NICE National Institute for Health and Care Excellence

NICE guidance

Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia

Technology appraisal guidance
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Your responsibility

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

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

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

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

Contents

This guidance replaces TA251.

This guidance partially replaces TA70.

1 Recommendations

1.1 Imatinib is recommended as an option for untreated, chronic-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults.

1.2 Dasatinib and nilotinib are recommended, within their marketing authorisations, as options for untreated chronic-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults. The drugs are recommended only if the companies provide them with the discounts agreed in the relevant patient access schemes.

2 The technologies

Description of the technologies	Dasatinib (Sprycel, Bristol-Myers Squibb), a tyrosine kinase inhibitor, 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. Imatinib (Glivec, Novartis Pharmaceuticals) is an orally active tyrosine kinase inhibitor, 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 chronic myeloid leukaemia (CML). Nilotinib (Tasigna, Novartis Pharmaceuticals), a tyrosine kinase inhibitor, 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.
Marketing authorisations	Dasatinib has a marketing authorisation for the treatment of 'adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase' and adult patients with 'chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate'. Imatinib has a marketing authorisation for the treatment of adult and paediatric patients with 'newly diagnosed Philadelphia chromosome (*bcr-abl*) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment' and for 'adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis'. Nilotinib has a marketing authorisation for the treatment of adult patients with 'newly diagnosed Philadelphia chromosome positive chronic myeloid 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'.

Adverse reactions	The most common reported side effects with dasatinib 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. The summary of product characteristics states: 'Dasatinib should be administered with caution to patients who have or may develop prolongation of the QT interval'. The most common side effects with imatinib are nausea, vomiting, oedema (fluid retention), muscle cramps, skin rash, diarrhoea, abdominal pain, headache and fatigue. 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 adverse reactions and contraindications, see the summary of product characteristics of the respective technologies.
Recommended doses and schedules	Dasatinib is administered orally. The recommended starting dosage is 100 mg once daily in the chronic phase and treatment should continue until disease progression or until no longer tolerated by the patient. Dose increase or reduction is recommended based on patient response and tolerability. Imatinib is administered orally. The recommended starting dosage is 400 mg once daily in the chronic phase and treatment should be continued as long as the patient continues to benefit. Nilotinib is administered orally. The recommended starting dosage is 300 mg twice daily for newly diagnosed chronic-phase CML and treatment should be continued as long as the patient continues to benefit.

Prices	Dasatinib is available at a cost of £2,504.96 for a pack of 30 100-mg tablets (excluding VAT; 'British national formulary' [BNF] online, accessed October 2016). The cost of dasatinib treatment is £30,477.00 per year, assuming a treatment regimen of 100 mg once daily once daily. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of dasatinib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. Imatinib was available at a cost of £1,604.00 for a 400-mg 30-tablet pack (excluding VAT; BNF edition 61) resulting in an annual cost of imatinib treatment of £39,033.00, assuming a treatment regimen of 400 mg twice daily. The cost of imatinib has increased to £1,836.48 for a 400-mg 30-tablet pack (excluding VAT; BNF online, accessed October 2016). The cost of imatinib treatment is now £44,718.00 per year assuming a treatment regimen of 400 mg twice daily. Costs may vary in different settings because of negotiated procurement discounts. Nilotinib is available at a cost of £2,432.85 for a pack of 112 150-mg tablets (excluding VAT; BNF online, accessed October 2016). The cost of nilotinib treatment is £31,715.00 per year, assuming a treatment regimen of 300 mg twice daily. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of nilotinib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

3.1 The appraisal committee (section 6) considered evidence submitted by Bristol-Myers Squibb and a review of this submission by the evidence review group. This appraisal was a Cancer Drugs Fund partial reconsideration of the published NICE technology appraisal guidance on dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. Sections 4.1 to 4.28 reflect the committee's consideration of the evidence submitted in the original appraisal (NICE technology appraisal guidance 251). Sections 4.29 to 4.32 reflect the committee's consideration of the additional evidence submitted for the Cancer Drugs Fund reconsideration. It focused on a cost-minimisation analysis using a revised patient access scheme, which provides a simple discount to the list price of dasatinib. The level of the discount is commercial in confidence.

3.2 See the committee papers for full details of the Cancer Drugs Fund reconsideration evidence and the history for full details of the evidence used for NICE's original technology appraisal guidance on dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia.

4 Committee discussion

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of dasatinib, having considered evidence on the nature of chronic myeloid leukaemia (CML) and the value placed on the benefits of dasatinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness (NICE technology appraisal guidance 251)

4.2 The committee discussed current clinical practice for the treatment of CML. The committee heard from the clinical experts that standard-dose imatinib is the usual first-line treatment for chronic-phase CML, in line with the guidance on first-line imatinib for CML (NICE technology appraisal guidance 70), and that clinical experience of dasatinib and nilotinib for chronic-phase CML is largely restricted to the context of clinical trials.

4.3 To understand the full CML treatment pathway, the committee discussed the possible treatment pathway for chronic-phase CML that has failed to respond to first-line tyrosine kinase inhibitor treatment. It was noted by the committee that nilotinib, but not dasatinib or high-dose imatinib, was recommended in the guidance on dasatinib, high-dose imatinib and nilotinib when standard-dose imatinib has failed because of resistance or intolerance. However, the clinical experts stated that, for a very small proportion of people whose CML is resistant to standard-dose imatinib or who are intolerant of imatinib, there may be clinical reasons for the use of dasatinib, including comorbidities and disease resistance to nilotinib. The committee also heard from the clinical experts that standard-dose imatinib could be a potential second-line treatment if dasatinib or nilotinib were to replace it as the standard first-line treatment. The committee noted the views of the clinical experts that the use of standard-dose imatinib in the second-line setting would preferably be limited to people who were intolerant to first-line dasatinib

or nilotinib, and that standard-dose imatinib would be less likely to be offered to people with resistance to first-line dasatinib or nilotinib because the clinical experts believed it is a less effective agent. The clinical experts also commented that hydroxyurea would not be used as a second-line treatment for CML in place of a tyrosine kinase inhibitor because it does not affect the progression of the disease and is used for palliative purposes or as a short-term measure between lines of treatment.

4.4 The committee discussed the clinical-effectiveness evidence for dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of CML. It was aware of 2 comparative trials, 1 that compared dasatinib with imatinib (DASISION) and 1 that compared nilotinib with imatinib (ENESTnd). It noted that no trials directly comparing dasatinib and nilotinib were available.

4.5 The committee considered that both trials were good quality international randomised controlled trials and that the demographic characteristics of the participants and the overall trial designs were sufficiently similar to enable indirect comparison of dasatinib and nilotinib. However, it was also noted that both the clinical trials were of short duration and provided only short-term data on progression-free and overall survival and that surrogate outcome measures were used. The committee also noted that the trial populations may not be completely representative of a UK CML population, because of the lower age at diagnosis compared with the general population. However, the committee was reassured by the views of the clinical experts that the age difference was not a major factor, and it concluded that the populations included in the trials were broadly relevant to UK clinical practice.

4.6 The committee considered the results of the clinical trials, which showed that statistically significantly more people receiving dasatinib and nilotinib had a complete cytogenetic response and a major molecular response than people receiving standard-dose imatinib at 12-month follow-up. The committee also noted the views of the clinical and patient experts that nilotinib and dasatinib are more effective drugs with a theoretically superior mechanism of action to standard-dose imatinib,

although imatinib remains very effective for most patients. The committee concluded that the available evidence suggests that dasatinib and nilotinib provided superior clinical benefit, as measured by surrogate outcome measures, to standard-dose imatinib in the first-line treatment chronic-phase CML.

4.7 The committee considered the results of the indirect comparison of dasatinib and nilotinib conducted by the assessment group, which showed no statistically significant differences in rates of complete cytogenetic response and major molecular response by 12 months between the 2 treatments. The committee was also aware of another published study, which conducted a matching-adjusted indirect comparison of dasatinib and nilotinib, and showed statistically significantly higher major molecular response rates and overall survival by 12 months for people taking nilotinib compared with dasatinib. The committee noted the comment from the clinical specialist that this study had been sponsored by Novartis. Overall, the committee concluded that there was insufficient evidence to distinguish between dasatinib and nilotinib in terms of clinical effectiveness.

4.8 The committee considered the assessment group's analysis of short-term surrogate response markers as predictors of longer-term patient-relevant outcomes. The committee noted that the clinical evidence was taken from a mixture of longer-term randomised and observational studies of imatinib only. However, the committee accepted that the results of the analysis, which showed that people with either a complete cytogenetic response or major molecular response after 12 months experienced better long-term survival, could be potentially applied to people receiving dasatinib or nilotinib.

4.9 The committee discussed the adverse side effects of tyrosine kinase inhibitors for people with CML. It noted from the clinical trials that all 3 drugs were well tolerated and that stopping rates because of adverse events for people taking dasatinib and nilotinib compared with standard-dose imatinib were similar. However, the committee noted that health-related quality of life was not reported in either trial. The committee also heard from the patient experts that, in their experience, side effects associated with tyrosine kinase inhibitors were considered to be easily

manageable over time, were not a major concern for people with CML, and that, although dasatinib and nilotinib were associated with different adverse effects, tolerability was similar between both drugs. The committee also noted that QT interval prolongation was listed in the special warnings and precautions for use in the summary of product characteristics for both dasatinib and nilotinib. However, the committee was reassured by the views of the clinical experts that there was no increased cardiovascular risk at the licensed doses. The committee concluded that all 3 drugs appeared to be well tolerated and represented important treatments for people with CML.

Cost effectiveness (NICE technology appraisal guidance 251)

4.10 The committee discussed the cost effectiveness of dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of CML. The committee noted that the acquisition costs of dasatinib and nilotinib were in excess of £30,000 per person per year, and that the cost of standard-dose imatinib had recently increased to approximately £20,000 per person per year. It also noted that the Department of Health had approved a patient access scheme for nilotinib, the details of which are commercial in confidence. The patient access scheme discount was reflected in the acquisition cost of nilotinib used in both the assessment group's and Novartis' cost-effectiveness analyses.

4.11 The committee considered the economic models provided by the companies, Bristol-Myers Squibb and Novartis, and also by the assessment group. It noted key differences in the treatment pathways and approaches to modelling overall survival in the 3 economic models. The committee also considered the comments received from both companies on the assessment group's economic model and the responses provided by the assessment group to these comments.

4.12 The committee noted that the assessment group's economic model included a range of scenarios because of uncertainty about the impact of dasatinib and nilotinib on long-term survival and about subsequent lines of treatment at the time of modelling. It noted that 4 base-case

scenarios were modelled, which varied according to the methodology used to estimate overall survival, subsequent second- and third-line treatment options and whether costs and quality-adjusted life years (QALYs) per person progressing beyond the first- and second-line tyrosine kinase inhibitor should be considered equal across treatment arms. The committee was aware that nilotinib was the only tyrosine kinase inhibitor considered as a possible second-line treatment in the assessment group's original economic analyses (in 2 of the 4 base-case scenarios), and that this reflected the guidance on dasatinib, high-dose imatinib and nilotinib when standard-dose imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241). The committee further noted that the assessment group had conducted extensive deterministic sensitivity analyses to explore uncertainty around key structural assumptions in its model. The committee concluded that, although assumptions in the modelling around survival and subsequent lines of treatment were associated with substantial uncertainty, the assessment group, by considering the impact of alternative assumptions, had made considerable effort to address this.

4.13 The committee considered the original outputs of the economic model developed by the assessment group as part of its assessment report sent for consultation (before revisions were made following the comments received on the assessment report). The committee acknowledged the wide variation in the cost-effectiveness results across the scenarios presented by the assessment group, which reflected the considerable structural uncertainty in the modelling of first-line tyrosine kinase inhibitors for CML. However, it also noted that in the base-case analysis for all scenarios, dasatinib was either dominated by nilotinib or generated incremental cost-effectiveness ratios (ICER) of more than £300,000 per QALY gained compared with imatinib. The committee noted that in the 2 scenarios that did not consider the use of second-line nilotinib following first-line treatment with dasatinib or standard-dose imatinib, the ICERs for nilotinib compared with standard-dose imatinib were £36,000 per QALY gained (scenario 1) and £26,000 per QALY gained (scenario 2). The committee also noted that in the scenarios that did consider second-line nilotinib following first-line treatment with dasatinib or standard-dose imatinib (that is, scenarios 3 and 4), nilotinib generated fewer QALYs but generated substantial cost savings

compared with imatinib followed by second-line nilotinib. The committee concluded that the assessment group's original base-case cost-effectiveness results indicated that dasatinib was not cost effective and that nilotinib was on the border of cost effectiveness (the range usually considered a cost-effective use of NHS resources is between £20,000 and £30,000 per QALY gained) in many of the analyses presented when the patient access scheme was applied.

4.14 The committee carefully considered the comments received from consultees on the assessment group's economic model and the assessment group's response to these comments. The committee noted the key criticisms from Bristol-Myers Squibb about the different modelling approaches used to estimate survival on first- and second-line treatment, which Bristol-Myers Squibb argued were inconsistent with the underlying disease and resulted in incorrect or unreliable treatment durations being modelled. However, the committee agreed that only short-term data were available for survival on first-line dasatinib and nilotinib and that the assessment group had adequately acknowledged and addressed the advantages and disadvantages of different survival modelling approaches by presenting a range of scenarios rather than a single base-case cost-effectiveness analysis. It noted that, by using a cumulative survival approach in its base-case scenario analyses, the assessment group had used a similar approach to modelling survival as Novartis in its economic model and that the surrogate survival approach used in its sensitivity analyses was similar to the approach used by Bristol-Myers Squibb in its model. The committee also noted that many of the weaknesses associated with these alternative approaches to modelling survival that were highlighted by Bristol-Myers Squibb were clearly acknowledged by the assessment group and were also reflected in both companies' models. It agreed with the assessment group that, although probabilistic sensitivity analysis has an important role in exploring parameter uncertainty in NICE appraisals, its usefulness is limited in situations in which there is substantial structural uncertainty: in this case there is extensive uncertainty around the possible treatment sequences following first-line tyrosine kinase inhibitor treatment failure and modelling of short-term survival data. The committee therefore concluded that the assessment group had adequately addressed this structural uncertainty by presenting a range of deterministic scenario

analyses.

4.15 The committee also considered the comments received from Novartis about the assessment group's economic model. The committee noted that the assessment group had accepted Novartis' comments in relation to the costs of medical management in the chronic phase and had subsequently reduced the cost in its model. The committee noted that when these changes were made, the revised base-case ICERs for the scenarios that compared nilotinib with imatinib followed by no second-line nilotinib were £25,000 (scenario 1) and £20,000 per QALY gained (scenario 2). The committee also noted that, in response to additional comments received from Novartis, the assessment group had also explored the effect of adjustments to the mean dose intensity of imatinib (increased from 100% to 106%) and mean survival after stem cell transplantation (reduced from 17.0 years to 7.5 years). The committee agreed that the adjustment to mean survival after stem cell transplantation, which resulted in ICERs of £17,000 and £18,000 per QALY gained in scenarios 1 and 2, was plausible, but that an increased dose of imatinib taken from a single time point in 1 trial could not be assumed to reflect the evidence as a whole or clinical practice. For all scenarios, dasatinib continued to be dominated by nilotinib or to generate ICERs of over £200,000 per QALY gained compared with imatinib. The committee was satisfied that the assessment group had appropriately addressed comments received from the companies on its economic model and that the ICERs generated from the assessment group's revised analysis provided a suitable basis for recommendation.

4.16 The committee considered which of the scenarios modelled by the assessment group gave the most realistic estimates of cost effectiveness for dasatinib, nilotinib and standard-dose imatinib. At the time of the first appraisal committee meeting, the committee was aware that there was considerable uncertainty about which treatments would be given to people with chronic-phase CML following first-line treatment – this was driven by uncertainty about the final guidance that would be issued by NICE on the second-line treatment of chronic and accelerated phase CML; that is, in adults whose CML is resistant to standard-dose imatinib or who are intolerant of imatinib (published as NICE technology appraisal guidance 241 by the time of the second appraisal committee

meeting). The committee was also aware at the first appraisal committee meeting that a scenario of second-line imatinib following first-line treatment with nilotinib or dasatinib had not been modelled by the assessment group despite clinical specialist opinion that this would be a plausible treatment pathway for people with CML that is intolerant to a first-line second-generation tyrosine kinase inhibitor. The committee also considered the comments received from consultees following consultation on the assessment consultation document that scenarios 1 and 2 of the assessment group's model did not reflect clinical practice and should not be used to inform the recommendations. The committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor. The committee therefore considered that scenarios 3 and 4 were initially incomplete (at the time of the first appraisal committee meeting) but that scenarios 1 and 2 of the assessment group's model provided only relatively approximate estimates of the cost effectiveness of first-line treatment with tyrosine kinase inhibitors.

4.17 The committee therefore considered the further additional analyses carried out by the assessment group after consultation on the appraisal consultation document. It noted that the assessment group had modelled 2 additional scenarios – 1 comprising first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. The committee agreed that these analyses were an important addition to the assessment group's model because they enabled a comparison in scenarios 3 and 4 of all the relevant first- and second-line treatment sequences.

4.18 The committee thus considered the ICERs from scenarios 3 and 4 of the assessment group's model, including the results from the further additional analyses presented by the assessment group following the first appraisal committee meeting. The committee noted that the ICER for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib was £11,000 per QALY gained for both scenarios and that this was in the range normally considered a cost-effective use of

NHS resources. It also noted that treatment with first-line nilotinib followed by imatinib resulted in more QALYs and lower costs than first-line treatment with dasatinib followed either by imatinib or nilotinib (that is, nilotinib dominated dasatinib). The implications of these results were consistent with those from scenarios 1 and 2. The committee concluded that the results of the assessment group's analyses indicated that nilotinib represented a cost-effective first-line treatment for people with chronic-phase CML, and that dasatinib did not.

4.19 With regard to imatinib, the committee was aware that the ICERs for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib were sensitive to a number of parameters, including assumptions about the dose intensity of nilotinib and the average time spent on second-line nilotinib or imatinib treatment. The committee noted that changes to these input parameters, notably adjusting the modelled dose intensity of first-line nilotinib to levels recommended in the summary of product characteristics, reversed the relative cost effectiveness of nilotinib and imatinib. In addition, the committee recognised that, although more of the sensitivity analyses produced favourable ICERs for nilotinib when compared with standard-dose imatinib, imatinib has a proven longer-term record of safety and efficacy: there were 7 years of survival data for first-line imatinib from the IRIS trial, with positive results for complete cytogenetic response and disease progression, while there were still only short-term survival data for dasatinib and nilotinib. Finally, the committee considered that it was important to have an alternative tyrosine kinase inhibitor treatment available if it is no more expensive than alternatives. The committee therefore concluded that it would be appropriate to recommend both nilotinib and standard-dose imatinib as options for the first-line treatment of people with chronic-phase CML. In addition it recognised that, given that imatinib and nilotinib have comparable cost effectiveness, should one of the drugs become significantly cheaper, it should be preferred (taking into consideration administration costs, required dose and product price per dose).

4.20 The committee further concluded that the recommendations for first-line tyrosine kinase inhibitors should be considered for review in 2 years' time when the price of standard-dose imatinib may be affected by the entry

of new companies.

4.21 The committee was aware that the additional analyses produced by the assessment group following the first appraisal committee meeting indicated that the ICERs for first-line nilotinib followed by imatinib compared with first-line nilotinib and no subsequent tyrosine kinase inhibitor were £57,000 and £31,000 per QALY gained using the assessment group's non-simplified method and simplified method, respectively. The committee also noted that the original analyses produced by the assessment group indicated that the ICERs for first-line imatinib followed by nilotinib compared with first-line nilotinib and no subsequent tyrosine kinase inhibitor were £213,000 and £50,000 per QALY gained using the non-simplified method and simplified method, respectively. The committee acknowledged that the analyses produced apparently inconsistent results (with NICE technology appraisal guidance 241) about the cost effectiveness of second-line treatment with a tyrosine kinase inhibitor but accepted that consideration of second-line treatments was outside the remit of this appraisal. It also accepted that the evidence on which to reach a definite conclusion was insufficient and conflicting, that there was considerable uncertainty around these ICERs, and that more data were needed to fully assess the cost effectiveness of first and second-line tyrosine kinase inhibitor treatments. Meanwhile it considered the implication of this appraisal, that both imatinib and nilotinib (with the agreed discount under the patient access scheme) should be available first and second line, to be reasonable.

4.22 The committee gave further consideration to its conclusion on the cost effectiveness of dasatinib compared with imatinib and nilotinib from the assessment group's model in the light of consultation points raised by Bristol-Myers Squibb. The committee noted that the ICERs for first-line treatment with dasatinib followed either by nilotinib or imatinib compared with first-line treatment with standard-dose imatinib followed by nilotinib exceeded £300,000 per QALY gained. The committee further noted that this result was broadly unaltered by changes to all input parameters in the deterministic sensitivity analyses. As described in section 4.18, it was also aware that first-line treatment with dasatinib followed either by imatinib or nilotinib was dominated by first-line nilotinib followed by

imatinib. The committee also noted that the conclusions from these estimates were corroborated by the results generated by the Bristol-Myers Squibb model, when corrected by the assessment group. These corrections (which concerned formulae errors and included the patient access scheme discount for nilotinib) resulted in an ICER of £46,000 per QALY gained for dasatinib compared with imatinib, with nilotinib dominating dasatinib. When the model was further adjusted by the assessment group so that dasatinib was not taken as a second- or third-line treatment after imatinib or nilotinib, the committee noted that the ICER for dasatinib compared with imatinib increased to £96,000 per QALY gained, which it agreed could not be considered cost effective.

4.23 The committee was aware that, as part of its response to the consultation on the appraisal consultation document, Bristol-Myers Squibb had made some adjustments to its model by incorporating changes that the assessment group had made to its own model following feedback from Novartis (see section 4.14). The committee noted from the information submitted from Bristol-Myers Squibb incorporating identical medical management costs to those used in the assessment group's model, correcting formulae errors, and incorporating an estimate of the discount for nilotinib agreed under the patient access scheme, led to an ICER for dasatinib compared with standard-dose imatinib of £34,400 per QALY gained. The committee heard from the assessment group, however, that the adjustments made by Bristol-Myers Squibb did not include the removal of dasatinib as a second- and third-line treatment option in line with the guidance on dasatinib, high-dose imatinib and nilotinib when imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241). It was also noted that the removal of second- and third-line dasatinib would increase the ICER for dasatinib compared with standard-dose imatinib considerably.

4.24 Following the second appraisal committee meeting, the committee was made aware of errors in the assessment report in the calculation of some of the relative risks and 95% confidence intervals. So the assessment group sent the committee an erratum to the assessment report, which outlined the incorrect and corrected values. This showed that correcting the errors did not affect the statistical significance of any of the results from the trials. The committee also heard that none of the incorrect

values had any impact on the results of the assessment group's cost-effectiveness analyses so the ICERs remained unchanged. Therefore the committee did not alter its view that imatinib and nilotinib, but not dasatinib, could be recommended as cost-effective first-line treatments for adults with chronic-phase CML.

4.25 The committee considered the comments received from some consultees after consultation on the appraisal consultation document that it was inappropriate to exclude dasatinib as a second or third-line treatment from the modelling. However, the committee agreed that, with the publication of the guidance on dasatinib, high-dose imatinib and nilotinib when imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241), it would not be appropriate to include dasatinib as a second or third-line treatment in the modelling for this appraisal. The committee was aware that NICE technology appraisal guidance 241 considered the use of the tyrosine kinase inhibitors in cases of imatinib resistance or intolerance only but had not considered their use following first-line treatment with nilotinib or dasatinib. The committee considered that this was because standard-dose imatinib was the only recommended first-line tyrosine kinase inhibitor for the treatment of chronic-phase CML at the time of appraisal, and it agreed that the same rationale that underpinned the recommendations in the guidance on dasatinib, high-dose imatinib and nilotinib when imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241) should also apply to the use of dasatinib after first-line treatment with an alternative first-line tyrosine kinase inhibitor. The committee noted that further adjustments to Bristol-Myers Squibb's model by the assessment group, to remove dasatinib as a second- and third-line treatment option in line with NICE technology appraisal guidance 241, resulted in an ICER for first-line dasatinib compared with standard-dose imatinib of at least £75,000 per QALY gained. The committee concluded that Bristol-Myers Squibb's modelling results, when adjusted by the assessment group to reflect second-line treatments approved by NICE, supported the results generated by the assessment group's model.

4.26 The committee heard from the clinical experts and some consultees that, for a small group of people with specific kinase domain mutations that

would make their CML resistant to nilotinib, dasatinib would be offered as second-line treatment. However, the committee considered that, because these mutations would be determined after first-line treatment failure, this would not be relevant to the first-line treatment decision for people presenting with chronic-phase CML. Furthermore, this subgroup of people with specific kinase domain mutations was not distinguished in the evidence base for dasatinib. The committee also heard from consultees after consultation on the appraisal consultation document that there are other important subgroups for whom dasatinib would be used rather than nilotinib, including people with long QT syndrome or diabetes. However, the committee noted that it had not been presented with any evidence to support this and therefore could not make any recommendations for dasatinib in these subgroups. The committee concluded that the ICERs for dasatinib were substantially outside the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained), and that dasatinib could not be recommended as a cost-effective use of NHS resources for the first-line treatment of adults with chronic-phase CML.

4.27 The committee recognised the innovative nature and substantial change in the treatment of CML that imatinib has provided since it has been introduced and recommended for use by NICE in the guidance on imatinib in CML (NICE technology appraisal guidance 70), and discussed whether dasatinib and nilotinib should be considered innovative treatments. The committee considered that while the introduction of dasatinib and nilotinib was also an important development in terms of pharmacological progress beyond imatinib, the critical innovation was the first-generation tyrosine kinase inhibitor. Furthermore, the committee had not been made aware of any benefits from this progress that were not captured in the QALYs modelled.

Equality issues (NICE technology appraisal guidance 251)

4.28 The committee discussed whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way. The committee considered that there were no issues directly relating to

the equalities legislation. However, the committee noted that in both companies' submissions, stem cell transplantation would be considered for people for whom first- and second-line tyrosine kinase inhibitor treatment fails and, because only a small number of people would be eligible for stem cell transplantation, this could raise potential equity issues in relation to race, age (older people), and people with comorbidities. However, the committee concluded that the recommendations do not differentiate between any groups of people, and therefore there was not considered to be an equalities issue.

Cancer Drugs Fund partial reconsideration of NICE technology appraisal guidance 251

4.29 This appraisal was a Cancer Drugs Fund partial reconsideration of the published NICE technology appraisal guidance on dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. The committee considered the company's (Bristol-Myers Squibb) submission for the Cancer Drugs Fund reconsideration that included:

- a revised patient access scheme that provides a simple discount to the list price of dasatinib
- longer follow-up data from the DASISION study
- an updated systematic literature review, the results of which were used to inform a network meta-analysis of dasatinib, nilotinib and imatinib
- a cost-minimisation analysis of dasatinib compared with nilotinib and imatinib.

Clinical and cost effectiveness

4.30 The committee discussed the appropriateness of the company's cost-minimisation analysis for dasatinib compared with nilotinib. The evidence review group (ERG) had highlighted that the use of a cost-minimisation analysis assumes that all health outcomes and treatment costs (other than drug acquisition) are equivalent. The committee recalled its judgement that dasatinib was slightly clinically superior to imatinib (see

section 4.6), and that there was insufficient evidence to distinguish between dasatinib and nilotinib in terms of clinical effectiveness (see section 4.7). The committee discussed the new evidence the company submitted as part of the reconsideration. It concluded that there was no new evidence that would change the conclusions it made during the previous technology appraisal. Therefore, the committee considered that, if drug acquisition costs of dasatinib were shown to be less than those of imatinib, it was likely that dasatinib would dominate imatinib (that is, be both more effective and less costly). Furthermore, it is plausible that a cost-minimisation analysis is appropriate because treatment with dasatinib is sufficiently similar to nilotinib.

4.31 The committee noted that nilotinib is available with a patient access scheme, which provides a simple discount to the list price of nilotinib. The level of the discount is commercial in confidence. The committee discussed the results of the ERG's cost-minimisation analysis, which took into account the list price of imatinib and the patient access schemes of both nilotinib and dasatinib. It concluded that, with the revised patient access scheme, it was likely that dasatinib was a cost-effective use of NHS resources and so should be recommended for untreated Philadelphia-chromosome-positive CML.

Pharmaceutical Price Regulation Scheme 2014

4.32 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TA426	Appraisal title: Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia	Section
Key conclusion		
Imatinib is recommended as an option for untreated, chronic-phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in adults.		1.1
Dasatinib and nilotinib are recommended, within their marketing authorisations, as options for untreated chronic-phase Philadelphia-chromosome-positive CML in adults. The drugs are recommended only if the companies provide them with the discounts agreed in the relevant patient access schemes.		1.2
The committee concluded that the available evidence suggested that dasatinib and nilotinib provided superior clinical benefit as measured by surrogate outcome measures, to standard-dose imatinib in the first-line treatment of people with chronic-phase CML.		4.6
Overall, the committee concluded that there was insufficient evidence to distinguish between dasatinib and nilotinib in terms of clinical effectiveness.		4.7
The committee noted that the incremental cost-effectiveness ratio (ICER) for first-line nilotinib was £11,000 per quality-adjusted life year (QALY) gained and concluded that the results of the assessment group's analyses indicated that nilotinib represented a cost-effective first-line treatment for people with chronic-phase CML.		4.18

The committee noted that changes to some input parameters, notably adjusting the modelled dose intensity of first-line nilotinib to levels recommended in the summary of product characteristics reversed the relative cost effectiveness of nilotinib and imatinib. In addition, the committee noted that imatinib has a proven longer-term record of safety and efficacy: there were 7-year survival data for first-line standard-dose imatinib from the IRIS trial (versus STI571), with favourable results for complete cytogenetic response and disease progression, while there were still only short-term survival data for dasatinib and nilotinib. The committee considered that it would be important to have an alternative tyrosine kinase inhibitor treatment available if it is no more expensive than alternatives. The committee therefore concluded that it would be appropriate to recommend both nilotinib and standard-dose imatinib as options for the first-line treatment of people with chronic-phase CML. In addition, it recognised that, given that imatinib and nilotinib have comparable cost effectiveness, should one of the drugs become significantly cheaper, it should be preferred (taking into consideration administration costs, required dose and product price per dose).	4.19
The committee noted that the ICERs for first-line treatment with dasatinib followed either by nilotinib or imatinib compared with first-line treatment with standard-dose imatinib followed by nilotinib exceeded £300,000 per QALY gained. The committee concluded that the ICERs for dasatinib were substantially outside the range normally considered a cost-effective use of NHS resources and that dasatinib could not be recommended as a cost-effective use of NHS resources for the first-line treatment of adults with chronic-phase CML.	4.22
The committee concluded that the ICERs for dasatinib were substantially outside the range normally considered a cost-effective use of NHS resources and that dasatinib could not be recommended as a cost-effective use of NHS resources for the first-line treatment of adults with chronic-phase CML.	4.26
Cancer Drugs Fund reconsideration: the committee concluded that, with the revised patient access scheme, it was likely that dasatinib was a cost-effective use of NHS resources and so should be recommended for untreated Philadelphia-chromosome-positive CML.	4.31
Current practice	

Clinical need of patients, including the availability of alternative treatments	The committee heard from the clinical experts that standard-dose imatinib is the usual first-line treatment for people presenting with chronic-phase CML, and that clinical experience of dasatinib and nilotinib for chronic-phase CML is largely restricted to the context of clinical trials.	4.3
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 considered that while the introduction of dasatinib and nilotinib was also an important development in terms of pharmacological progress beyond imatinib, the critical innovation was the first-generation tyrosine kinase inhibitor. Furthermore, the committee had not been made aware of any benefits from this progress that was not captured in the QALYs modelled.	4.27
What is the position of the treatment in the pathway of care for the condition?	The committee heard from the clinical experts that standard-dose imatinib is the usual first-line treatment for chronic-phase CML, in line with the guidance on first-line imatinib for CML (NICE technology appraisal guidance 70), and that clinical experience of dasatinib and nilotinib for chronic-phase CML is largely restricted to the context of clinical trials.	4.2

Adverse effects	The committee noted from the clinical trials that dasatinib, nilotinib and standard-dose imatinib were well tolerated and that stopping rates because of adverse events for people taking dasatinib and nilotinib compared with standard-dose imatinib were similar. The committee heard from patient experts that, in their experience, side effects associated with tyrosine kinase inhibitors were considered to be easily manageable over time. The committee was also aware that QT interval prolongation was listed in the special warnings and precautions for use in the summary of product characteristics for both dasatinib and nilotinib. However, the committee was reassured by the views of the clinical experts that there was no increased cardiovascular risk at the licensed doses. The committee concluded that all 3 drugs appeared to be well tolerated and represented important treatments for people with CML.	4.9
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee was aware of 2 comparative clinical trials, 1 that compared dasatinib with imatinib and 1 that compared nilotinib with imatinib. It also noted that no trials directly comparing dasatinib and nilotinib were available. The committee considered that both trials were good quality international randomised controlled trials and that the demographic characteristics of the participants and the overall trial designs were sufficiently similar to enable indirect comparison of dasatinib and nilotinib.	4.4, 4.5
Relevance to general clinical practice in the NHS	The committee noted that the populations in the 2 clinical trials may not be completely representative of a UK CML population, because of the lower age at diagnosis compared with the general population. However, the committee was reassured by the views of the clinical experts that the age difference was not a major factor, and it concluded that the populations included in the trials were broadly relevant to UK clinical practice.	4.5

Uncertainties generated by the evidence	The committee noted that the clinical trials were of short duration and provided only short-term data on progression-free and overall survival and that surrogate outcome measures were used. The committee noted that the clinical evidence used in the assessment group's analysis of short-term surrogate response markers as predictors of longer-term patient-relevant outcomes was taken from a mixture of longer-term randomised and observational studies of imatinib only. However, the committee agreed that the results of the analysis could be potentially applied to people receiving dasatinib or nilotinib.	4.5, 4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No clinically relevant subgroups for which there is evidence of differential effectiveness were identified by the committee.	–

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee considered the results of the clinical trials, which showed that statistically significantly more people receiving dasatinib and nilotinib had a complete cytogenetic response and a major molecular response than people receiving imatinib at 12-month follow-up. The committee also noted the views of the clinical and patient experts that nilotinib and dasatinib are more effective drugs with a theoretically superior mechanism of action to standard-dose imatinib, although imatinib remains very effective for the majority of patients. The committee concluded that the available evidence suggests that dasatinib and nilotinib provided superior clinical benefit as measured by surrogate outcome measures than standard-line imatinib in the first-line treatment of people with chronic-phase CML. The committee considered the results of the indirect comparison of dasatinib and nilotinib conducted by the assessment group, which showed no statistically significant differences in rates of complete cytogenetic response and major molecular response by 12 months between the 2 treatments. The committee was also aware of another published study, which conducted a matching-adjusted indirect comparison of dasatinib and nilotinib, and showed statistically significantly higher major molecular response rates and overall survival by 12 months for people taking nilotinib compared with dasatinib. The committee noted the comment from the clinical specialist that this study had been sponsored by Novartis. Overall, the committee concluded that there was insufficient evidence to distinguish between dasatinib and nilotinib in terms of clinical effectiveness.	4.6, 4.7
Evidence for cost effectiveness		
Availability and nature of evidence	The committee considered the economic models provided by the companies, Bristol-Myers Squibb and Novartis and also by the assessment group. It noted key differences in the treatment pathways and approaches to modelling overall survival in the 3 models.	4.11

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee noted that the assessment group's modelling included a range of scenarios because of uncertainty about the impact of dasatinib and nilotinib on long-term survival and about subsequent lines of treatment. It noted that 4 base-case scenarios were modelled, which varied according to the methodology used to estimate overall survival, subsequent second- and third-line treatment options and whether costs and QALYs per person progressing beyond the first- and second-line tyrosine kinase inhibitor should be considered equal across treatment arms. The committee was aware that nilotinib was the only tyrosine kinase inhibitor considered as a possible second-line treatment in the assessment group's model (in 2 of the 4 base-case scenarios), and that this reflected the guidance on dasatinib, high-dose imatinib and nilotinib when standard-dose imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241). The committee further noted that the assessment group had conducted extensive deterministic sensitivity analyses to explore uncertainty around key structural assumptions in its model. The committee concluded that, although assumptions in the modelling around survival and subsequent lines of treatment were associated with substantial uncertainty, the assessment group, by considering the impact of alternative assumptions, had made considerable effort to address this.	4.12

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	No potential significant and substantial health-related benefits that had not been included in the economic models were identified.	–
Are there specific groups of people for whom the technology is particularly cost effective?	No specific groups of people for whom the technologies are particularly cost effective were identified.	–
What are the key drivers of cost effectiveness?	The committee noted that the acquisition costs of dasatinib and nilotinib were in excess of £30,000 per person per year, and that the cost of standard-dose imatinib had recently increased to approximately £20,000 per person per year.	4.10

	The committee was aware that the ICERs for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib were sensitive to a number of parameters, including assumptions about the dose intensity of nilotinib and the average time spent on second-line nilotinib or imatinib treatment.	4.19
	The committee noted that the cost effectiveness of dasatinib was unaltered by changes to all input parameters in the deterministic sensitivity analyses.	4.22
Most likely cost-effectiveness estimate (given as an ICER)	The committee acknowledged the wide variation in the cost-effectiveness results across the scenarios presented by the assessment group, which reflected the considerable structural uncertainty in the modelling of first-line tyrosine kinase inhibitors for CML. The committee concluded that the assessment group's original base-case cost-effectiveness results indicated that dasatinib was not cost effective and that nilotinib was on the border of cost effectiveness in many of the analyses presented when the patient access scheme was applied.	4.13
	The committee was satisfied that the assessment group had appropriately addressed comments received from the companies on its economic model and that the ICERs generated from the assessment group's revised analysis provided a suitable basis for recommendation.	4.15
	The committee accepted that hydroxyurea and stem cell transplantation would not be used routinely in the second-line setting in place of a tyrosine kinase inhibitor and that therefore scenarios 1 and 2 of the assessment group's model provided only relatively approximate estimates of the cost effectiveness of first-line treatment with tyrosine kinase inhibitors.	4.16

	The committee noted that the assessment group had modelled 2 additional scenarios – 1 comprising first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising first-line treatment with dasatinib followed by second-line standard-dose imatinib. The committee agreed that these analyses were an important addition to the assessment group's model because they enabled a comparison in scenarios 3 and 4 of all the relevant first- and second-line treatment sequences.	4.17
	The committee noted that the ICER for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib was £11,000 per QALY gained in scenarios 3 and 4 of the assessment group's model and that this was within the range normally considered a cost-effective use of NHS resources.	4.18
	The committee noted that dasatinib was associated with fewer QALYs and was more costly than nilotinib in all scenarios and that the ICERs for dasatinib compared with standard-dose imatinib exceeded £200,000 per QALY gained.	4.15, 4.18, 4.22
	The committee recognised that, although more of the sensitivity analyses in the assessment group's model produced favourable ICERs for nilotinib compared with standard-dose imatinib, imatinib has a proven longer-term record of safety and efficacy: there were 7 years of survival data for first-line imatinib from the IRIS trial, with positive results for complete cytogenetic response and disease progression, while there were still only short-term survival data for dasatinib and nilotinib.	4.19
	The committee acknowledged that the additional analyses by the assessment group produced apparently inconsistent results (with NICE technology appraisal guidance 241) about the cost effectiveness of second-line treatment with a tyrosine kinase inhibitor but accepted that consideration of second-line treatments was outside the remit of this appraisal.	4.21

	Cancer Drugs Fund reconsideration: the committee concluded that, with the revised patient access scheme, it was likely that dasatinib was a cost-effective use of NHS resources.	4.31
Additional factors taken into account		
Patient access schemes (PPRS)	The committee noted that the Department of Health had approved a patient access scheme for nilotinib, which makes it available with a discount applied to all invoices. The size of the discount is commercial in confidence.	4.10
	Cancer Drugs Fund reconsideration: the committee noted that the Department of Health had approved a patient access scheme for dasatinib, which makes it available with a discount on the list price. The size of the discount is commercial in confidence.	4.29
End-of-life considerations	–	–
Equalities considerations and social value judgements	The committee concluded that the recommendations do not differentiate between any groups of people, and therefore there was not considered to be an equalities issue.	4.28

5 Implementation

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

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has Philadelphia-chromosome-positive chronic myeloid leukaemia and the doctor responsible for their care thinks that one of the recommended technologies is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Bristol-Myers Squibb have agreed that dasatinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company 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 Bristol-Myers Squibb at MG-UKPASADMIN@bms.com.

5.5 The Department of Health and Novartis Pharmaceuticals have agreed that nilotinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company 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's commercial operations team on 01276 698717 or Commercial.Team@novartis.com.

6 Appraisal committee members and NICE project team

Appraisal committee members

TA251

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

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.

Cancer Drugs Fund partial reconsideration of TA251

This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the minutes of the appraisal committee meeting, which are posted on the NICE website.

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.

NICE project team

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

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