

# Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia

Technology appraisal guidance

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[www.nice.org.uk/guidance/ta425](https://www.nice.org.uk/guidance/ta425)

## Your responsibility

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

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

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

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

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This guidance replaces TA241.

This guidance partially replaces TA70.

# 1 Recommendations

- 1.1 Dasatinib and nilotinib are recommended as options for treating only chronic- or accelerated-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults, if:
- they cannot have imatinib, or their disease is imatinib-resistant and
  - the companies provide the drugs with the discounts agreed in the relevant patient access schemes.
- 1.2 High-dose imatinib (that is, 600 mg in the chronic phase or 800 mg in the accelerated and blast-crisis phases) is not recommended for treating Philadelphia-chromosome-positive chronic myeloid leukaemia in adults whose disease is imatinib-resistant.
- 1.3 This guidance is not intended to affect the position of patients whose treatment with imatinib or dasatinib was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

## 2 The technologies

<b>Description of the technologies</b>	<p>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.</p> <p>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).</p> <p>Nilotinib (Tasigna, Novartis Pharmaceuticals), a tyrosine kinase inhibitor (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.</p>
<b>Marketing authorisations</b>	<p>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'.</p> <p>Imatinib has a marketing authorisation for the treatment of 'adult and paediatric patients with newly diagnosed Philadelphia chromosome (<i>bcr-abl</i>) 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'.</p> <p>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'.</p>

<p><b>Adverse reactions</b></p>	<p>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'.</p> <p>The most common side effects with imatinib are nausea, vomiting, oedema (fluid retention), muscle cramps, skin rash, diarrhoea, abdominal pain, headache and fatigue.</p> <p>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.</p> <p>For full details of adverse reactions and contraindications, see the summary of product characteristics of the respective technologies.</p>
<p><b>Recommended doses and schedules</b></p>	<p>Dasatinib is administered orally. The recommended starting dosage is 100 mg once daily in the chronic phase or 140 mg once daily in the accelerated and blast-crisis 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.</p> <p>Imatinib is administered orally. The recommended starting dosage is 400 mg once daily in the chronic phase or 600 mg once daily in the accelerated and blast-crisis phase and treatment should be continued as long as the patient continues to benefit. Dose increase to 600 mg once daily in the chronic phase or 800 mg (400 mg twice daily) in the accelerated and blast-crisis phase may be considered for people who have imatinib resistance.</p> <p>Nilotinib is administered orally. The recommended starting dosage is 400 mg twice daily for imatinib-resistant or intolerant CML in the chronic phase and 400 mg twice daily in the accelerated phase and treatment should be continued as long as the patient continues to benefit.</p>

<b>Prices</b>	<p>Dasatinib is available at a cost of £2,504.96 for both a pack of 30 100-mg or 140-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 or 140 mg 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.</p> <p>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.</p> <p>Nilotinib is available at a cost of £2,432.85 for a pack of 112 200-mg tablets (excluding VAT; BNF online, accessed October 2016). The cost of nilotinib treatment is £31,736.00 per year, assuming a treatment regimen of 400 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.</p>
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### 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, 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. Sections [4.1 to 4.32](#) reflect the committee's consideration of the evidence submitted in the original appraisal (NICE technology appraisal guidance 241). Sections [4.33 to 4.40](#) 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, 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.



## 4 Committee discussion

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of dasatinib, high-dose imatinib and nilotinib for the treatment of chronic myeloid leukaemia (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 experts. It also took into account the effective use of NHS resources.

### Clinical effectiveness (NICE technology appraisal guidance 241)

4.2 The committee discussed current clinical practice for treating CML. The committee heard from the clinical experts that standard-dose imatinib is given in line with NICE technology appraisal guidance 70 to people presenting with chronic-phase CML. The clinical experts 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 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 experts 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 experts 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.

- 4.4 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 experts 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 experts' view that for CML that is resistant to standard-dose imatinib, high-dose imatinib was unlikely to be as beneficial as dasatinib and nilotinib.
- 4.5 The committee heard from the clinical experts 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 stopped, or may be changed to hydroxycarbamide and/or, if suitable, stem cell transplantation.
- 4.6 The committee heard from the clinical experts that in more than 50% of people with imatinib-resistant CML who have 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 experts 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 experts 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.
- 4.7 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 1 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.

- 4.8 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 1 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 and clinical experts. The committee noted the poor quality of the evidence base. However, it heard from the clinical experts and patient experts that clinical benefits, particularly of dasatinib and nilotinib, have been demonstrated. In addition, the clinical experts 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.
- 4.9 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 experts.
- 4.10 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.

- 4.11 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. The committee concluded that dasatinib and nilotinib are better tolerated than imatinib, and that older treatments, particularly interferon alfa, can be poorly tolerated.
- 4.12 The committee considered the treatment of the blast-crisis phase of CML in clinical practice. The committee heard from the clinical experts that at the blast-crisis stage of the disease, life expectancy is about 3 to 6 months. The committee also heard from the clinical experts 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.

## Cost effectiveness (NICE technology appraisal guidance 241)

- 4.13 The committee then considered the economic models provided by the companies and the assessment groups for chronic-phase CML that is resistant to standard-dose imatinib. In each it took particular note of the incremental cost-effectiveness ratio (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 experts stated that these were closely related.

4.14 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 quality-adjusted life year (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 company's original economic analysis.

4.15 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 stopped 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 £2,400 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.

- 4.16 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.
- 4.17 The committee considered the economic model developed by Peninsula Technology Assessment Group (PenTAG) and subsequently updated by Southampton Health Technology Assessments Centre (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.
- 4.18 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 experts; see [section 4.5](#)).

- 4.19 The committee did not consider that a conclusive ICER had been presented in any of the economic models, but agreed that, taking all the models' assumptions into account, 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 to 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.
- 4.20 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.
- 4.21 The committee noted that Novartis had agreed a patient access scheme with the Department of Health. The company had presented ICERs for the scheme based on an analysis reflecting the scenario considered most plausible by the committee, outlined in section 4.19.



4.22 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 company argued that a number of further changes to the SHTAC analysis should be made, namely:

- a reduction in treatment duration from 10.0 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.

4.23 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 company makes nilotinib available with the discount agreed as part of the patient access scheme.

- 4.24 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 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.
- 4.25 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 4.15. 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.
- 4.26 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 experts' 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.

- 4.27 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 3 of the estimates it saw, 1 from PenTAG and 2 from Bristol-Myers Squibb 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.
- 4.28 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, 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 when 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.

- 4.29 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.

## End-of-life considerations (NICE technology appraisal guidance 241)

- 4.30 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.

- 4.31 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 to 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.

## Equality issues (NICE technology appraisal guidance 241)

4.32 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 (older people), 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.

## Cancer Drugs Fund partial reconsideration of NICE technology appraisal guidance 241

4.33 This appraisal was a Cancer Drugs Fund partial reconsideration of the published NICE technology appraisal guidance on 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 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
- an updated systematic literature review, which provided a naive comparison of clinical outcomes of dasatinib compared with nilotinib
- a cost-minimisation analysis of dasatinib compared with nilotinib and high-dose imatinib.

## Clinical and cost effectiveness

4.34 The committee discussed the appropriateness of the company's cost-minimisation analysis for dasatinib compared with imatinib. The committee noted that high-dose imatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib (see sections [4.24](#) and [4.26](#)). Therefore the committee considered that a cost-minimisation analysis of dasatinib compared with high-dose imatinib was uninformative in providing evidence that dasatinib is a cost-effective use of NHS resources.

4.35 The committee discussed the appropriateness of the company's cost-minimisation analysis for dasatinib compared with nilotinib in chronic- and accelerated-phase CML. The evidence review group (ERG) 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 that there was no good evidence to distinguish between dasatinib and nilotinib in terms of clinical effectiveness (see [section 4.9](#)). The committee discussed the clinical evidence the company submitted as part of the reconsideration and concluded that there was no new evidence that would change the conclusions it made during the previous technology appraisal. Therefore, the committee considered that it was plausible that cost-minimisation analysis was appropriate to inform its decision-making because treatment with dasatinib is sufficiently similar to nilotinib.

4.36 The committee recalled that nilotinib does not have a marketing

authorisation for treating blast-crisis phase CML, and that treatment for this phase of the disease is different from that used in the other phases (see [section 4.27](#)). Therefore the committee considered that a cost-minimisation analysis of dasatinib compared with nilotinib would not be appropriate to inform a recommendation for dasatinib for blast-crisis phase CML.

- 4.37 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 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 Philadelphia-chromosome-positive CML in the chronic or accelerated phase in adults who cannot have imatinib, or when their disease is imatinib-resistant.

## End-of-life considerations

- 4.38 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [final Cancer Drugs Fund technology appraisal process and methods](#).
- 4.39 The committee concluded that applying this advice would not change the conclusion that was made in NICE technology appraisal guidance 241 that dasatinib does not fulfil the end-of-life criteria for people with blast-crisis phase CML (see [section 4.31](#)).

## Pharmaceutical Price Regulation Scheme 2014

- 4.40 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

TA425	Appraisal title: Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia	Section
<b>Key conclusion</b>		
<p>Dasatinib and nilotinib are recommended as options for treating chronic- or accelerated-phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in adults, only if:</p> <ul style="list-style-type: none"> <li>• they cannot have imatinib or their disease is imatinib-resistant and</li> <li>• the companies provide the drugs with the discounts agreed in the relevant patient access schemes.</li> </ul>		1.1
<p>High-dose imatinib (that is, 600 mg in the chronic phase or 800 mg in the accelerated and blast-crisis phases) is not recommended for treating Philadelphia-chromosome-positive CML in adults whose disease is imatinib-resistant.</p>		1.2
<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 incremental cost-effectiveness ratios (ICERs) were higher than those normally considered acceptable for the NHS, and were highly likely to be above the figures suggested.</p>		4.23, 4.24, 4.25
<p>High-dose imatinib was dominated (that is, more expensive and less effective than another treatment) in all models.</p>		4.24
<p><b>Cancer Drugs Fund reconsideration:</b> 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.</p>		4.37
<b>Current practice</b>		



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.	4.2
	The clinical experts 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
	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 experts 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.	4.12, 4.29
<b>The technology</b>		
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
	The committee heard from the clinical experts 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 experts' view that for CML that is resistant to standard-dose imatinib, high-dose imatinib was unlikely to be as beneficial as dasatinib and nilotinib.	4.6
	The committee was aware that continued use of imatinib is not an option for people with imatinib intolerance.	4.10



	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.	4.30
What is the position of the treatment in the pathway of care for the condition?	The committee heard from the clinical experts 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 experts' view that for CML that is resistant to standard-dose imatinib, high-dose imatinib was unlikely to be as beneficial as dasatinib and nilotinib.	4.4
Adverse effects	The committee concluded that dasatinib and nilotinib are better tolerated than imatinib, and that older treatment, particularly interferon alfa, can be poorly tolerated.	4.11
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The committee was aware of only 1 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.	4.7
	The committee noted that the clinical trials available were non-comparative, of short duration and had used surrogate outcomes to predict overall survival.	4.8
	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.	4.12
	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.	4.10

Relevance to general clinical practice in the NHS	The clinical experts 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.	4.8
Uncertainties generated by the evidence	The committee agreed that the limited evidence base means that the magnitude of the benefit (for people with imatinib-resistant CML) is uncertain.	4.9
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	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.	4.11
Estimate of the size of the clinical effectiveness including strength of supporting evidence	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.	4.9
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The committee considered the economic models provided by the companies and the assessment groups.	4.13
Uncertainties around and plausibility of assumptions and inputs in the economic model	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.	4.14

	<p>It noted the additional analysis provided by Bristol-Myers Squibb, and considered that the assumption that 30.8% of people who stopped 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>	4.15
	<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 quality-adjusted life year (QALY) gained would be likely to increase.</p>	4.17
	<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>	4.22
	<p>The committee noted the Peninsula Technology Assessment Group model did not link treatment duration with overall survival and that some of the results were not plausible. It understood that the Southampton Health Technology Assessments Centre base-case treatment durations still did not reflect the fact that in clinical practice, people will receive treatment until progression or death.</p>	4.17, 4.18

<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>4.15</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>4.22</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>4.28</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>Not applicable.</p>	<p>-</p>
<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>4.24</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.</p> <p>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>4.25</p>

	<p>The committee noted the clinical experts' 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>	4.26
	<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>	4.27
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The committee did not consider that a conclusive ICER had been presented in any of the economic models.</p>	4.19
	<p>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.</p>	4.20
	<p>It noted that high-dose imatinib was dominated (more expensive and less effective) in all models.</p>	4.24
	<p>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.</p>	4.23

	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.	4.25
	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 3 estimates of cost effectiveness it saw to be highly speculative with a very poor evidence base supporting the calculations.	4.27
	<b>Cancer Drugs Fund reconsideration:</b> the committee concluded that, with the revised patient access scheme, it was likely that dasatinib was a cost-effective use of NHS resources.	4.37
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	The committee noted that the company of nilotinib had agreed a patient access scheme with the Department of Health.	4.21
	<b>Cancer Drugs Fund reconsideration:</b> the committee noted that the company of dasatinib had agreed a patient access scheme with the Department of Health.	4.33

<p>End-of-life considerations</p>	<p>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.</p>	<p>4.31</p>
<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 older people), 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>4.32</p>

## 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](mailto:Commercial.Team@novartis.com).

## 6 Appraisal committee members and NICE project team

### Appraisal committee members

#### TA241

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 TA241

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), a technical adviser and a project manager.

## **TA241**

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