.
- 4.2.6 In the Institute's previous guidance (*NICE Technology Appraisal Guidance No. 50*), the ICER for imatinib treatment when compared with HU was estimated to be between £36,000 and £38,000 per QALY as a second-line treatment in chronic-phase CML, between £21,800 and £56,000 per QALY in the accelerated phase, and between £33,275 and £64,750 per QALY in the blast-crisis phase.

## 4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of imatinib for CML, having considered evidence on the nature of the condition and the value placed on the benefits of imatinib from people with CML, those who represent them, and clinical experts. It was also mindful of the need to take account of the efficient use of NHS resources.
- 4.3.2 The Committee was mindful of the current licensed indications for the use of imatinib and the previous guidance produced by the Institute regarding the use of imatinib in the circumstance of intolerance or resistance to first-line IFN- $\alpha$  treatment, which was based on evidence primarily from case series. Conversely, the new licensed indication for imatinib as first-line therapy is supported by a single RCT. However, the Committee's deliberations were hampered by the absence of long-term

survival data. Thus, the published supportive evidence from the RCT relied principally on the surrogate measures of efficacy such as the achievement of an HR and/or a CR.

- 4.3.3 The extent to which CR (particularly) and HR, as surrogate measures, predict survival is central to the judgment about the clinical and cost effectiveness of imatinib. After reviewing the available data, the Committee considered it likely – based on current evidence of the significance of CR and HR in CML, and knowledge of the effect of imatinib – that the relationship between CR and survival is sufficiently strong to support the use of CR, in particular, as a surrogate measure of survival in people with chronic-phase CML.
- 4.3.4 The Committee was therefore persuaded, by the current evidence and by that presented by the experts for this appraisal, that the RCT reviewed for the first-line use of imatinib indicated that there was likely to be a significant survival advantage for imatinib over IFN- $\alpha$  in this clinical situation. However, the Committee did not believe it was possible, based on the current evidence, to determine precisely the absolute survival gain that would result from switching from IFN- $\alpha$  to imatinib as first-line treatment.
- 4.3.5 The Committee considered the implications of high crossover rates in the IRIS trial, and the appropriateness of using intention-to-treat and per protocol analyses. The Committee thought that the degree of the benefit of imatinib treatment would have been underestimated because of the high crossover rate in the IFN- $\alpha$  and Ara-C combination group.
- 4.3.6 The Committee additionally reviewed the clinical effectiveness evidence from the Assessment Report for other treatment options in chronic-phase CML, in particular IFN- $\alpha$  and HU. It discussed in detail the appropriateness of these comparator treatments in the context of first-line treatment with imatinib for chronic-phase CML. The Committee concluded that, although it was reasonable to regard HU as a comparator treatment in this context, current clinical practice (prior to the licensing of imatinib) uniformly considered IFN- $\alpha$  as the principal treatment of choice for people in the chronic phase of CML, provided it can be tolerated.

- 4.3.7 The Committee also carefully considered the cost effectiveness of imatinib treatment compared with alternatives, including both IFN- $\alpha$  and HU. Compared with IFN- $\alpha$ , the Committee considered that imatinib was a cost-effective option. The results from the independent model suggested, however, that the cost effectiveness of imatinib when compared with HU was not acceptable, with an ICER of around £87,000 per QALY. The ICER of IFN- $\alpha$  compared with HU was very much higher, in excess of £1 million per QALY.
- 4.3.8 In line with the considerations outlined in Section 4.3.5, the Committee asked the Assessment Team to test the impact of using per protocol values instead of intention-to-treat values on the cost-effectiveness results. The additional analysis using new assumptions, including the use of per protocol values, resulted in slightly improved ICERs for imatinib, to around £60,000 when compared with HU.
- 4.3.9 The Committee further discussed the issues of comparing imatinib with IFN- $\alpha$  versus HU. If IFN- $\alpha$  would not be considered a cost-effective treatment compared with HU, then how should the ICER of imatinib compared with IFN- $\alpha$  be viewed by the Committee? The Committee was, however, persuaded that, because IFN- $\alpha$  is currently accepted as a standard first-line treatment for people with CML (although it might not be considered cost-effective), it was appropriate to compare imatinib with IFN- $\alpha$  in terms of its ICER.
- 4.3.10 The Committee considered the implications of this decision on the overall cost effectiveness of first-line treatment of CML. Although imatinib treatment was not cost effective when compared with HU, the introduction of imatinib as a first-line therapy for chronic-phase CML would displace the use of IFN- $\alpha$  for this purpose, except in people currently satisfactorily treated with IFN- $\alpha$ . The Committee therefore considered that this may result in a better use of NHS resources for CML.
- 4.3.11 The Committee considered the continuing use of imatinib in chronic-phase CML for people who had not achieved the principal endpoints of treatment as identified in the IRIS trial. The 13-month data from the IRIS trial suggested that only 6.5% in the imatinib arm fell into this category and thus were treated by dose escalation as per protocol. The clinical



experts suggested that this group may be larger in clinical practice than was reflected in the trial. The effect of dose escalation on the cost effectiveness of imatinib in this situation was discussed by the Committee. They also reviewed the sensitivity analysis provided in the Assessment Team's economic model relating to differing doses of imatinib. The Committee was persuaded that, for the majority of people receiving imatinib, dose escalation would not be required and that for those that did, further information on the effectiveness of this strategy was required in the longer term to inform the appraisal review.

4.3.12 The Committee considered the use of imatinib in people who were diagnosed in chronic-phase CML but then progressed to the accelerated phase or blast crisis without a trial of imatinib treatment. The Committee was persuaded that imatinib may provide a clinically and cost-effective treatment option for these people.

4.3.13 The Committee considered the situation in which individuals progressed from the chronic phase to the accelerated phase or blast crisis while they were receiving imatinib. The Committee was aware that in this circumstance there is currently no clinical consensus of the correct therapeutic approach. In addition, there is no evidence on the clinical and cost effectiveness of continuing imatinib treatment by escalating the dose after it has failed to prevent disease progression in the chronic phase. The Committee was also fully aware of the implications regarding the significantly increased cost-effectiveness ratios where dosages of imatinib greater than 400 mg/day were used. Therefore, the Committee concluded that, for individuals who progress to the accelerated or blast-crisis phase whilst taking imatinib, the continuing use of the drug could only be recommended on the basis of collection of prospective data to inform the clinical and cost effectiveness of dose-escalation strategies. The information gathered will enable the Institute to review its guidance on the use of imatinib in 2006.

4.3.14 For people currently receiving IFN- $\alpha$  treatment for chronic-phase CML, the decision about whether to change to imatinib should be dictated by the current response of the disease to treatment and by the tolerance of the person to IFN- $\alpha$ . This decision should be made after informed discussion between the person with CML and the responsible clinician,

taking full account of the evidence on the effects of imatinib and the wishes of the person.

## 5 Recommendations for further research

5.1 It is strongly advised that a national registry should be set up to provide valuable information on the long-term effectiveness of imatinib treatment. It is also strongly recommended that data collection from original registration studies should be continued in order to:

- investigate the comparative long-term efficacy of imatinib in terms of QoL and survival, for all phases of CML
- investigate the adverse effects and the potential for the development of treatment resistance of long-term imatinib use.

5.2 Further good-quality studies are also needed to investigate:

- the efficacy of imatinib in combination with other treatment options
- the clinical and cost effectiveness of dose escalation (within licensed indications)
- the need for, and duration of, long-term imatinib therapy in those who respond to initial treatment
- the definition of inadequate response to imatinib treatment.

## 6 Implications for the NHS

- 6.1 The total cost impact on the NHS will depend on the number of people eligible for first-line treatment with imatinib, the uptake of first-line treatment with imatinib and the incremental cost of imatinib.
- 6.2 The manufacturer estimated that the additional cost of imatinib treatment to the NHS (over and above current spending) would be around £2 million for the first year, rising to £15 million at 5 years. The analysis presented in the Assessment Report suggested slightly higher costs (between £4 million and £6 million in the first year, rising to between £16 million and £20 million at 5 years).

## 7 Implementation and audit

- 7.1 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within 3 months of this guidance being published. This means that, if a patient has chronic myeloid leukaemia and the doctor responsible for their care thinks that imatinib is the right treatment, it should be available for use, in line with NICE's recommendations.
- 7.2 All clinicians who treat people with CML should review their current policies and practice in line with the guidance set out in [Section 1](#).
- 7.3 Local guidelines or care pathways for the care of patients with CML should incorporate the guidance.
- 7.4 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in [Appendix C](#).
- 7.4.1 Imatinib is provided as first-line treatment for the management of an individual with Philadelphia-chromosome-positive CML in the chronic phase.
- 7.4.2 Imatinib is considered as an option for the treatment of an individual with Philadelphia-chromosome-positive CML who initially presents in the accelerated phase or in blast crisis or who presents in the chronic phase and then progresses to the accelerated phase or blast crisis if he or she has not received imatinib previously.
- 7.4.3 For an individual in chronic-phase CML who is currently receiving IFN- $\alpha$  as first-line treatment, the decision to change to imatinib is informed by the response of the disease to current treatment and the individual's tolerance of IFN- $\alpha$ , after informed discussion between the individual and the clinician responsible for treatment.

## 8 Related guidance

The Institute issued guidance on the use of imatinib for people with CML in the chronic phase after failure of IFN- $\alpha$ , in the accelerated phase and in blast crisis in October 2002, which is now replaced by this current guidance.

## 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 2006.

Andrew Dillon  
Chief Executive  
October 2003

# 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 three times 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 interests, are posted on the [NICE website](#).

**Dr Jane Adam**

Radiologist, St George's Hospital, London

**Dr Sunil Angris**

General Practitioner, Waterhouses Medical Practice, Staffordshire

**Dr Darren Ashcroft**

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical sciences, University of Manchester

**Professor David Barnett (Chair)**

Professor of Clinical Pharmacology, University of Leicester

**Professor John Brazier**

Health Economist, University of Sheffield



**Professor John Cairns**

Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

**Professor Mike Campbell**

Statistician, Institute of General Practice & Primary Care, Sheffield

**Dr Peter I Clark**

Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Wirral, Merseyside

**Dr Mike Davies**

Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

**Dr Cam Donaldson**

PPP Foundation Professor of Health Economics, School of Population and Health Sciences & Business School, Business School – Economics, University of Newcastle upon Tyne

**Professor Jack Dowie**

Health Economist, London School of Hygiene

**Dr Paul Ewings**

Statistician, Taunton & Somerset NHS Trust, Taunton

**Dr George Levvy**

Lay Representative, Chief Executive, Motor Neurone Disease Association, Northampton

**Dr Gill Morgan**

Chief Executive, NHS Confederation, London

**Dr Stephen Saltissi**

Consultant Cardiologist, Royal Liverpool University Hospital

**Mr Miles Scott**

Chief Executive, Harrogate Health Care NHS Trust

**Professor Andrew Stevens (Vice-Chair)**

Professor of Public Health, University of Birmingham

**Dr Norman Waugh**

Department of Public Health, University of Aberdeen

## **B. NICE Project Team**

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

**Dr Dogan Fidan**

Technical Lead, NICE project team

**Nina Pinwill**

Project Manager, NICE project team

## Appendix B. Sources of evidence considered by the Committee

The following documentation and opinions were made available to the Committee:

**A** The Assessment Report for this appraisal was prepared by the Peninsula Technology Assessment Group, University of Exeter, and Southampton Health Technology Assessment, Wessex Institute for Health Research and Development, University of Southampton.

**I** Dalziel K, Round A, Stein K et al. *The effectiveness and cost-effectiveness of imatinib for first line treatment of chronic myeloid leukaemia in chronic phase*, 28 March 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 were provided with the opportunity to appeal against the Final Appraisal Determination.

**I** Manufacturer/sponsors:

- Novartis Pharmaceuticals UK Ltd

**II** Professional/specialist and patient/carer groups:

- British Committee on Standards in Haematology (British
- Society for Haematology)
- British Oncology Pharmacy Association
- CancerBACUP
- Cancer Research UK
- Cmlsupport.org
- Department of Health

- Joint Collegiate Council for Oncology (Royal College of Physicians and the Royal College of Radiologists)
- Leukaemia CARE
- Leukaemia Society (UK)
- Macmillan Cancer Relief
- Royal College of Nursing
- Royal College of Pathologists
- Royal Pharmaceutical Society of Great Britain
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- British National Formulary
- Institute of Cancer Research
- Leukaemia Research Fund
- MRC Clinical Trials Unit
- NHS Confederation
- NHS Quality Improvement Scotland

**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 by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Michael Barnett, Professor of Transplantation Oncology, St Bartholomew's, London

- Ms Sandy Craine, Patient Advocate and co-founder of [cmlsupport.org](http://cmlsupport.org)
- Ms Margaret Edgar, Patient Advocate, British Society for Haematology
- Dr Steven O'Brien, Consultant Haematologist, Royal Victoria Infirmary, Newcastle upon Tyne
- Ms Elizabeth Rees, Patient Advocate, [cmlsupport.org](http://cmlsupport.org)
- Dr Simon Rule, Consultant Haematologist, Derriford Hospital, Plymouth
- Dr Pat Shepherd, Consultant Haematologist, Western General Hospital, Edinburgh

# Appendix C. Detail on criteria for audit of the use of imatinib for chronic myeloid leukaemia

## Possible objectives for an audit

An audit could be carried out to ensure appropriate treatment with imatinib for patients with Philadelphia-chromosome-positive CML.

## Possible patients to be included in the audit

An audit could be carried out on individuals being treated for Philadelphia-chromosome-positive CML, over a reasonable period for audit, for example, 1 year.

## Measures that could be used as a basis for audit

The measures that could be used in an audit on the appropriateness of treating people who have Philadelphia-chromosome-positive CML with imatinib are as follows.

Criterion	Standard	Exception	Definition of terms
1. Imatinib is provided as first-line treatment for the management of an individual with Philadelphia-chromosome-positive CML in the chronic phase	100% of patients in the chronic phase	None	If CML phases are not routinely coded, local specialists will have to agree on how to identify patients in the chronic phase for audit purposes Clinicians need to agree locally on any exceptions such as patient declining treatment

<p>2. Imatinib is considered as an option for the treatment of an individual with Philadelphia chromosome-positive CML in the following circumstances.</p> <p>a. The individual initially presents in the accelerated phase or blastcrisis or</p> <p>b. The individual presents in the chronic phase and then progresses to the accelerated phase or blast crisis and has not received imatinib previously</p>	<p>100% of patients who present in accelerated or blast-crisis phase or who present in chronic phase and then progress to accelerated phase or blast crisis and who have not previously received imatinib</p>	<p>None</p>	<p>If CML phases are not routinely coded, local specialists will have to agree on how to identify patients in the accelerated or blast-crisis phase for audit purposes Clinicians need to agree locally on how consideration of treatment as an option will be documented for audit purposes and on any exceptions</p>
<p>3. For an individual in chronic-phase CML who is currently receiving IFN-<math>\alpha</math> as first-line treatment, the decision about whether to change to imatinib is informed by the response of the disease to current treatment and the individual's tolerance of IFN-<math>\alpha</math>, after informed discussion between the individual and the clinician responsible for treatment</p>	<p>100% of patients in the chronic phase who are currently receiving or have received IFN-<math>\alpha</math> and are changing to imatinib as first-line treatment</p>	<p>None</p>	<p>Clinicians should agree locally on how informed discussion is recorded for audit purposes The informed discussion should take full account of the evidence on the risks and benefits of imatinib and the wishes of the patient</p>

## Calculation of compliance

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

<p>Number of patients whose care is consistent with the <b>criterion plus</b> number of patients who meet any <b>exception</b> listed</p>	<p>x 100</p>
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Number of patients to whom the <b>measure</b> applies	
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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.

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