

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance

1 Guidance

- 1.1 Nilotinib is recommended for the treatment of chronic or accelerated phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in adults:
- whose CML is resistant to treatment with standard-dose imatinib
 - or**
 - who have imatinib intolerance
 - and**
 - if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme.
- 1.2 Dasatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase CML in adults with imatinib intolerance or whose CML is resistant to treatment with standard-dose imatinib.
- 1.3 High-dose imatinib¹ is not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-

¹ The summary of product characteristics (SPC) for imatinib states that the dose may be increased from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from

chromosome-positive CML that is resistant to standard-dose imatinib.

- 1.4 People who are currently receiving dasatinib or high-dose imatinib for the treatment of CML should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

2 Clinical need and practice

- 2.1 CML is a cancer of myeloid blood cells characterised by a proliferation of granulocytes in blood and bone marrow. More than 90% of people with CML have an acquired chromosomal abnormality, the Philadelphia chromosome, which is caused by reciprocal translocations between chromosomes 9 and 22. These translocations result in a *BCR-ABL* fusion gene that encodes an active tyrosine kinase protein. This protein leads to uncontrolled cell proliferation. People with Philadelphia-chromosome-negative CML have different translocations that result in the same *BCR-ABL* fusion gene and its tyrosine kinase protein.
- 2.2 CML has three phases. The duration of the initial chronic phase is variable, but may be several years. In this phase the symptoms are usually mild and non-specific and can include fatigue, weight loss, night sweats, anaemia, a feeling of 'fullness' and a tender lump on the left side of the abdomen caused by enlargement of the spleen. Around 90% of CML is diagnosed during the chronic phase, and approximately 40% of this is asymptomatic and is diagnosed as a result of a routine blood test. The disease may then enter an accelerated phase. During this phase disease progression is more

600 mg to a maximum of 800 mg in patients with accelerated phase or blast crisis (see SPC for full details). High dose imatinib refers to doses of 600 mg or 800 mg in the chronic phase disease or 800 mg in the accelerated phase or blast crisis.

rapid, and immature blast cells in blood and bone marrow proliferate. Symptoms include bruising, bleeding and infections. The final phase is called the blast-crisis phase because there is a rapid increase in immature forms of cells (blasts), which replace normal cells in bone marrow and affect other organs. Symptoms include fever, sweating, pain and enlargement of organs. When this phase is reached CML is often fatal within 3–6 months.

- 2.3 CML is diagnosed by finding characteristic cells in blood and bone marrow. The Philadelphia chromosome is identified using cytogenetic techniques to detect products of the *BCR-ABL* gene. Various criteria, including the percentage of blast cells in blood or bone marrow, have been proposed to define the accelerated and blast-crisis phases.
- 2.4 It is estimated that about 560 people are diagnosed with CML in the UK each year. Slightly more men than women are diagnosed (annual age-standardised rate 1.2 per 100,000 for men and 0.7 per 100,000 for women). The median age at diagnosis is 60 years.
- 2.5 A potential cure for CML is an allogeneic stem cell transplant, also known as bone marrow transplantation, but individual characteristics and the lack of availability of a matched donor preclude this option for many people with CML.
- 2.6 However, the progression of CML can be slowed by imatinib, which is a tyrosine kinase inhibitor. Imatinib produces high rates of remission in the chronic phase but is less effective when the disease has progressed. Imatinib is associated with improved survival, with the latest results from the 8-year follow-up of the International Randomised Study of Interferon versus STI571 (imatinib) (known as the IRIS trial) showing overall survival of 85%. After the introduction of imatinib into routine clinical practice, 5-year

relative survival increased from 27.1% in 1990–92 to 48.7% in 2002–04 for all age groups combined ($p < 0.0001$ for the trend).

- 2.7 Current NICE guidance ('Guidance on the use of imatinib for chronic myeloid leukaemia'; NICE technology appraisal guidance 70 [TA70]) recommends the standard dosage of imatinib (400 mg once daily) as first-line treatment for Philadelphia-chromosome-positive CML in the chronic phase. It also recommends imatinib for CML that initially presents in the accelerated phase or blast-crisis phase, and for CML that presents in the chronic phase and then progresses to the accelerated or blast-crisis phase, if imatinib has not been used previously.
- 2.8 Some CML is resistant to imatinib. The resistance may be primary (if there is a poor initial response) or acquired (following a period of successful treatment). The marketing authorisation for imatinib allows for dose increased in this circumstance (see section 3.7 below) TA70 recommends dose escalation of imatinib following the development of imatinib resistance only in the context of further clinical studies.
- 2.9 Some people with CML have imatinib intolerance. Imatinib intolerance can be defined as any of the following: a grade 3 non-haematological or grade 4 haematological adverse event that persists for more than 7 days; grade 3 or 4 adverse events that persist in spite of optimal supportive measures; or grade 2 adverse events that persist for 1 month or longer, or that recur more than three times, as well as no major cytogenetic response.
- 2.10 Apart from dasatinib and nilotinib (appraised here together with high-dose imatinib), treatment options for people with imatinib-resistant CML and people with CML who have imatinib intolerance

include interferon alfa, hydroxycarbamide and allogeneic stem cell transplantation.

2.11 Response to treatment is assessed haematologically by white cell count and cytogenetically by searching for the Philadelphia chromosome in bone marrow aspirates. A molecular response can be assessed using polymerase chain reaction techniques.

2.12 A complete haematological response has been defined as all of the following being maintained for at least 4 weeks:

- white blood cell count no higher than the upper limit of normal
- absolute neutrophil count at least 1×10^9 per litre
- platelet count below 450×10^9 per litre and no higher than the upper limit of normal
- no blast cells or promyelocytes in peripheral blood
- less than 2% basophils in peripheral blood
- no extramedullary involvement.

2.13 A complete cytogenetic response is defined as absence of the Philadelphia-positive chromosome among at least 20 cells in metaphase in a bone marrow aspirate. A partial cytogenetic response is defined as 35% or fewer Philadelphia-positive chromosomes in metaphase in a bone marrow aspirate. A major cytogenetic response is defined as either a complete cytogenetic response or a partial cytogenetic response.

2.14 A major molecular response is defined as either a *BCR-ABL/ABL* ratio of less than 0.10% or a 3-log reduction in *BCR-ABL* transcripts. A complete molecular response is defined as undetectable levels of *BCR-ABL*.

3 The technologies

Dasatinib

- 3.1 Dasatinib (Sprycel, Bristol-Myers Squibb), a TKI, is an orally active inhibitor of Src and the Src family of tyrosine kinases. These are involved in cell growth, differentiation, migration and survival, and many are involved in oncogenesis, tumour metastasis and angiogenesis. Dasatinib has been shown to directly inhibit 21 out of 22 mutant forms of *BCR-ABL* that are resistant to imatinib.
- 3.2 Dasatinib has a marketing authorisation for the treatment of 'adult patients with newly diagnosed Philadelphia-chromosome-positive chronic myelogenous leukaemia in the chronic phase' and 'adult patients with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate'.
- 3.3 The most common reported side effects in the trials are headache, pleural effusion, shortness of breath, cough, diarrhoea, nausea, vomiting, abdominal pain, skin rash, musculoskeletal pain, infections, haemorrhage, superficial oedema, fatigue, fever, neutropenia, thrombocytopenia and anaemia. For full details of side effects and contraindications, see the summary of product characteristics (SPC).
- 3.4 Dasatinib is available at a cost of £2504.96 for a 100 mg 30-tablet pack (excluding VAT; 'British national formulary' [BNF] edition 61). The cost of dasatinib treatment is £30,477 per year, assuming a treatment regimen of 100 mg once daily. Costs may vary in different settings because of negotiated procurement discounts.

Imatinib

- 3.5 Imatinib (Glivec, Novartis Pharmaceuticals) is an orally active TKI, designed to competitively inhibit *BCR-ABL* tyrosine kinase activity. By blocking specific signals in cells expressing *BCR-ABL*, imatinib reduces the uncontrolled proliferation of white blood cells that is a characteristic feature of CML.
- 3.6 Imatinib has a marketing authorisation for the treatment of adult and paediatric patients with newly diagnosed Philadelphia-chromosome- (*BCR-ABL*) positive chronic myelogenous leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment, and for 'adult and paediatric patients with Philadelphia-chromosome-positive CML in chronic phase after failure of interferon alfa therapy (recommended dose 400 mg once daily) or in accelerated phase or blast crisis (recommended dose 600 mg once daily)'.
- 3.7 The marketing authorisation states that dose escalations in 200 mg increments up to a maximum of 400 mg twice daily may be considered in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: 'disease progression (at any time); failure to achieve a satisfactory haematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved haematological and/or cytogenetic response'.
- 3.8 The most common side effects with imatinib are nausea, vomiting, oedema (fluid retention), muscle cramps, skin rash, diarrhoea, abdominal pain, headache and fatigue. For full details of side effects and contraindications, see the SPC.

3.9 Imatinib was available at a cost of £1604 for a 400 mg 30-tablet pack (excluding VAT; BNF edition 61) resulting in an annual cost of imatinib treatment of £39,033, assuming a treatment regimen of 400 mg twice daily. The cost of imatinib increased in December 2010 to £1724 for a 400 mg 30-tablet pack (excluding VAT; 'Monthly Index of Medical Specialties' [MIMS] April 2011). The cost of imatinib treatment is now £41,960 per year assuming a treatment regimen of 400 mg twice daily. Costs may vary in different settings because of negotiated procurement discounts.

Nilotinib

- 3.10 Nilotinib (Tasigna, Novartis Pharmaceuticals), a TKI, is an orally active phenylaminopyrimidine derivative of imatinib. Studies suggest that nilotinib inhibits 32 of 33 mutant *BCR-ABL* forms that are resistant to imatinib.
- 3.11 Nilotinib has a marketing authorisation for the treatment of 'adult patients with newly diagnosed Philadelphia-chromosome-positive chronic myelogenous leukaemia (CML) in the chronic phase' and 'adult patients with chronic phase and accelerated phase Philadelphia-chromosome-positive CML with resistance or intolerance to prior therapy including imatinib'. The SPC states that 'efficacy data in patients with CML in blast crisis are not available'.
- 3.12 The most common side effects with nilotinib are thrombocytopenia, neutropenia, anaemia, headache, nausea, constipation, diarrhoea, rash, pruritus, fatigue and increased blood levels of lipase and bilirubin. Nilotinib prolongs the QT interval and is therefore contraindicated in people with hypokalaemia, hypomagnesaemia or long QT syndrome. For full details of side effects and contraindications, see the SPC.

- 3.13 Nilotinib is available at a cost of £2643 for a 200-mg tablet pack (excluding VAT; BNF edition 61). The cost of nilotinib treatment is £31,711 per year, assuming a treatment regimen of 400 mg twice daily. The manufacturer of nilotinib has agreed a patient access scheme with the Department of Health that makes nilotinib available with a discount (see section 5.2). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

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 The Peninsula Technology Assessment Group (PenTAG) conducted a systematic review of evidence on the comparative clinical efficacy of dasatinib and nilotinib in imatinib-resistant CML and in people with CML and imatinib intolerance. PenTAG found 15 relevant studies. Only one was a randomised controlled trial (RCT) that compared dasatinib with high-dose imatinib (that is, 600 to 800 mg per day, depending on the CML phase) in imatinib-resistant CML. Two studies (on dasatinib) were dose-finding RCTs. Twelve studies were observational (seven of dasatinib, four of nilotinib and one retrospective study of both technologies). Dasatinib was used at the licensed dosage in only one arm of the dose-finding dasatinib trials.
- 4.1.2 The Southampton Health Technology Appraisal Centre (SHTAC) Assessment Group partially updated the PenTAG review. The SHTAC report updated the evidence on the clinical efficacy of dasatinib and nilotinib, and included evidence on an additional

technology, high-dose imatinib. The SHTAC review also updated the evidence on CML that is resistant to standard-dose imatinib (that is, 400 to 600 mg per day, depending on the CML phase). The SHTAC report did not address imatinib intolerance. In total 11 studies were identified, of which 8 had been reviewed by PenTAG. The additional evidence identified by SHTAC included three single-arm studies of high-dose imatinib and one updated publication of the RCT comparing dasatinib with high-dose imatinib that was included in the PenTAG review. The SHTAC Assessment Group did not identify any new or updated studies of nilotinib for imatinib-resistant CML.

- 4.1.3 Both Assessment Groups noted that the design of single-arm studies makes it difficult to assess and generalise the results. However, they also noted that some of the identified single-arm cohort studies were multicentre and recruited people consecutively, which could reduce the risk of bias. The Assessment Groups expressed concerns about the RCTs because they had not reported methods of allocation concealment, were of an open-label design and did not present power calculations. The Assessment Groups noted that the only comparative head-to-head RCT (dasatinib compared with high-dose imatinib) had methodological limitations and a high level of asymmetric crossover (80% of people had crossed over from imatinib to dasatinib after 13 weeks). Because of these concerns, the Assessment Groups decided that the treatment arms should be considered separately (that is, non-comparatively).

Chronic phase – dasatinib

- 4.1.4 Four studies provided data on dasatinib for imatinib-resistant chronic-phase CML. All of these studies had been identified by PenTAG; however, one had been updated at the time of the

SHTAC Assessment Group review. Two of the studies were single-arm cohort studies; the third was a dose-ranging RCT that compared different dosages of dasatinib; and the fourth was an RCT that compared dasatinib with high-dose imatinib. The dose-ranging RCT was the only study of dasatinib that used the dosage in the UK marketing authorisation, that is, 100 mg once daily for chronic-phase CML. All other studies used higher dosages of dasatinib.

4.1.5 In the two single-arm cohort studies, complete cytogenetic response ranged from 27.8% at 6-month follow-up to 44.1% at 24-month follow-up. In the dose-ranging RCT, complete cytogenetic response reached 43.5% with dasatinib 100 mg once daily, and in the comparative RCT complete cytogenetic response reached 43.6% at 26 months (although it was noted that there was a high level of crossover from the high-dose imatinib arm before 26 months). PenTAG provided pooled summary results for three outcomes. A complete cytogenetic response was reported in 37.4% of people (95% confidence interval [CI] 34.2 to 40.5%), a major cytogenetic response in 50.9% (95% CI 47.6 to 54.1%) and a complete haematological response in 89.2% (95% CI 87.2 to 91.3%). The update of the comparative RCT reported a major molecular response in 28.7% of the people who received dasatinib. Of the 37.4% of people in whom a complete cytogenetic response was seen and molecular response was assessed, a major molecular response was seen in 63.4%.

4.1.6 Progression-free survival was reported in one of the single-arm studies, the dose-ranging RCT and the comparative RCT; no updated progression-free survival data were included in the update of the comparative RCT. In general, the data on progression-free survival were immature, and median survival had not been

reached. At least 75% of people with CML in the chronic phase had no disease progression for 2 years or more. Estimates of overall survival were reported in two studies and were also immature. According to the data, more than 80% of people with chronic-phase CML were alive for at least 3 years.

- 4.1.7 PenTAG found four non-comparative studies of dasatinib in chronic-phase CML that identified people with imatinib intolerance separately. PenTAG's summary of results reported that a complete cytogenetic response was seen in 68.1% of people (95% CI 62.7 to 73.5%), a major cytogenetic response was seen in 75.5% (95% CI 70.5 to 80.5%) and a complete haematological response was seen in 93.7% (95% CI 89.5 to 97.9%). These percentages were higher than those observed in the subgroup of people with imatinib-resistant CML.
- 4.1.8 After follow-up of up to 3 years, none of the cohorts from the studies had reached median survival for dasatinib. These cohorts were mixed populations of people with imatinib-resistant CML and people with CML who had imatinib intolerance, and different doses of dasatinib were used across the cohorts.
- 4.1.9 The most common adverse events associated with dasatinib were haematological. The incidence of grade 3 and 4 thrombocytopenia was 57.4% and grade 3 and 4 neutropenia was 63.4%. Other common adverse effects of dasatinib in the comparative RCT included diarrhoea, fluid retention, fatigue and nausea. The lowest rates of treatment discontinuation were in the dose-ranging RCT when the UK licensed dose was used; however, results were not reported separately for people with imatinib-resistant CML and those with imatinib intolerance. Discontinuation because of intolerable events was reported separately for people with imatinib-

resistant CML only in the comparative RCT. In this study 23 out of 101 people (22.8%) had discontinued dasatinib treatment at 26-month follow-up.

Chronic phase – high-dose imatinib

- 4.1.10 Three single-arm cohort studies that assessed high-dose imatinib and an update of the comparative RCT of dasatinib and high-dose imatinib were identified. In these studies complete cytogenetic response rates ranged from 18.4–36.4% and major cytogenetic response rates ranged from 32.7–63.5%. The comparative RCT reported that a major cytogenetic response was maintained at 18 months in 74% of people (95% CI 49 to 100%). Three of the studies reported complete haematological response rates ranging from 55.5% (18-month follow-up) to 91.8% (36-month follow-up). No pooled results were provided by the SHTAC Assessment Group. In the updated comparative RCT, a major molecular response was seen in 12.2% of people who received high-dose imatinib and in 55.6% of people who had a complete cytogenetic response. A complete molecular response was seen in 13.5% of people in one single-arm study. In another single-arm study a reduction in *BCR-ABL/ABL* of more than 50% was seen in 56.3% of people within 6 months.
- 4.1.11 Three of the studies (two single-arm studies and the RCT) reported progression-free or event-free survival. SHTAC reported these together because they appeared to measure similar outcomes. One single-arm study reported event-free survival of 34% at 2 years. Higher estimated progression-free survival rates were reported in the other two studies (65 and 87% respectively). The two single-arm studies reported overall survival rates of 85 and 93% in chronic-phase CML.

4.1.12 Haematological adverse events were reported by all studies. Grade 3–4 adverse events with anaemia occurred in 8–30% of people, neutropenia in 18–39%, leukopenia in 16–31% and thrombocytopenia in 0–21%. One single-arm study reported a low proportion of people with anaemia and neutropenia (0–3%), but did not report toxicity levels by grade. The most commonly reported adverse events of any grade were anorexia, diarrhoea, fatigue, muscle spasms, musculoskeletal pain, nausea, superficial or peripheral oedema and rash. Treatment discontinuation because of adverse events was reported in three of the four studies and ranged from 0 to 20.4%.

Chronic phase – nilotinib

4.1.13 Two single-arm studies of nilotinib for imatinib-resistant chronic-phase CML were identified. No new trials of nilotinib in imatinib-resistant chronic-phase CML were identified by the SHTAC Assessment Group. One of the studies was a phase I dose-ranging study and the other was a phase II multicentre trial in chronic-phase CML. PenTAG noted that the evidence presented was ambiguous and that the available follow-up data were immature (with lengthier follow-up available only in abstract form).

4.1.14 The pooled results from the two studies (using 6-month follow-up data from the multicentre study) showed that when nilotinib was used to treat chronic-phase imatinib-resistant CML, a complete cytogenetic response was seen in 30.3% of people (95% CI 24.1 to 36.5%), a major cytogenetic response was seen in 46.5% (95% CI 35.7 to 57.6%) and a complete haematological response was seen in 78.9% (95% CI 55.9 to 100.0%). Molecular response was not reported in the PenTAG or SHTAC Assessment Group reports.

- 4.1.15 For nilotinib, PenTAG found only one study that identified people with imatinib intolerance separately. PenTAG's summary of results reported that when nilotinib was used to treat people with chronic-phase CML and imatinib intolerance, a complete cytogenetic response was seen in 34.9% (95% CI 24.9 to 45.9%), a major cytogenetic response was seen in 46.5% (95% CI 35.7 to 57.6%), and a complete haematological response was seen in 90.0% (95% CI 78.2 to 96.7%).
- 4.1.16 Limited data on progression-free survival were available and no published studies were identified. Only the multicentre phase II study provided estimates of overall survival with nilotinib (400 mg twice daily); these estimates indicated that slightly fewer than 90% of people with imatinib-resistant chronic-phase CML treated with nilotinib would be alive after 18 months.
- 4.1.17 The most common grade 3–4 adverse effects noted in the chronic phase were haematological. Of the mixed population of people with imatinib-resistant CML and people with imatinib intolerance in the multicentre study, 42 out of 280 people (15%) discontinued nilotinib because of adverse events. However, the rates of discontinuation were not reported separately for the people with imatinib-resistant CML and those with imatinib intolerance.

Accelerated and blast-crisis phases – dasatinib

- 4.1.18 One dose-ranging RCT and one single-arm cohort study were identified that reported results for dasatinib in accelerated-phase CML. The Assessment Groups considered that the RCT was of low methodological quality because it did not report allocation concealment and had an open-label design. There was also an imbalance in the number of people with complete haematological response across treatment arms at baseline. The single-arm study

was considered to be of reasonable quality, although the inherent low reliability of single-arm studies was noted.

- 4.1.19 Complete cytogenetic response ranged from 25.3% at 8-month follow-up to 32.8% at 15-month follow-up in the two studies. The pooled results showed that when dasatinib was used to treat people with imatinib-resistant accelerated-phase CML, a complete cytogenetic response was seen in 30.9% of people (95% CI 26.4 to 35.5%), a major cytogenetic response was seen in 38.8% (95% CI 34.0 to 43.6%) and a complete haematological response was seen in 48.2% (95% CI 43.3 to 53.1%). The trials did not report time to progression-free or overall survival separately for the people with imatinib-resistant accelerated-phase CML. Molecular response was not reported in the PenTAG or SHTAC Assessment Group reports.
- 4.1.20 PenTAG identified two studies of dasatinib in accelerated-phase CML that identified people with imatinib intolerance separately. PenTAG's summary of results reported that, of people with accelerated-phase CML and imatinib intolerance, a complete cytogenetic response was seen in 36.9% (95% CI 27.3 to 46.5%), a major cytogenetic response was seen in 44.3% (95% CI 34.4 to 54.2%) and a complete haematological response was seen in 46.3% (95% CI 36.4 to 56.1%). The trials did not report time to progression-free or overall survival separately for the people with imatinib intolerance.
- 4.1.21 In accelerated-phase CML, a mixed population of people with imatinib-resistant CML and people with imatinib intolerance had median progression-free survival of 25.2 months (imatinib-resistant CML with a dosage regimen of 140 mg once daily) and 26.1 months (imatinib intolerance with a dosage regimen of 70 mg twice daily). One trial reported median overall survival of

30.8 months in accelerated-phase CML in a mixed population of people with imatinib-resistant CML and people with imatinib intolerance.

- 4.1.22 The most commonly reported adverse effects of dasatinib in the accelerated phase were haematological. The rate of discontinuation because of adverse events in the people with imatinib-resistant CML was reported separately only in the single-arm study and was 9.9%.
- 4.1.23 Limited data on the effectiveness of dasatinib in the blast-crisis phase were available. One study identified in the original systematic review conducted by PenTAG included a mixed population of people with imatinib-resistant CML and imatinib intolerance, both with blast-crisis phase CML. Median progression-free survival was 2.8–5.8 months.

Accelerated and blast-crisis phases – high-dose imatinib

- 4.1.24 No trials of high-dose imatinib in the accelerated or blast-crisis phase were identified in the systematic review performed by SHTAC. One of the single-arm studies previously noted included a small number of people with accelerated-phase (n = 3) and blast-crisis phase (n = 4) CML; however, the results were not included in the SHTAC Assessment Group's analyses.

Accelerated phase – nilotinib

- 4.1.25 One single-arm cohort study included some people with accelerated-phase CML. As previously noted, this was a dose-ranging phase I study, and as such the results of this study were viewed with caution by the Assessment Groups.
- 4.1.26 Of the 56 people in this study who had accelerated-phase CML, a complete cytogenetic response was seen in 8 people (14.3%), and

a partial cytogenetic response was seen in 7 people (12.5%). A complete haematological response was seen in 26 out of 51 people (51%). Molecular response was not reported in the PenTAG report or the SHTAC addendum. No results on progression-free survival, overall survival or adverse events in people with imatinib-resistant accelerated-phase CML were available. For accelerated-phase CML the evidence did not allow separate calculations for people with imatinib intolerance. Nilotinib does not have a UK marketing authorisation for the treatment of CML in the blast-crisis phase.

4.2 Cost effectiveness

- 4.2.1 The two manufacturers submitted cost-effectiveness models; in addition, a model was developed by PenTAG, and updated by SHTAC with minor modifications.

Manufacturers' submissions

Bristol-Myers Squibb – dasatinib

- 4.2.2 Bristol-Myers Squibb initially developed two economic models. One compared dasatinib, high-dose imatinib or nilotinib with standard-dose imatinib, allogeneic stem cell transplantation or interferon alfa in imatinib-resistant CML (the imatinib resistance model). The other compared dasatinib with nilotinib or high-dose imatinib in people with imatinib intolerance or imatinib-resistant CML (the imatinib resistance and/or intolerance model). After consultation, Bristol-Myers Squibb also compared dasatinib, high-dose imatinib or nilotinib with hydroxycarbamide followed by allogeneic stem cell transplantation (for a proportion of people) as an addition to its imatinib resistance model.
- 4.2.3 The models were developed to estimate long-term costs and outcomes (life years and quality-adjusted life years [QALYs] gained) from failure of prior therapy (imatinib) to death. The

analyses were conducted from a UK NHS and personal social services (PSS) perspective using a 40-year time horizon with costs and benefits discounted at 3.5% per annum.

- 4.2.4 The models allow people to start in each of the three phases of CML: chronic phase, accelerated phase and blast-crisis phase. The models assume that CML phases are consecutive (that is, people cannot revert back to the chronic phase if they have a more advanced phase of the disease). People are assumed to receive treatment with the different interventions until disease progression or until the treatment is no longer tolerated, after which they receive 'post-failure treatments'.
- 4.2.5 Drug acquisition costs from the imatinib-resistant model were taken from BNF 60 and based on the recommended doses in the SPCs for the technologies. Costs associated with outpatient visits, tests and hospitalisations were also included in the model. The expected level of resource use was linked to initial best response using a survey of UK clinical specialists. Adverse event costs were included for treatment-related grade 3–4 serious adverse events. Utility values were calculated from a cross-sectional study in the UK general population using the time trade-off method and the EQ-5D. Utility values were: 0.85 for the chronic phase with response; 0.68 for the chronic phase with no response; 0.79 for the accelerated phase with response; 0.50 for the accelerated phase with no response; 0.50 for the blast-crisis phase with response; and 0.31 for the blast-crisis phase with no response.
- 4.2.6 Incremental base-case results from the imatinib resistance model showed that high-dose imatinib and nilotinib were dominated by dasatinib (that is, dasatinib provided greater benefit for less cost). Therefore the cost-effectiveness estimate of dasatinib was

compared with that of interferon alfa for people starting with chronic-phase CML. The results indicated that 0.65 years of interferon alfa treatment was associated with 3.56 years of overall survival (1.664 QALYs) at a total cost of £129,292, and 7.46 years of dasatinib treatment was associated with 11.76 years of overall survival (6.425 QALYs) at a total cost of £314,413.

- 4.2.7 The base-case incremental cost-effectiveness ratio (ICER) of dasatinib compared with interferon alfa was £38,883 per QALY gained.
- 4.2.8 In one-way sensitivity analysis the key factors that had the greatest effect on the ICER were the utility values assigned to the health state of responders, starting age in the model, and the time horizon of the model. The results of the probabilistic sensitivity analysis showed that the probability of dasatinib being cost effective compared with stem cell transplantation was 81% if the maximum acceptable amount to pay for an additional QALY is £30,000.
- 4.2.9 Results from the imatinib resistance model were also presented for people starting with accelerated- or blast-crisis phase CML. For those starting with accelerated-phase CML, the ICERs were £36,594 per QALY gained for dasatinib compared with high-dose imatinib, and £32,405 per QALY gained for dasatinib compared with high-dose nilotinib. When compared with bone marrow stem cell transplantation, dasatinib was associated with fewer QALYs and lower costs, and the ICER of £231,650 would represent savings per QALY lost.
- 4.2.10 Results from the imatinib resistance model for people starting with blast-crisis phase CML showed that dasatinib dominated high-dose imatinib (that is, treatment with dasatinib was more effective and less costly). Treatment with dasatinib was associated with fewer

QALYs and lower costs compared with bone marrow stem cell transplantation; therefore the ICER of £54,093 would represent savings per QALY lost.

4.2.11 For the imatinib resistance and/or intolerance model dasatinib was associated with costs of £280,619 and 6.21 QALYs gained, compared with nilotinib, which was associated with costs of £278,087 and 5.91 QALYs gained. For people with imatinib-resistant CML, high-dose imatinib was associated with costs of £251,120 and 4.35 QALYs gained. In people with accelerated-phase CML, the manufacturer's estimates for dasatinib in people with imatinib-resistant CML and/or imatinib intolerance were costs of £135,570 and 2.28 QALYs gained, compared with, for nilotinib, costs of £105,545 and 1.46 QALYs gained and for high-dose imatinib, costs of £78,190 and 0.65 QALYs gained.

4.2.12 For people with blast-crisis phase CML, only dasatinib and high-dose imatinib are licensed. In the imatinib resistance and/or intolerance model, dasatinib was associated with costs of £88,181 and 0.46 QALYs gained, compared with costs of £99,367 and 0.19 QALYs gained for high-dose imatinib. These estimates were associated with considerable uncertainty because of a lack of comparative efficacy data. PenTAG commented that the data used by Bristol-Myers Squibb to estimate the effectiveness of high-dose imatinib in an imatinib-resistant population were questionable because they were based on an imatinib-naïve comparator population who received standard-dose and low-dose imatinib. In addition, the manufacturer assumed a much shorter-tailed overall survival curve fit for patients taking high-dose imatinib than was seen in the trial.

4.2.13 PenTAG was also asked to provide results of an analysis modelling 'no treatment' instead of high-dose imatinib using the blast-phase model provided by Bristol-Myers Squibb. For no treatment, the results of this analysis were a cost of £80,318 and QALYs gained of 0.16, and for dasatinib they were a cost of £87,906 and QALYs gained of 0.46. The results of the incremental analysis suggested an ICER of £25,531 per QALY gained for dasatinib compared with no treatment.

Novartis – nilotinib

4.2.14 Novartis developed three economic models. One compared nilotinib or high-dose imatinib with stem cell transplantation and hydroxycarbamide in people with imatinib-resistant CML. One compared nilotinib with high-dose imatinib in people with imatinib-resistant CML. And one compared nilotinib with hydroxycarbamide in people with imatinib intolerance.

4.2.15 The models were developed to estimate long-term costs and outcomes (life years and QALYs gained) from failure of prior therapy (imatinib) to death. The analyses were conducted from a UK NHS and PSS perspective using a lifetime horizon, with costs and benefits discounted at a rate of 3.5% per annum.

4.2.16 The models consist of four health states, with people entering during the chronic phase and then progressing through the accelerated and blast-crisis phases and ending in death. The models also allow people to die from other causes in the chronic and accelerated phases. The models assume that CML phases are consecutive (that is, people cannot revert back to the chronic phase if they are in more advanced phases of the disease). People in whom the interventions fail are assumed to stay in the chronic

phase before progressing to accelerated phase or blast-crisis phase. The models assume people receive a third-line treatment.

- 4.2.17 Drug acquisition costs in the imatinib-resistant CML model that compared nilotinib or high-dose imatinib with stem cell transplantation and hydroxycarbamide were taken from BNF 60. Costs associated with adverse events, routine appointments and end-of-life care were also included in the model. If published data were not available, advice was sought from clinical specialists. Utility values were based on EQ-5D responses taken from a study of standard-dose imatinib. The health states were assigned the following utility values: chronic phase 0.854; accelerated phase and blast-crisis phase 0.595. Disutilities corresponding to grade 3 and 4 adverse events were taken from a nilotinib trial and were modelled during the first 18 months of treatment in the chronic phase. A decrement was applied to the long-term utility value for 52% of people after stem cell transplantation. Disutilities for adverse events for each intervention were: nilotinib 0.049; high-dose imatinib 0.027; stem cell transplantation 0.079; and no disutility for hydroxycarbamide.
- 4.2.18 The base-case results from the imatinib-resistant CML model that compared nilotinib or high-dose imatinib with stem cell transplantation and hydroxycarbamide showed that high-dose imatinib was dominated by nilotinib (that is, nilotinib provided greater benefit for less cost). Exploratory analyses indicated that treatment with hydroxycarbamide and stem cell transplantation was associated with 4.21 years of overall survival (3.18 QALYs) at a total cost of £80,933 and 2.00 years of nilotinib treatment was associated with 5.80 years of overall survival (4.51 QALYs) at a total cost of £139,216.

- 4.2.19 The ICER for nilotinib compared with hydroxycarbamide and stem cell transplantation was £44,028 per QALY gained. Various efficacy assumptions, health utility values, costs and other parameters were considered in sensitivity analyses. The deterministic results were most sensitive to reducing the time horizon to 5 years and extending high-dose imatinib time to discontinuation from 14.0 months to 19.4 months.
- 4.2.20 The results from the imatinib-resistant CML model that compared nilotinib with high-dose imatinib suggested that nilotinib is less costly and more effective than high-dose imatinib. The results for people with accelerated-phase CML suggested that nilotinib has a cost per QALY gained of £18,541 compared with high-dose imatinib. Nilotinib was associated with costs of £57,571 and 1.41 QALYs compared with high-dose imatinib, which was associated with costs of £53,144 and 1.17 QALYs. This represents an increase in costs of nearly £4500 and 0.24 in QALYs.
- 4.2.21 For the imatinib intolerance model, treatment with dasatinib was estimated to result in a gain of 3.6 QALYs compared with hydroxycarbamide at an incremental cost of £211,045, resulting in an ICER of £58,590 per QALY gained for dasatinib compared with hydroxycarbamide. For people with accelerated-phase CML and imatinib intolerance, treatment with nilotinib was estimated to result in a gain of 1.14 QALYs compared with hydroxycarbamide at an incremental cost of £90,966, resulting in an ICER of £79,914 per QALY gained for nilotinib compared with hydroxycarbamide.

PenTAG's model

- 4.2.22 PenTAG conducted a systematic review of available literature on the cost effectiveness of dasatinib and nilotinib for CML in people who have imatinib-resistant CML or imatinib intolerance. Nine

abstracts and two reports were identified that met the specified inclusion criteria. Seven studies reported on dasatinib and four reported on nilotinib. All studies used high-dose imatinib as the comparator.

- 4.2.23 All 11 studies included people with imatinib-resistant CML or imatinib intolerance. In some studies, it was not clear whether people had imatinib-resistant CML, imatinib intolerance or both. Most of the studies of dasatinib modelled cost effectiveness based on people in the chronic, accelerated and blast-crisis phases of CML separately. The studies of nilotinib modelled cost effectiveness based on people starting in chronic-phase CML and progressing through the accelerated and blast-crisis phases. Not all studies stated the source of data on clinical effectiveness, but those that did cited the phase II trials of dasatinib and nilotinib, with two studies using data from a subgroup of IRIS (interferon alfa versus imatinib) to predict long-term overall survival for dasatinib and nilotinib. The cost-effectiveness results for dasatinib and nilotinib showed that each was less costly and more effective than imatinib, with ICERs of £22,000 per QALY gained for nilotinib, and up to CAN \$173,922 per QALY gained and US \$205,405 per life year gained for dasatinib.
- 4.2.24 PenTAG produced a new model restricted to imatinib-resistant CML or imatinib intolerance in the chronic phase, because it was unable to identify suitable effectiveness data for the comparator treatments with which to populate the model in the accelerated and blast-crisis phases.
- 4.2.25 Two separate models were used: one with people who had CML that showed (or developed) resistance to standard-dose imatinib (imatinib resistant) and one with people who had been unable to

continue imatinib treatment because of adverse events (imatinib intolerant). The comparators were high-dose imatinib or interferon alfa for people in chronic-phase imatinib-resistant CML and interferon alfa for people in chronic-phase CML who had imatinib intolerance.

- 4.2.26 The models were conducted from a UK NHS and PSS perspective using a lifetime horizon with costs and benefits discounted at 3.5% per year. The models used best initial response to treatment to predict overall survival and trial data to extrapolate treatment duration and progression-free survival. Duration of treatment was estimated on the basis of progression-free survival with a deduction to account for premature discontinuations. Overall survival was estimated by extrapolating from the surrogate outcome of major cytogenetic response. The costs for the interventions used in the analyses were taken from BNF 58.
- 4.2.27 For imatinib-resistant CML three technologies were considered: dasatinib, nilotinib and high-dose imatinib. The clinical adviser to PenTAG noted that interferon alfa is not a realistic comparator because it is not used in clinical practice. The cost-effectiveness analysis carried out by PenTAG showed that all three technologies resulted in relatively similar gains in survival, with median overall survival of 9.11 years for nilotinib, 9.46 years for high-dose imatinib, and 9.53 years for dasatinib. Gains in survival with interferon alfa were predicted to be 7.11 years.
- 4.2.28 The base-case results for imatinib-resistant CML from PenTAG's model showed that high-dose imatinib produced an ICER of £13,273 per QALY gained compared with nilotinib, and dasatinib produced an ICER of £3,206,512 per QALY gained compared with high-dose imatinib.

- 4.2.29 The probabilistic sensitivity analysis for imatinib-resistant CML demonstrated substantial uncertainty about the effectiveness of the new technologies. The cost-effectiveness evaluation demonstrated that high-dose imatinib (the comparator) was the option most likely to be cost effective up to a maximum acceptable amount to pay of £66,000 for an additional QALY, at which point nilotinib became the most likely to be cost effective. Dasatinib became the option most likely to be cost effective when the maximum acceptable amount to pay for an additional QALY rose to £150,000.
- 4.2.30 For people with imatinib intolerance PenTAG's economic analysis compared the technologies under review with interferon alfa plus cytarabine. PenTAG used interferon alfa as a comparator for this population on the assumption that it is the most effective technology available if imatinib cannot be tolerated and the technologies under review are assumed to be unavailable. PenTAG's expert advisers were not unanimous on this point, with some arguing that hydroxycarbamide would be appropriate as a comparator. However, others stated that interferon alfa was the standard of care for this population before the development of tyrosine kinase inhibitors (as confirmed by its use as the comparator in regulatory studies of effectiveness of first-line, standard-dose imatinib).
- 4.2.31 PenTAG's deterministic base-case incremental cost–utility analysis for people with chronic-phase CML and imatinib intolerance showed that nilotinib (cost £193,613; 7.09 QALYs) was more expensive and less effective than interferon alfa plus cytarabine (cost £39,747; 5.88 QALYs) with an ICER of £128,000 per QALY gained for nilotinib. Dasatinib (cost £280,639; 8.19 QALYs) when compared with interferon alfa plus cytarabine, had an ICER of £104,500 per QALY gained.

- 4.2.32 For accelerated-phase CML PenTAG performed a review, a critical appraisal and an exploration of the cost-effectiveness analyses in the manufacturers' submissions. PenTAG had concerns about the manufacturer's model of dasatinib. The model predicted a much shorter-tailed overall survival curve for high-dose imatinib and nilotinib than was seen in the trials and assumed that all treatments are always taken at the recommended dose. All of these factors would contribute to an increase in the final ICER for dasatinib in accelerated-phase CML.
- 4.2.33 PenTAG also had important concerns about the manufacturer's submission for nilotinib in accelerated-phase CML. The data used to estimate the effectiveness of high-dose imatinib in imatinib-resistant CML were questioned. When PenTAG made its corrections to the model, it predicted that nilotinib would be less effective and less costly than high-dose imatinib. PenTAG was also concerned about the manufacturer's degree of extrapolation of progression-free survival, in particular for the imatinib-intolerant subgroup, which made all cost-effectiveness results highly uncertain. Again the manufacturer assumed that all treatments are always taken at the recommended dose.
- 4.2.34 For blast-crisis phase CML, PenTAG found that the data used by the manufacturer of dasatinib to estimate the effectiveness of high-dose imatinib in an imatinib-resistant population were questionable, being based on an imatinib-naive comparator population receiving standard-dose and low-dose imatinib. In addition, the model predicts a much shorter-tailed overall survival curve for high-dose imatinib than was seen in the study of high-dose imatinib.

New analyses by the SHTAC Assessment Group using PenTAG's model

- 4.2.35 The SHTAC Assessment Group conducted new analyses using PenTAG's model for people with imatinib-resistant CML, with minor modifications. No structural changes to the model were made. The PenTAG analyses were limited to people starting in the chronic phase of CML because of the lack of data on the clinical effectiveness of the comparator treatments in the accelerated and blast-crisis phases. Because the updated systematic review did not find any suitable data to analyse the cost effectiveness of these phases of CML, the new analysis was limited to people starting in the chronic phase of CML.
- 4.2.36 In the SHTAC Assessment Group's base-case analyses, progression-free survival for dasatinib is assumed to be the same as that for nilotinib, based on the view of their clinical specialist. For the comparator, the SHTAC Assessment Group took data on hydroxycarbamide from the Novartis model and data on standard-dose imatinib and stem cell transplantation from the Bristol-Myers Squibb model. The SHTAC Assessment Group derived its best estimates of the following parameters: monthly treatment cost, treatment duration, overall survival and health state utility values for the chronic-phase treatment period. Without any reliable data for the comparators, the SHTAC Assessment Group was unable to derive survival curves from clinical data and selected an estimate of overall survival using a pragmatic approach. Similarly, the SHTAC Assessment Group was unable to provide estimates of the clinical data and so instead used plausible estimates of treatment duration for each of the parameters.
- 4.2.37 The costs for the interventions used in the SHTAC Assessment Group's analyses were taken from three sources:

- the cost of dasatinib, high-dose imatinib, nilotinib and interferon alfa were taken from the PenTAG report
- the costs of standard-dose imatinib and hydroxycarbamide were taken from BNF 60
- the cost of stem cell transplantation was taken from the Bristol-Myers Squibb submission and includes the additional cost of £80,000 for the stem cell transplant.

4.2.38 In the base-case analysis, dasatinib, high-dose imatinib and nilotinib were compared with hydroxycarbamide (the cheapest comparator), with the treatments ordered by increasing effectiveness. An incremental analysis was performed, in which each treatment was compared with the next least effective treatment that was neither dominated (that is, more expensive and less effective than the alternative) nor extendedly dominated (that is, more expensive and less effective than a combination of two other alternatives).

4.2.39 In the analysis, interferon alfa, standard-dose imatinib, stem cell transplantation and high-dose imatinib were dominated or extendedly dominated. Treatment with 1.5 years of hydroxycarbamide was associated with 3.5 years of overall survival (2.20 QALYs) at a cost of £18,128; 2.4 years of nilotinib treatment was associated with 12.98 years of overall survival (7.63 QALYs) at a cost of £161,667, and 3.1 years of dasatinib treatment was associated with 13.4 years of overall survival (7.85 QALYs) at a cost of £172,473. The ICER of nilotinib compared with hydroxycarbamide was £26,434 per QALY gained, and the ICER of dasatinib compared with nilotinib was £50,016 per QALY gained.

4.2.40 The SHTAC Assessment Group conducted a number of different sensitivity analyses. The parameters that had the most impact on

the model results were overall survival, treatment efficacy and treatment duration. The SHTAC Assessment Group explored the uncertainty about the results using probabilistic sensitivity analyses. At a threshold of £20,000 per QALY gained, hydroxycarbamide is the most cost-effective treatment (probability 100%). At a threshold of £30,000 per QALY gained the probabilities of being cost effective are 60% for nilotinib, 28% for dasatinib, 12% for hydroxycarbamide and 0% for high-dose imatinib.

- 4.2.41 The SHTAC Assessment Group explored the case in which dasatinib has a longer treatment duration than high-dose imatinib and nilotinib by varying the progression-free survival for dasatinib between 3.1 years (as in the SHTAC base case) and 6.5 years (as in the PenTAG base case), while keeping progression-free survival for high-dose imatinib and nilotinib constant. Extending the progression-free survival and treatment duration of dasatinib results in higher costs for dasatinib with no change in QALYs. Therefore the longer the treatment duration the less favourable the results compared with the other interventions.
- 4.2.42 The SHTAC Assessment Group also performed two scenario analyses that assumed treatment durations of 6.5 years and 10 years for each intervention (that is, dasatinib, high-dose imatinib and nilotinib). In these analyses the overall survival and QALY estimates remained the same for each intervention as in the base case.
- 4.2.43 In the first scenario (treatment duration set to 6.5 years), high-dose imatinib costs were £238,594, nilotinib costs were £222,093 and dasatinib costs were £221,325. High-dose imatinib and nilotinib were dominated (that is, more expensive and less effective) by

dasatinib and the ICER for dasatinib compared with hydroxycarbamide was £36,007 per QALY gained.

- 4.2.44 In the second scenario (treatment duration set to 10 years), high-dose imatinib costs were £300,182, nilotinib costs were £266,204 and dasatinib costs were £265,521. High-dose imatinib and nilotinib were dominated (that is, more expensive and less effective) by dasatinib and the relevant ICER was again dasatinib compared with hydroxycarbamide, which produced an ICER of £43,816 per QALY gained.

Comparison of economic models by the SHTAC Assessment Group

- 4.2.45 The SHTAC Assessment Group noted that the imatinib-resistant CML models provided by PenTAG, Bristol-Myers Squibb and Novartis generated ICERs greater than £30,000 per QALY gained for all treatments compared with the base-case treatment (interferon alfa). All of the models generated the lowest ICERs for nilotinib. The SHTAC Assessment Group also noted that the total costs of nilotinib and high-dose imatinib in the Bristol-Myers Squibb model are more than double those in the other models. This is a result of the longer treatment duration in the Bristol-Myers Squibb model. The SHTAC Assessment Group noted that treatment duration and drug costs are similar for nilotinib and high-dose imatinib in the models provided by PenTAG and Novartis, and that treatment duration is much longer for dasatinib than for the other interventions in PenTAG's model.
- 4.2.46 The SHTAC Assessment Group noted that QALYs and life years in the Novartis model were about half those in the models provided by PenTAG and Bristol-Myers Squibb. This may be because of the assumed high mortality associated with stem cell transplantation. The SHTAC Assessment Group noted that the number of life years

for interferon alfa is much higher in PenTAG's model than in the Bristol-Myers Squibb model. The SHTAC Assessment Group also noted that a clinical specialist indicated the overall survival for interferon alfa would be considerably less than 6.5 years and possibly as low as 1–2 years.

- 4.2.47 The SHTAC Assessment Group noted that survival estimates for the interventions in chronic-phase CML in the models provided by PenTAG and Bristol-Myers Squibb are similar, and are about double those in the Novartis model. Survival estimates in the accelerated phase and the blast-crisis phase for the interventions range from around 0.4 years in the Novartis model to 0.8 years in the Bristol-Myers Squibb model and 1.7 years in the PenTAG model.

Manufacturers' modelling responses to consultation on the preliminary recommendations issued in April 2011

- 4.2.48 The manufacturer of dasatinib, Bristol-Myers Squibb, provided additional economic analyses during consultation that compared dasatinib with hydroxycarbamide, and included bone marrow stem cell transplantation as a third-line treatment, in CML that is resistant to standard-dose imatinib.
- 4.2.49 The Bristol-Myers Squibb analysis assumed that 31% of people were eligible to receive bone marrow stem cell transplantation, with associated costs of £80,000 before transplantation and £2400 per month afterwards. Hydroxycarbamide was associated with a cost of £150.62 per month. The manufacturer assumed that in 8.1% of people receiving dasatinib there is no response to treatment (Shah et al. 2008), and that 10% discontinue treatment (PenTAG's report). Efficacy and discontinuation rates of hydroxycarbamide were assumed to be the same as those of interferon alfa in the

manufacturer's original economic analyses (that is, there is no response to treatment in 100%, and 55.5% discontinue treatment).

- 4.2.50 Dasatinib was estimated to result in a gain of 4.969 QALYs compared with hydroxycarbamide at an incremental cost of £138,791, resulting in an ICER of £27,932 per QALY gained for dasatinib compared with hydroxycarbamide.
- 4.2.51 The manufacturer of nilotinib, Novartis, provided an additional economic analysis that compared nilotinib with hydroxycarbamide, using the SHTAC model with a number of modifications. The modifications included:
- a mean dose intensity (defined as the amount of drug administered in a study as a proportion of the amount that would have been administered if there had been no dose reductions or dose interruptions) for dasatinib (instead of 100% dose intensity)
 - the same survival and therefore same QALY gain as dasatinib (instead of lower survival for nilotinib)
 - a reduction to 0.78 in the utility value associated with hydroxycarbamide in the chronic phase (instead of 0.85)
 - overall survival associated with hydroxycarbamide treatment of 3 years (instead of 3.5 years).
- 4.2.52 Novartis also provided an analysis that included a discount on the cost of nilotinib. When they applied the discount in the base-case analysis, the ICERs for nilotinib compared with hydroxycarbamide were £27,035 per QALY gained when a treatment duration of 6.5 years was assumed and £30,776 per QALY gained when a treatment duration of 10 years was assumed. When the modifications outlined in section 4.2.49 were also applied, the ICERs for nilotinib compared with hydroxycarbamide decreased to

£22,792 per QALY gained when a treatment duration of 6.5 years was assumed, and £24,993 per QALY gained when a treatment duration of 10 years was assumed.

- 4.2.53 When the SHTAC Assessment Group replicated the analysis, the results were slightly different from those presented by the manufacturer. When the modifications and the discount were included, the SHTAC replicated analysis resulted in ICERs for nilotinib compared with hydroxycarbamide of £22,964 per QALY gained when a treatment duration of 6.5 years was assumed, and £25,303 per QALY gained when a treatment duration of 10 years was assumed. When the replicated analysis only included the discount, the ICERs for nilotinib compared with hydroxycarbamide were £27,324 per QALY gained when a treatment duration of 6.5 years was assumed and £31,296 per QALY gained when a treatment duration of 10 years was assumed. SHTAC noted that this was because of the slightly different cost of nilotinib when the proposed discount was applied.

4.3 *Consideration of the evidence*

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of dasatinib, high-dose imatinib and nilotinib for the treatment of CML that is resistant to standard-dose imatinib, and of dasatinib and nilotinib for the treatment of CML in people with imatinib intolerance, having considered evidence on the nature of CML and the value placed on the benefits of the interventions by people with the condition, those who represent them and clinical specialists. It also took into account the effective use of NHS resources.
- 4.3.2 The Committee discussed current clinical practice for the treatment of CML. The Committee heard from the clinical specialists that

standard-dose imatinib is given in line with NICE technology appraisal guidance 70 to people presenting with chronic-phase CML. The clinical specialists stated that in approximately 60% of people there is a good response to standard-dose imatinib, and that these people will continue to receive the treatment for life and have a normal life expectancy. The Committee recognised the innovative nature and major change in the treatment of CML that imatinib had provided. However, it heard that 40% of people develop intolerance or resistance to standard-dose imatinib.

4.3.3 The Committee heard that high-dose imatinib, dasatinib and nilotinib are in widespread use and are a major advance over earlier therapies, that is, interferon alfa and hydroxycarbamide. The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care, and that for many people hydroxycarbamide or interferon alfa are considered to be little better than best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used, although it carries high risks and is restricted to fit, younger people. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib.

4.3.4 The Committee noted that high-dose imatinib had been recommended only in the context of clinical research in NICE technology appraisal guidance 70. It heard from the clinical specialists that high-dose imatinib is being used in clinical practice for people whose CML has previously had a good response to treatment with standard-dose imatinib. The Committee acknowledged the clinical specialists' view that for CML that is

resistant to standard-dose imatinib, high-dose imatinib was unlikely to be as beneficial as dasatinib and nilotinib.

- 4.3.5 The Committee heard from the clinical specialists that, in clinical practice, treatment with dasatinib, high-dose imatinib and nilotinib is given in accordance with European guidelines, which specify time-dependent targets. If the CML is responding to treatment, the treatment will be continued until progression or until the person dies (from non-CML causes). If CML does not respond to dasatinib or nilotinib within 12 months, treatment may be discontinued, or may be changed to hydroxycarbamide and/or, if suitable, stem cell transplantation.
- 4.3.6 The Committee heard from the clinical specialists that in more than 50% of people with imatinib-resistant CML treated with dasatinib or nilotinib, there is a good response to treatment and that this response is usually as good as the initial response to standard-dose imatinib. The clinical specialists expected that these people would receive dasatinib or nilotinib treatment for the rest of their lives, and possibly have a nearly normal life expectancy (that is, at least 10 more years). For people receiving interferon alfa or hydroxycarbamide in the chronic phase, the prognosis is poor, with a median life expectancy of around 5 years. It heard from the clinical specialists that with modern therapy the accelerated phase is no longer considered to be a distinct disease phase, so in effect the disease progresses from a prolonged chronic phase to blast-crisis phase.
- 4.3.7 The Committee discussed the clinical-effectiveness evidence for dasatinib, high-dose imatinib and nilotinib for the treatment of chronic-phase CML that is resistant to standard-dose imatinib. It was aware of only one comparative trial, which compared dasatinib

with high-dose imatinib, but noted the restricted comparison (only with high-dose imatinib) and the comments from the Assessment Groups on the interpretation of this trial.

- 4.3.8 The Committee noted that the clinical trials available were non-comparative, of short duration and had used surrogate outcomes to predict overall survival. The Committee noted the wide range of results across the interventions, with major cytogenetic response rates ranging from 33.3 to 58.9% with dasatinib, 32.7 to 42.5% with high-dose imatinib (but with one outlying result of 63.5%), and 35.3 to 56.1% with nilotinib. The Committee discussed the clinical trial evidence in light of the views of the patient experts and clinical specialists. The Committee noted the poor quality of the evidence base. However, it heard from the clinical specialists and patient experts that clinical benefits, particularly of dasatinib and nilotinib, have been demonstrated. In addition, the clinical specialists argued that the people in the clinical trials did not reflect the population seen in clinical practice because the trials included people who had worse disease prognoses than would be seen in current clinical practice.
- 4.3.9 The Committee concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for people with imatinib-resistant CML. However, the Committee agreed that the limited evidence base means that the magnitude of the benefit is uncertain. The Committee also agreed that there was no good evidence to distinguish between dasatinib and nilotinib; a conclusion supported by the clinical specialists.
- 4.3.10 The Committee was aware that continued use of imatinib is not an option for people with imatinib intolerance. It noted that most of the clinical-effectiveness evidence came from trials that included a

mixed population of people with imatinib-resistant CML and people with imatinib intolerance. The Committee noted that in the trials that reported response rates separately, CML in people with imatinib intolerance generally had a higher response rate to dasatinib and nilotinib than people with imatinib-resistant CML, and that this was reflected in the estimates of overall survival used in the economic analyses. The Committee agreed that this was a reasonable assumption given that people with imatinib intolerance generally have had a shorter duration of prior treatment than those whose CML develops resistance to imatinib over time.

4.3.11 The Committee discussed the side effects of treatment for imatinib-resistant CML and for people with CML who have imatinib intolerance. It noted the adverse effects reported in the trials with dasatinib, high-dose imatinib and nilotinib in imatinib-resistant CML (see sections 4.1.9, 4.1.12, 4.1.17 and 4.1.22). The Committee concluded that dasatinib and nilotinib are better tolerated than imatinib, and that older treatments, particularly interferon alfa, can be poorly tolerated.

4.3.12 The Committee considered the treatment of the blast-crisis phase of CML in clinical practice. The Committee heard from the clinical specialists that at the blast-crisis stage of the disease, life expectancy is about 3–6 months. The Committee also heard from the clinical specialists that the treatment strategy in the blast-crisis phase of the disease is different from that in the accelerated or chronic phases, with dasatinib and high-dose imatinib given as adjuvant treatment with intensive chemotherapy for acute leukaemia. The Committee was aware that no evidence was presented on the use of dasatinib or high-dose imatinib in this way and that the evidence base for the blast-crisis phase of the disease is very limited.

- 4.3.13 The Committee then considered the economic models provided by the manufacturers and the Assessment Groups for chronic-phase CML that is resistant to standard-dose imatinib. In each it took particular note of the ICER for the comparison between the most cost effective of the tyrosine kinase inhibitors (given that dasatinib and nilotinib are considered equal), and the most cost effective of the older treatments (given that none were definitively favoured). In all the comparisons, the Committee also took particular note of the relationship between treatment duration and overall survival; because these are the main influences on costs and benefits and the clinical specialists stated that these were closely related.
- 4.3.14 From the model developed by Bristol-Myers Squibb, the Committee particularly noted the comparison between dasatinib and interferon alfa, which generated an ICER of £38,900 per QALY gained. The estimated treatment duration with interferon alfa was 0.65 years (at a total estimated cost of £129,000), resulting in 3.56 years of overall survival, and the estimated treatment duration with dasatinib was 7.46 years (at a cost of £314,000), resulting in 11.76 years of overall survival. The Committee considered that the model had a number of limitations, of which the most important were that it estimated the cost for people receiving interferon alfa to be higher than (in some cases double) that of all the other economic models, and it did not include a comparison with hydroxycarbamide. After consultation on the appraisal consultation document, Bristol-Myers Squibb provided an additional economic analysis. The Committee noted that the additional analysis included hydroxycarbamide as a comparator and bone marrow stem cell transplantation as a third-line treatment. It noted that Bristol-Myers Squibb calculated the ICER for dasatinib to be £28,000 per QALY gained compared with hydroxycarbamide, and the total QALYs and

costs associated with treatment with dasatinib in the additional economic analysis were more favourable to dasatinib than those in the manufacturer's original economic analysis.

4.3.15 The Committee compared these findings with those of the other economic models, and examined the assumptions that had been used in the additional analysis. Bristol-Myers Squibb's estimates for comparator costs were higher than had been used in other economic models. The Committee considered that the assumption that 30.8% of people who discontinued treatment would receive bone marrow stem cell transplantation was likely to be an overestimate given contraindications to bone marrow stem cell transplantation and the lack of availability of a matched donor for many people. Secondly, the Committee considered that the assumed ongoing monthly cost of £2400 after bone marrow stem cell transplantation (at £80,000) was an unreasonably high estimate, given that only a minority of people who survive transplantation develop complications that incur high ongoing costs. Thirdly, the Committee considered the utility value estimate of 0.6 for the health state associated with successful transplantation to be unreasonable, in view of the utility value of 0.85 for successful dasatinib treatment, and the utility value of 0.68 for failed dasatinib treatment. The Committee noted that these utility values were not derived from a common source. The Committee therefore concluded that the ICER from this analysis was not reliable and could not form a suitable basis for a recommendation.

4.3.16 The Committee considered the economic model developed by Novartis for chronic-phase CML that is resistant to standard-dose imatinib. It noted that in the base-case analysis, nilotinib dominated (that is, it was less expensive and more effective than) high-dose

imatinib and, in an exploratory analysis, nilotinib compared with a combination of hydroxycarbamide and stem cell transplantation resulted in an ICER of £44,000 per QALY gained. The estimated treatment duration with hydroxycarbamide and stem cell transplantation resulting in 4.21 years of overall survival (at a cost of £80,900) was not reported, and the estimated treatment duration with nilotinib was 2 years, resulting in 5.8 years of overall survival (at a cost of £139,000). The Committee noted that if the treatment duration and overall survival seen in clinical practice were more accurately modelled and if hydroxycarbamide alone was a comparator, the base-case ICER of £44,000 per QALY gained would be likely to increase.

4.3.17 The Committee considered the economic model developed by PenTAG and subsequently updated by SHTAC for chronic-phase CML that is resistant to standard-dose imatinib. The Committee noted that the PenTAG model did not link treatment duration with overall survival and that some of the results were not plausible. In particular, it noted that the estimated overall survival for interferon alfa was implausible and the treatment duration for people receiving nilotinib was lower than would be seen in clinical practice, given the estimated overall survival.

4.3.18 The Committee understood that the model updated by SHTAC attempted to correct PenTAG's overestimate of survival on interferon alfa and the discrepancy between the nilotinib and dasatinib treatment durations, but the SHTAC base-case treatment durations still did not reflect the fact that in clinical practice, people will receive treatment until progression or death (this was confirmed by the clinical specialists; see section 4.3.6).

- 4.3.19 The Committee did not consider that a plausible ICER had been presented in any of the economic models, but agreed that the least implausible analysis was the SHTAC scenario in which the treatment durations of dasatinib, high-dose imatinib and nilotinib were set to 10 years with overall survival estimates of 12.4–13.4 years. It noted that in this analysis both high-dose imatinib and nilotinib were dominated (that is, more expensive and less effective) by dasatinib, and dasatinib compared with hydroxycarbamide resulted in an ICER of £43,800 per QALY gained. The Committee noted its earlier conclusions that more than 50% of people receiving these treatments are likely to do so for more than 10 years, with many people receiving them until death. The Committee agreed that if treatment is continued for most of the person's lifetime, then the ICERs would increase. The Committee concluded that there was no evidence to distinguish between dasatinib and nilotinib and that the ICERs for these treatments compared with hydroxycarbamide were uncertain and likely to be higher than £43,800 per QALY gained.
- 4.3.20 The Committee discussed the cost effectiveness of the technologies for the treatment of chronic-phase CML in people who have imatinib intolerance. It acknowledged the difficulties of undertaking an assessment of cost effectiveness without reasonable comparative evidence, relying on surrogate outcomes and uncertain treatment durations. However, it was aware that the effectiveness of dasatinib and nilotinib was likely to be greater in people with imatinib intolerance than in people with imatinib-resistant CML. Noting the uncertainties in these analyses, particularly about treatment duration, the Committee concluded that dasatinib and nilotinib were likely to be at least as cost effective in people with imatinib intolerance as in people with imatinib-resistant

CML and, as such, the cost effectiveness of dasatinib and nilotinib for people with imatinib intolerance could be inferred from the cost effectiveness in people with imatinib-resistant CML.

4.3.21 The Committee noted that the manufacturer of nilotinib had agreed a patient access scheme with the Department of Health. The manufacturer had presented ICERs for the scheme based on an analysis reflecting the scenario considered most plausible by the Committee, outlined in 4.3.19.

4.3.22 The Committee noted that the Novartis adjusted analysis based on the SHTAC update of the PenTAG model resulted in an ICER of £30,800 per QALY gained. It also noted that when SHTAC replicated the analysis the ICER increased slightly to £31,300 per QALY gained. It also noted that the manufacturer argued that a number of further changes to the SHTAC analysis should be made, namely:

- a reduction in treatment duration from 10 to 6.5 years
- a lower dose intensity of nilotinib based on clinical trial data
- an assumption of survival benefit equal to that of dasatinib
- a lower utility value associated with hydroxycarbamide treatment in the chronic phase, and
- a lower estimate of overall survival for hydroxycarbamide treatment.

The Committee noted that when the modifications and the discount were applied, the ICERs for nilotinib compared with hydroxycarbamide decreased to £22,800 per QALY gained when a treatment duration of 6.5 years was assumed, and £25,000 per QALY gained when a treatment duration of 10 years was assumed. The Committee agreed that some of these adjustments were

plausible, but not all. The treatment duration could be less than 10 years but the estimate of 6.5 years, which was based on treatment being withdrawn in all people who did not have a complete cytogenetic response, was not plausible. Also the Committee did not agree with Novartis that the utility value for people treated with hydroxycarbamide should be lower for the same health states achieved by other treatments. It accepted that health state durations were shorter with hydroxycarbamide but thought that this should not be compounded by utility value adjustments.

4.3.23 The Committee therefore concluded that the Novartis adjusted ICER of £22,800 per QALY gained was too optimistic. However, the Committee accepted that with the patient access scheme in place and its earlier conclusion that some of the adjustments to the model were plausible, the ICER for nilotinib is likely to be less than the SHTAC replicated ICER of £31,300 per QALY gained. The Committee concluded that the use of nilotinib for the treatment of imatinib-resistant CML could be regarded as a cost-effective use of NHS resources. The Committee therefore recommended the use of nilotinib for the treatment of adults with chronic- and accelerated-phase CML that is resistant to standard-dose imatinib or who have imatinib intolerance, if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme.

4.3.24 The Committee then reflected on all of the models and results presented for high-dose imatinib for the treatment of CML that is resistant to standard-dose imatinib, together with the clinical specialists' and patient experts' views on the use of the technologies. It noted that high-dose imatinib was dominated (that is, more expensive and less effective than another treatment) in all models. Therefore the Committee agreed that high-dose imatinib

could not be recommended as a cost-effective use of NHS resources for the treatment of CML that is resistant to standard-dose imatinib.

- 4.3.25 The Committee then considered the cost effectiveness of dasatinib for the treatment of CML that is resistant to standard-dose imatinib. The Committee noted its earlier conclusion that the updated economic analysis provided by Bristol-Myers Squibb could not form a suitable basis for a recommendation given the limitations described in section 4.3.15 It also noted that all other estimated ICERs were higher than those normally considered acceptable for the NHS, and were highly likely to be above the figures suggested. Therefore the Committee concluded that dasatinib could not be recommended as a cost-effective use of NHS resources for the treatment of adults with chronic phase CML that is resistant to standard-dose imatinib, or who have imatinib intolerance. Furthermore, the Committee noted that, given the patient access scheme for nilotinib and the assumed equivalence of effectiveness of dasatinib and nilotinib, dasatinib is considerably more expensive but no more effective than nilotinib.
- 4.3.26 The Committee then considered the cost-effectiveness evidence for dasatinib, high-dose imatinib and nilotinib for the treatment of the accelerated and blast-crisis phases of CML. The Committee noted the clinical specialists' view that there is no longer considered to be a distinguishable accelerated phase of CML. However, it acknowledged that this phase continues to be recognisable for some people, and saw no reason not to recommend nilotinib for treatment of CML in the accelerated phase. The Committee noted that, as for the chronic phase, high-dose imatinib continued to be dominated (that is, it was more expensive and less effective than another treatment), and dasatinib continued to be as effective but

more expensive, and concluded that neither drug could be recommended for the treatment of accelerated-phase CML.

4.3.27 The Committee noted that nilotinib does not have a marketing authorisation for the treatment of blast-crisis phase CML. It noted that treatment for the blast-crisis phase is different from that used in the other phases, with interventions generally used as adjuvant treatment to intensive chemotherapy for acute leukaemia. The Committee was aware that no evidence using the interventions in this way had been submitted. To the extent that dasatinib could be considered a stand-alone treatment, the Committee concluded that the evidence was particularly limited. The Committee considered that all three of the estimates it saw, one from PenTAG and two from BMS to be highly speculative. The PenTAG model comparing dasatinib with best supportive care included cost estimates of £88,000 and £80,000 for dasatinib and no treatment respectively. The Committee considered that the small cost difference from which this was derived was unlikely to reflect reality, as the costs for best supportive care included in the no treatment arm would also be incurred in the dasatinib treatment arm after treatment with dasatinib is stopped. Neither of the Bristol-Myers Squibb models included best supportive care as a comparator and the Committee was not convinced that high-dose imatinib and bone marrow stem cell transplantation were sufficient comparators. This compounded the very poor evidence base supporting the calculations and the Committee concluded that dasatinib could not be considered a cost-effective use of NHS resources for the treatment of blast-crisis phase CML.

4.3.28 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are

licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

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

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

4.3.29 The Committee discussed the possibility that the end-of-life criteria defined by NICE in its supplementary advice might be met by dasatinib or high-dose imatinib for people with blast-crisis phase CML. The Committee noted that in the blast crisis phase of CML, life expectancy is short (about 3–6 months). The Committee also agreed that this is a very small population, because fewer than 10% of all people with CML will present at the blast-crisis stage. However, the Committee agreed that the available evidence on life extension in the blast crisis phase was too weak and was not considered to be robust. In addition, no data were presented for the interventions as used in clinical practice. The Committee concluded that dasatinib and high-dose imatinib do not fulfil the end-of-life criteria for people with blast-crisis phase CML.

- 4.3.30 The Committee recognised the innovative nature and major change in the treatment of CML that imatinib has provided since it has been introduced and recommended for use by NICE (technology appraisal guidance 70, October 2003), and discussed whether dasatinib and nilotinib should be considered to be innovative treatments. The Committee considered that the development of dasatinib and nilotinib was not a step change in the treatment of CML where standard dose imatinib had failed because of resistance or intolerance and did not identify any potential significant and substantial health-related benefits that had not been included in the economic models.
- 4.3.31 The Committee discussed whether NICE's duties under the equalities legislation required it to alter or add to its preliminary recommendations in any way. It noted that the submission from Bristol-Myers Squibb highlighted that if dasatinib, high-dose imatinib or nilotinib are not recommended for the treatment of imatinib-resistant CML, then allogeneic stem cell transplantation is the only treatment that may deliver clinical efficacy. Because only a small number of people who have imatinib-resistant CML are eligible for allogeneic stem cell transplantation, this could raise equality issues in relation to race, age (the elderly), and comorbidities. However, the Committee concluded that allowing for clinical decisions relating to a range of possible treatments based on individual assessment of risk and benefit does not limit access to the technology for any specific protected group compared with other people.
- 4.3.32 The Committee noted the importance of registries in gathering data on CML, particularly when treatment with standard-dose imatinib has failed. It supported collecting information in a suitable registry about treatments, long-term outcomes (particularly overall survival)

and treatment-related adverse events in CML that is resistant to standard-dose imatinib.

Summary of Appraisal Committee's key conclusions

| TAXXX | Appraisal title: Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance | Section |
|---|---|---------|
| Key conclusion | | |
| <p>Nilotinib is recommended for the treatment of chronic or accelerated phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in adults:</p> <ul style="list-style-type: none"> • whose CML is resistant to treatment with standard-dose imatinib or • who have imatinib intolerance and • if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme. | 1.1 | |
| <p>Dasatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase CML in adults with imatinib intolerance or whose CML is resistant to treatment with standard-dose imatinib.</p> | 1.2 | |
| <p>High-dose imatinib² is not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib.</p> | 1.3 | |
| <p>The Committee accepted that, with the patient access scheme in place, the use of nilotinib for the treatment of imatinib-resistant CML could be regarded as a cost-effective use of NHS resources. All other estimated ICERs were higher than those normally considered acceptable for the NHS, and were highly likely to be above the figures suggested.</p> | 4.3.23, 4.3.24, 4.3.25 | |
| <p>High-dose imatinib was dominated (that is, more expensive and less effective than another treatment) in all models.</p> | 4.3.24 | |

² The summary of product characteristics (SPC) for imatinib states that the dose may be increased from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg in patients with accelerated phase or blast crisis (see SPC for full details). High dose imatinib refers to doses of 600 mg or 800 mg in the chronic phase disease or 800 mg in the accelerated phase or blast crisis.

| Current practice | | |
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| Clinical need of patients, including the availability of alternative treatments | The Committee heard that 40% of people develop intolerance or resistance to standard-dose imatinib. | 4.3.2 |
| | The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care, and that for many people hydroxycarbamide or interferon alfa are considered to be little better than best supportive care. It also heard that bone marrow stem cell transplantation could be used, although it carries high risks and is restricted to fit, younger people. | 4.3.3 |
| | The Committee heard that fewer than 10% of all people with CML will present with the blast-crisis phase of the disease, and that at this stage life expectancy is about 3–6 months. It also heard from the clinical specialists that treatment strategy in the blast-crisis phase of the disease is different from that in the accelerated or chronic phases, with dasatinib and high-dose imatinib given as adjuvant treatment with intensive chemotherapy for acute leukaemia. | 4.3.12, 4.3.29 |
| The technology | | |
| Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | The Committee heard that high-dose imatinib, dasatinib and nilotinib are a major advance over earlier therapies, that is, interferon alfa and hydroxycarbamide. | 4.3.3 |
| | The Committee heard from the clinical specialists that in more than 50% of people with imatinib resistant CML treated with dasatinib or nilotinib, there is a good response to treatment and that this response is usually as good as the initial response to standard-dose imatinib. The Committee acknowledged the clinical specialists' view that for CML that is resistant to standard-dose imatinib, high-dose imatinib was unlikely to be as beneficial as dasatinib and nilotinib. | 4.3.6 |
| | The Committee was aware that continued use of imatinib is not an option for people with imatinib intolerance. | 4.3.10 |
| | The Committee considered that the development of dasatinib and nilotinib was not a step change innovation, and did not identify any potential significant and substantial health-related benefits that had not been included in the economic models. | 4.3.30 |

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| <p>What is the position of the treatment in the pathway of care for the condition?</p> | <p>The Committee heard from the clinical specialists that high-dose imatinib is being used in clinical practice for people whose CML has previously had a good response to treatment with standard-dose imatinib. The Committee acknowledged the clinical specialists' view that for CML that is resistant to standard-dose imatinib, high-dose imatinib was unlikely to be as beneficial as dasatinib and nilotinib.</p> | <p>4.3.4</p> |
| <p>Adverse effects</p> | <p>The Committee concluded that dasatinib and nilotinib are better tolerated than imatinib, and that older treatment, particularly interferon alfa, can be poorly tolerated.</p> | <p>4.3.11</p> |
| <p>Evidence for clinical effectiveness</p> | | |
| <p>Availability, nature and quality of evidence</p> | <p>The Committee was aware of only one comparative trial, which compared dasatinib with high-dose imatinib, but noted the restricted comparison (only with high-dose imatinib) and the comments from the Assessment Groups on the interpretation problems with this trial.</p> | <p>4.3.7</p> |
| | <p>The Committee noted that the clinical trials available were non-comparative, of short duration and had used surrogate outcomes to predict overall survival.</p> | <p>4.3.8</p> |
| | <p>The Committee was aware that no evidence was presented on the use of dasatinib or high-dose imatinib given as adjuvant treatment with intensive chemotherapy for acute leukaemia and that the evidence base in the blast-crisis phase of the disease is very limited.</p> | <p>4.3.12</p> |
| | <p>The Committee noted that most of the clinical effectiveness evidence came from trials that included a mixed population of people with imatinib-resistant CML and people with imatinib intolerance.</p> | <p>4.3.10</p> |
| <p>Relevance to general clinical practice in the NHS</p> | <p>The clinical specialists argued that the people in the clinical trials did not reflect the population seen in clinical practice because the trials included people who had worse disease prognoses than would be seen in current clinical practice.</p> | <p>4.3.8</p> |
| <p>Uncertainties generated by the evidence</p> | <p>The Committee agreed that the limited evidence base means that the magnitude of the benefit (for people with imatinib-resistant CML) is uncertain.</p> | <p>4.3.9</p> |

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| <p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p> | <p>The Committee noted that in the trials that reported response rates separately, CML in people with imatinib intolerance generally had a higher response rate to dasatinib and nilotinib than people with imatinib-resistant CML, and that this was reflected in the estimates of overall survival used in the economic analyses. The Committee agreed that this was a reasonable assumption given that people with imatinib intolerance generally have had a shorter duration of prior treatment than those whose CML develops resistance to imatinib over time.</p> | <p>4.3.11</p> |
| <p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p> | <p>The Committee concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for people with imatinib-resistant CML, but that the limited evidence base means that the magnitude of the benefit is uncertain.</p> | <p>4.3.9</p> |
| <p>Evidence for cost-effectiveness</p> | | |
| <p>Availability and nature of evidence</p> | <p>The Committee considered the economic models provided by the manufacturers and the Assessment Groups.</p> | <p>4.3.13</p> |

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| <p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p> | <p>The Committee considered that the model developed by Bristol-Myers Squibb had a number of limitations, of which the most important were that it estimated the cost for people receiving interferon alfa to be higher than (in some cases double) that of all the other economic models, and it did not include a comparison with hydroxycarbamide.</p> | <p>4.3.14</p> |
| | <p>It noted the additional analysis provided by Bristol-Myers Squibb, and considered that the assumption that 30.8% of people who discontinued treatment would receive bone marrow stem cell transplantation was likely to be an overestimate. Also, the estimated ongoing monthly cost of bone marrow stem cell transplantation was unreasonably high. Finally, the Committee considered the utility value estimate for the health state associated with successful transplantation to be unreasonable.</p> | <p>4.3.15</p> |
| | <p>The Committee considered the economic model developed by Novartis for chronic-phase CML that is resistant to standard-dose imatinib. The Committee noted that if the treatment duration and overall survival seen in clinical practice were more accurately modelled and if hydroxycarbamide alone was a comparator, the base-case ICER of £44,000 per QALY gained would be likely to increase.</p> | <p>4.3.17</p> |
| | <p>The Committee considered the Novartis adjusted analysis and concluded that the treatment duration which was based on treatment being withdrawn in all people who did not have a complete cytogenetic response, or the utility value for people treated with hydroxycarbamide should be lower for the same health states achieved by other treatments, were not plausible. It accepted that health state durations were shorter with hydroxycarbamide but thought that this should not be compounded by utility value adjustments.</p> | <p>4.3.22</p> |
| | <p>The Committee noted the PenTAG model did not link treatment duration with overall survival and that some of the results were not plausible. It understood that the SHTAC base-case treatment durations still did not reflect the fact that in clinical practice, people will receive treatment until progression or death.</p> | <p>4.3.17, 4.3.18</p> |

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| <p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p> | <p>The Committee considered the Bristol-Myers Squibb additional analysis, and noted the utility value estimate of 0.6 for the health state associated with successful transplants to be unreasonable, in view of the utility value of 0.85 for successful dasatinib treatment, and the utility value of 0.68 for failed dasatinib treatment.</p> <p>The Committee did not agree with the assumption in the Novartis adjusted analysis that the utility value for people treated with hydroxycarbamide should be lower for the same health states achieved by other treatments.</p> <p>The Committee did not identify any potential significant and substantial health-related benefits that had not been included in the economic models.</p> | <p>4.3.15</p> <p>4.3.22</p> <p>4.3.30</p> |
| <p>Are there specific groups of people for whom the technology is particularly cost effective?</p> | <p>Not applicable</p> | <p>-</p> |

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| <p>What are the key drivers of cost effectiveness?</p> | <p>The Committee noted that high-dose imatinib was dominated (that is, more expensive and less effective than another treatment) in all models.</p> | <p>4.3.24</p> |
| | <p>The Committee concluded that the updated economic analysis provided by Bristol Myers Squibb could not form a suitable basis for a recommendation, and also noted that all other estimated ICERs were higher than those normally considered acceptable for the NHS, and were highly likely to be above the figures suggested. Furthermore, the Committee noted that, given the patient access scheme for nilotinib and the assumed equivalence of effectiveness of dasatinib and nilotinib, dasatinib is considerably more expensive but no more effective than nilotinib.</p> | <p>4.3.25</p> |
| | <p>The Committee noted the clinical specialists' view that there is no longer considered to be a distinguishable accelerated phase of CML. It saw no reason not to recommend nilotinib for treatment of CML in the accelerated phase. The Committee noted that, as for the chronic phase, high-dose imatinib continued to be dominated (that is, it was more expensive and less effective than another treatment), and dasatinib continued to be as effective but more expensive.</p> | <p>4.3.26</p> |
| | <p>The Committee noted that nilotinib does not have a marketing authorisation for the treatment of blast-crisis phase CML. It considered that the interventions used to treat blast-crisis phase CML are generally used as adjuvant treatment to intensive chemotherapy for acute leukaemia. It was aware that no evidence using the interventions in this way had been submitted. To the extent that dasatinib could be considered a stand-alone treatment, the Committee concluded that the evidence was particularly limited.</p> | <p>4.3.27</p> |

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| Most likely cost-effectiveness estimate (given as an ICER) | The Committee did not consider that a plausible ICER had been presented in any of the economic models. | 4.3.19 |
| | The Committee concluded that dasatinib and nilotinib were likely to be at least as cost effective in people with imatinib intolerance as in people with imatinib-resistant CML | 4.3.20 |
| | It noted that high-dose imatinib was dominated (more expensive and less effective) in all models. | 4.3.24 |
| | The Novartis' adjusted ICER of £22,800 per QALY gained was too optimistic, however, with the patient access scheme in place, the use of nilotinib for the treatment of imatinib-resistant CML could be regarded as a cost-effective. | 4.3.23 |
| | Given the Committee's conclusion that updated economic analysis provided by Bristol-Myers Squibb could not form a suitable basis for a recommendation all other estimated ICERs were higher than those normally considered acceptable for the NHS, and were highly likely to be above the figures suggested. | 4.3.25 |
| | Committee noted that treatment for the blast-crisis phase is different from that used in the other phases. To the extent that dasatinib could be considered a stand-alone treatment, the Committee concluded that the evidence was particularly limited. The Committee considered all three estimates of cost effectiveness it saw to be highly speculative with a very poor evidence base supporting the calculations. | 4.3.27 |
| Additional factors taken into account | | |
| Patient access schemes (PPRS) | The Committee noted that the manufacturer of nilotinib had agreed a patient access scheme with the Department of Health. | 4.3.21 |
| End-of-life considerations | The Committee noted that in the blast crisis phase of CML, life expectancy is short (about 3–6 months). The Committee also agreed that this is a very small population, because fewer than 10% of all people with CML will present at this stage. However, the Committee agreed that the available evidence on life extension in the blast crisis phase was too weak and was not considered to be robust. In addition, no data were presented for the interventions as used in clinical practice. The Committee concluded that dasatinib and high-dose imatinib do not fulfil the end-of-life criteria for people with blast-crisis phase CML. | 4.3.29 |

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| <p>Equalities considerations and social value judgements</p> | <p>The Committee noted the argument that if dasatinib, high-dose imatinib or nilotinib are not recommended for the treatment of imatinib-resistant CML and that this could raise issues in relation to race, age (the elderly), and comorbidities. However, the Committee concluded that allowing for clinical decisions relating to a range of possible treatments based on individual assessment of risk and benefit does not limit access to the technology for any specific protected group compared with other people.</p> | <p>4.3.31</p> |
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5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 The Department of Health and the manufacturer have agreed that nilotinib will be available to the NHS with a patient access scheme which makes nilotinib available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the manufacturer at the following e-mail address: **NICE to include at time of publication**

5.3 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

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

6 Related NICE guidance

Published

- Improving outcomes in haematological cancers – the manual. NICE cancer service guidance (2003). Available from www.nice.org.uk/guidance/CSGHO
- Guidance on the use of imatinib for chronic myeloid leukaemia. NICE technology appraisal guidance 70 (2003). Available from www.nice.org.uk/guidance/TA70

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (including part-review of NICE technology appraisal guidance 70). NICE technology appraisal. Publication expected May 2012.

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in September 2014.

Andrew Stevens
Chair, Appraisal Committee
July 2011

Appendix A: Appraisal Committee members, and NICE project team

A *Appraisal Committee members*

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

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

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

Dr Kathryn Abel

Reader and Consultant Psychiatrist / Director of Centre for Women's Mental Health, University of Manchester

Dr David Black

Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden

Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett

Director for Health Improvement and Medical Director, NHS Barnet, London

Professor Mike Campbell

Statistician, Institute of Primary Care and General Practice, University of Sheffield

David Chandler

Lay Member

Dr Mary Cooke

Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

Dr Chris Cooper

General Practitioner, St John's Way Medical Centre, London

Professor Peter Crome

Consultant Geriatrician and Professor of Geriatric Medicine, Keele University

Dr Christine Davey

Research Adviser, North and East Yorkshire Alliance Research and Development Unit, York

Richard Devereaux-Phillips

Director, Public Policy and Advocacy NW Europe, BD, Oxford

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Stephen Greep

Chief Executive of Hull and East Yorkshire Hospitals NHS Trust

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Henry Marsh

Consultant Neurosurgeon, St George's Hospital, London

Professor Gary McVeigh

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

Professor Eugene Milne

Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Dr Neil Myers

General Practitioner, Glasgow

Dr Richard Nakielny

Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Ruth Oliver-Williams

Head of Nursing / Quality Improvement Lead Surgical Services, Royal Derby Hospital

Dr Danielle Preedy

Lay Member

Dr Martin Price

Head of Outcomes Research, Janssen-Cilag, Buckinghamshire

Ellen Rule

Programme Director, NHS Bristol

Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington

Dr Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Andrew Stevens

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

Dr John Stevens

Lecturer in Bayesian Statistics in Health Economics, School of Health and Related Research, Sheffield

Dr Matt Stevenson

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

Professor Paul Trueman

Professor of Health Economics, Brunel University, London

Dr Judith Wardle

Lay Member

B NICE project team - Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance

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

Scott Goulden / Joao Vieira

Technical Lead(s)

Rebecca Trowman / Helen Knight / Janet Robertson / Bhash Naidoo

Technical Adviser

Lori Farrar / Laura Malone

Project Manager

Appendix B: Sources of evidence considered by the Committee for Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance

The assessment reports for this appraisal were prepared by Peninsula Health Technology Assessment Group and Southampton Health Technology Assessment Centre:

- A Thompson Coon et al. (2009) Dasatinib and nilotinib for imatinib-resistant or -intolerant chronic myeloid leukaemia: A systematic review and economic evaluation.
- B Loveman E, Cooper K, Bryant J, Colquitt JL, Frampton GK, Clegg A. (2011) Dasatinib, high dose imatinib and nilotinib for the treatment of imatinib resistant chronic myeloid leukaemia: A systematic review and economic evaluation *Health Technology Assessment*.
- C The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Bristol-Myers Squibb
- Novartis Pharmaceuticals

II Professional/specialist and patient/carer groups:

- Chronic Myeloid Leukaemia Support Group
- Leukaemia CARE
- Leukaemia Research Fund

- Macmillan Cancer Support
- British Committee for Standards in Haematology
- British Society for Haematology
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health
- Welsh Government
- Wiltshire PCT

IV Commentator organisations (without the right of appeal):

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Bristol-Myers Squibb
- MSD
- Leukaemia & Lymphoma Research
- National Institute for Health Research Health Technology Assessment
- Peninsula Technology Assessment Group, University of Exeter (PenTAG)
- Southampton Health Technology Assessment Centre
- National Collaborating Centre for Cancer

D The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on Dasatinib, high dose imatinib and nilotinib for the treatment of chronic myeloid leukaemia (part review of TA70) by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Stephen O'Brien, Consultant Haematologist, nominated by Royal College of Pathologists – clinical specialist
- Professor Jane Apperley, Professor of Haematology, nominated by NCRI/RCP/RCR/ACP.JCCO – clinical specialist
- Professor Richard Clark, Consultant Haematologist, nominated by British Society of Haematology and Royal College of Pathologists – clinical specialist
- Sandy Craine, nominated by The CML Support Group UK – patient expert
- Robert Osborn, nominated by The CML Support Group UK – patient expert
- Tony Gavin, Director of Campaigning and Patient Advocacy, Leukaemia CARE, patient expert
- Lynsey Wombwell, representing Leukaemia CARE, patient expert

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

- Bristol-Myers Squibb
- Novartis Pharmaceuticals