NICE National Institute for Health and Care Excellence

NICE guidance

Bosutinib for previously treated 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

1 Recommendations

1.1 Bosutinib is recommended as an option, within its marketing authorisation, for chronic, accelerated and blast phase Philadelphia chromosome positive chronic myeloid leukaemia in adults, when:

- they have previously had 1 or more tyrosine kinase inhibitor and
- imatinib, nilotinib and dasatinib are not appropriate and
- the company provides bosutinib with the discount agreed in the patient access scheme (as revised in 2016).

2 The technology

Description of the technology	Bosutinib (Bosulif, Pfizer) is a second-generation tyrosine kinase inhibitor that inhibits Abl-kinases, including Bcr-Abl kinase. It also inhibits the Src family kinases, which have been implicated in driving chronic myeloid leukaemia (CML) progression.
Marketing authorisation	It has a UK marketing authorisation for 'the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options'.
Adverse reactions	The summary of product characteristics lists the following adverse reactions as being the most common (that is, affecting more than 1 in 20 people): thrombocytopenia, anaemia, diarrhoea, nausea, vomiting, abdominal pain, fever, rash and increased levels of liver enzymes. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Bosutinib is administered orally. The recommended dose is 500 mg once daily. The dose can be increased up to 600 mg if there has not been a complete haematological response by week 8 or a complete cytogenetic response by week 12.
Price	Bosutinib costs £3,436.67 for 28 × 500 mg tablets and £859.17 for 28 × 100 mg tablets (excluding VAT; British national formulary [BNF], accessed online May 2016). The average cost is £122.74 for 500 mg/day. The annual cost of bosutinib at this dose is £44,799 per patient. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of bosutinib, 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

The appraisal committee (see section 6) considered evidence submitted by Pfizer and a review of this submission by the evidence review group (ERG). This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on bosutinib for previously treated chronic myeloid leukaemia. It focused on cost-effectiveness analyses using a revised patient access scheme, which provides a simple discount to the list price of bosutinib. The level of the discount is commercial in confidence. 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 bosutinib.

4 Committee discussion

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

4.1 The committee noted that the marketing authorisation for bosutinib is for treating Philadelphia chromosome positive CML, that is, 'for adults with chronic, accelerated or blast phase CML previously treated with 1 or more tyrosine kinase inhibitors and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options'. It noted that NICE technology appraisal guidance on dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70) and 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 give guidance on first- and second-line treatments for CML. The committee discussed the company's decision problem. It noted that the population covered by the marketing authorisation and addressed by the company in its decision problem was narrower than the population outlined in the final scope issued by NICE. However, it considered that the company's decision problem reflected the marketing authorisation for bosutinib and that this was appropriate. The committee further noted that the company had considered hydroxycarbamide to approximate best supportive care and the clinical experts confirmed that a patient on hydroxycarbamide is not receiving disease-modifying treatment. The committee concluded that the decision problem was appropriate for its decision-making.

4.2 The committee considered the treatment pathway for chronic, accelerated and blast phase CML and the likely position of bosutinib in the pathway. It heard from the clinical experts that nilotinib and standard-dose imatinib are first-line treatments for chronic phase CML. However, around 90% of people would start on imatinib because of

longer experience with it and a favourable adverse event profile compared with nilotinib. In addition, imatinib would be used by people with diabetes mellitus because taking nilotinib requires fasting and it is thought to worsen diabetes. The clinical experts stated that most of the people who receive their first-line tyrosine kinase inhibitors during the chronic phase of CML will remain on life-long treatment with no reduction in life expectancy. For people whose disease does not respond or who are intolerant of their first tyrosine kinase inhibitor, a second tyrosine kinase inhibitor would be the next treatment option. The clinical experts estimated that around 60% of chronic phase CML responds to imatinib and that the other 40% of patients either have intolerance to, or have CML that is refractory to, imatinib. Of those whose CML is refractory, the clinical experts estimated that around 20% would also have CML refractory to second-line nilotinib. In the third-line setting, another tyrosine kinase inhibitor would be prescribed if possible rather than hydroxycarbamide because hydroxycarbamide does not affect the natural history of CML. The committee heard that people who are intolerant of, but whose CML is not resistant to, first-line nilotinib would receive second-line imatinib. It heard that the marketing authorisation for imatinib covers people with chronic, accelerated or blast phase CML, but that the marketing authorisation for nilotinib does not cover blast phase CML. The committee recognised that use of the Cancer Drugs Fund means that some people receive dasatinib despite it not being recommended by NICE. The committee further noted that the company had said that bosutinib would be used third line or later. The committee concluded that bosutinib would be likely to be a third- or fourth-line tyrosine kinase inhibitor.

4.3 The committee heard that stem cell treatment is an option for CML but less than 10% of people with newly diagnosed CML would be expected to go on to receive a transplant. It heard that stem cell transplant was primarily used third line after imatinib and nilotinib or for people presenting in the advanced phases. In all cases, stem cell transplant only applies for fit people with good donor matches. The patient experts further stated that stem cell transplant would be a patient's last choice. The committee noted that some people whose CML does not respond to, or who are intolerant of, imatinib, nilotinib and dasatinib would benefit from an alternative tyrosine kinase inhibitor treatment option, and that

stem cell transplant was an option for a minority of patients and would be likely to be used after all tyrosine kinase inhibitor options had failed. The committee considered the marketing authorisation for bosutinib and concluded that, within this marketing authorisation, bosutinib was likely to be mainly used third line or later, but would be used before stem cell transplantation in clinical practice.

4.4 The patient experts explained how treatments for CML affect quality of life. The committee heard that successful treatment with a tyrosine kinase inhibitor can improve quality of life to a level similar to that before the onset of CML symptoms and tyrosine kinase inhibitors are convenient because they can be taken at home. For people with CML, intolerance to tyrosine kinase inhibitors has a large impact on quality of life. The committee heard from a patient expert that, in their own experience, previous tyrosine kinase inhibitors had resulted in them being unable to work, and needing cardiac and surgical interventions. However, bosutinib had been tolerated. The committee noted that the main side effects of bosutinib were rashes, and gastrointestinal and haematological side effects. The clinical experts said that bosutinib is a very selective inhibitor of Bcr-Abl and has fewer off-target effects because of its mechanism of action. They said that it is these off-target effects that may underpin some of the adverse effects seen with other tyrosine kinase inhibitors, such as haematological toxicity, rashes and pleural effusion. Overall, the clinical experts stated that bosutinib is well tolerated. They stated that, in people whose CML responds but who switch tyrosine kinase inhibitors because of intolerance, the response would be maintained if they switch to a new tyrosine kinase inhibitor, and that there is no cross intolerance between tyrosine kinase inhibitors. The committee noted that bosutinib offers a treatment option for people who are intolerant of other tyrosine kinase inhibitors at the expense of clinically manageable side effects, and that people who are intolerant of other tyrosine kinase inhibitors may benefit from bosutinib.

Clinical effectiveness

4.5 The committee discussed the evidence for bosutinib from the phase I/II trial Study 200. It noted that this was a single-arm study and that only a small proportion of the trial population (52 out of 546 people) met the

licensed indication for bosutinib, meaning they had unmet medical need (first-line imatinib had failed and the population had a mutation expected to confer resistance to dasatinib or nilotinib, or they had medical conditions or prior toxicities predisposing them to unacceptable risk with nilotinib or dasatinib treatment). The committee noted that marketing authorisation was granted on the basis of evidence presented in Study 200. It concluded that, although there were limitations to Study 200 because it was a single-arm study and only a small proportion of people met the licensed indication for bosutinib, it provided the only evidence for bosutinib on which to base its decision.

4.6 The committee discussed the efficacy estimates from Study 200 for bosutinib. It noted that Study 200 had assessed both haematological response and cytogenetic response. It discussed the clinical relevance of the response measures for CML. It heard from the clinical experts that people whose CML has a complete cytogenetic response can be considered 'operationally cured' if this response is maintained and they remain on treatment. The clinical experts said that CML that has a complete cytogenetic response in the advanced phases effectively returns to chronic phase. It noted a proportion of CML in all phases and CML in the unmet medical need cohort had a complete cytogenetic response; the proportion of people who had received bosutinib second line whose CML had complete cytogenetic response ranged from 20% in the blast phase cohort to 43% in the chronic phase cohort. The committee heard from clinical experts that people would continue to receive a tyrosine kinase inhibitor if a complete cytogenetic response is maintained, but people may also continue to receive bosutinib if a haematological response is maintained. The committee noted that the proportion of people in whom there was complete haematological response who had received bosutinib second line ranged from 15% in the blast phase cohort to 85% in the chronic phase cohort. The committee concluded that bosutinib had shown efficacy in Study 200 in terms of haematological and cytogenetic responses.

4.7 The committee discussed whether the efficacy of bosutinib would be expected to be the same for people who had stopped tyrosine kinase inhibitor treatment because of resistance or intolerance. It heard from the clinical experts that, in people who switched to another tyrosine

kinase inhibitor because of intolerance, CML would be expected to respond better than in people who switched because of resistance. The company stated that, in Study 200, results for the chronic phase population had been presented separately for people who were intolerant of or whose CML was resistant to imatinib and dasatinib, or imatinib and nilotinib. It was further stated that the clinical outcomes were similar in the subgroup of people whose CML was resistant to tyrosine kinase inhibitors and the subgroup of people who were intolerant of tyrosine kinase inhibitors. The committee concluded that, although it was plausible that subgroups of people whose CML was resistant to or who were intolerant of tyrosine kinase inhibitor treatment may have a different response to bosutinib, the available data from Study 200 did not suggest that there was a substantially different clinical effect between the subgroups to warrant considering them separately.

4.8 The committee considered the limitations of Study 200 in terms of its generalisability to clinical practice in England and Wales with regard to the position of bosutinib in the treatment pathway and how this resulted in uncertainty about the overall survival estimates from Study 200 and estimates of likely treatment duration with bosutinib. The committee considered treatment after bosutinib failed, and noted that it was unclear from Study 200 if patients in the trial had received further treatment. The company clarified that approximately 45% of people in Study 200 had received 'anticancer therapy' (no definition was available) after stopping treatment with bosutinib; 13% of these people received hydroxycarbamide (which was included in the anticancer therapy group). Although the committee considered the treatment discontinuation data from Study 200 to be mature (sufficiently complete to make an accurate estimate of time on treatment for the whole population), it discussed how this might differ if bosutinib were the last-line tyrosine kinase inhibitor available because it would be expected to be in clinical practice, as opposed to the Study 200 circumstances in which many patients received further active treatments. The committee noted that the overall survival estimates for the chronic phase population were immature. It considered that, although the overall survival data for the accelerated phase and blast phase populations were sufficiently mature to make an estimate, the overall survival estimates for bosutinib from Study 200 were uncertain in all disease phases because some people had received

additional treatments after stopping bosutinib. The committee concluded that there was uncertainty about whether treatment duration with bosutinib in Study 200, in which people could receive further active treatments, would reflect treatment duration with bosutinib when taken as the last-line tyrosine kinase inhibitor in clinical practice. It also concluded that there was uncertainty about the long-term outcomes from Study 200 because treatments received by some of the study population after bosutinib may have affected survival.

4.9 The committee discussed the studies that had been identified through systematic review by the company for the comparator treatments and whether it was possible to make a comparison between the outcomes reported in these studies and the outcomes for bosutinib from Study 200. The committee noted that all of the data for the comparators were from small, non-randomised studies in which the relevant data were single arm. It was concerned that the patient characteristics and prior treatments in these studies were likely to differ from Study 200, and that it was not clear what proportion of people in these studies had unmet medical need. The committee further noted that the efficacy estimates for hydroxycarbamide were based on data from 61 people who had received a mix of treatments after imatinib, of whom only 12 received hydroxycarbamide; no data were available for interferon alfa. The committee noted that complete cytogenetic response data for hydroxycarbamide had not been presented by the company and heard from the clinical experts that patients having hydroxycarbamide would not have a complete cytogenetic response. The committee noted that, for the chronic phase population 2-year overall survival estimates were between 84% and 91% with bosutinib, 72% with stem cell transplant and 77% with hydroxycarbamide. It noted that the availability of survival data for people with advanced phase or blast phase CML receiving the comparator treatments was more limited. Two-year survival estimates were 66% for accelerated phase and 35% for blast phase with bosutinib; a 3-year survival estimate after stem cell transplant in the accelerated phase was 55%. The committee concluded that, in addition to the limitations of the data for bosutinib (see section 4.5), the available data for the comparators were also limited and that there was uncertainty about how comparable the data were to Study 200. It also concluded that, although there were indicative data on the survival of patients

receiving bosutinib and the comparator treatments, the relative treatment effect between bosutinib and the comparators was subject to uncertainty. The committee accepted that there were no further data available for bosutinib or the comparator treatments and accepted that these were the only data on which it could base its decision.

Cost effectiveness

4.10 The committee discussed the assumptions of the company's economic model. It noted that, in the company's model, time off treatment in the bosutinib arm (after active treatment with bosutinib but before progression to the next disease phase) was calculated by subtracting time on bosutinib from an estimate of overall survival; and during the off-treatment period all people received hydroxycarbamide. Furthermore, for chronic phase CML, the overall survival estimate was made from a surrogate outcome. It discussed the evidence review group's (ERG's) concerns that this approach resulted in the length of time a person received hydroxycarbamide after bosutinib in the bosutinib arm being greater than overall survival with hydroxycarbamide in the hydroxycarbamide arm in all disease phases. The committee considered that the resulting increased survival on hydroxycarbamide after bosutinib, which resulted from the company's surrogate outcome modelling approach, meant that the company ascribed a considerable post-treatment benefit to bosutinib in chronic phase CML. The committee agreed that the overall survival estimate, derived from both the company's surrogate outcome approach and the assumed substantial post-treatment effect of bosutinib after stopping it, needed careful interrogation.

4.11 The committee noted that the alternative cumulative survival approach presented by the ERG assumed that survival on hydroxycarbamide after bosutinib would be similar to survival on hydroxycarbamide taken earlier in the treatment pathway (that is, in the previous line of therapy). It noted that the cumulative survival approach did not assume that there was a post-treatment benefit with bosutinib. However, the committee considered that, because of the uncertainty surrounding overall survival with hydroxycarbamide taken at different positions in the treatment pathway, there was the possibility that, despite not having this aim, a

small post-treatment benefit could have been ascribed with the cumulative survival approach as people who take hydroxycarbamide earlier would be expected to have a greater life expectancy. The committee noted that no evidence was presented in the company's submission for a post-treatment benefit with bosutinib, but that evidence had been submitted during consultation (see section 4.14). The committee considered that, with the ERG's cumulative survival approach, overall survival in the bosutinib arm was assumed to depend on the time on treatment with bosutinib and the estimate for survival on hydroxycarbamide after bosutinib. The committee concluded that the key to determining whether the company or the ERG's modelling assumptions were more likely to reflect survival with bosutinib in clinical practice were (1) the overall survival estimates for bosutinib and hydroxycarbamide after bosutinib and (2) whether a post-treatment benefit would be expected with bosutinib.

4.12 The committee discussed the surrogate approach that the company had used to estimate overall survival with bosutinib in the chronic phase. It accepted that the overall survival estimates from Study 200 for this population were immature. The committee discussed whether a surrogate relationship was plausible. It noted a comment received during consultation from the CML Support Group (CMLSG) stating that the European Leukaemia Net guidelines are testament to the existence of a surrogate relationship between major cytogenetic response and overall survival. The committee accepted that there is a relationship between major cytogenetic response and overall survival but discussed whether the relationship from a study that had assessed imatinib escalation for CML (Jabbour 2009) could plausibly apply to bosutinib taken third line. The committee noted that, in Jabbour, most of the patients had received tyrosine kinase inhibitors for a long time, with a median follow-up of 5 years. It considered the company's response during consultation that there were no suitable third-line studies and that Jabbour is the longest study of a tyrosine kinase inhibitor used as second-line treatment. It also noted that the ERG expected that overall survival for people taking bosutinib as a last line of treatment would be shorter than for people taking a second-line tyrosine kinase inhibitor. Critically the responses from consultation did not resolve the committee's doubts that the patients' treatment response in the Jabbour study, in which patients

were treated at an earlier position in the pathway and could therefore receive further treatments after the study treatment, would reflect the response in patients taking last-line bosutinib. The committee concluded that there was considerable uncertainty about the company's estimate of overall survival for bosutinib taken last line in chronic phase CML.

4.13 The committee discussed the company's estimate of overall survival for people receiving treatment with hydroxycarbamide in the chronic phase of their disease in relation to the ERG's estimate. The committee understood that the company's estimate was 3.5 years in the base-case analysis, compared with the ERG's estimate of 7 years. It considered that these estimates varied widely. The committee heard from the clinical experts that 7 years of overall survival was possibly an overestimate; a median survival time of 5 years would be more plausible given that hydroxycarbamide does not treat the disease (see section 4.2).The committee also discussed the estimate of 2.33 years, which the company had suggested in its response to consultation. It understood that this was calculated as one-third of the ERG's estimate, on the basis that the ERG had stated that patients would stay on treatment three times as long in the third-line population as in the second-line population (which had been used to estimate the figure of 7 years). The committee heard from the company that 2.33 years was not a revised base-case estimate, but supported the company's claim that, for a third-line population, 7 years would be too high. The company confirmed that 3.5 years was still its base-case estimate. The committee considered comments received by the CMLSG that, because the most likely line of treatment with bosutinib would be third or later, overall survival with hydroxycarbamide if taken at this point in the treatment pathway was more likely to be at the lower end of the 3.5-year to 7-year survival range considered by the committee in the appraisal consultation document. The committee was persuaded by the comment from the CMLSG and concluded that the most plausible survival estimate for hydroxycarbamide when taken third line or later was 3.5 years.

4.14 The committee considered whether it is reasonable to assume a post-treatment survival gain for bosutinib, recognising that this was the central difference in the approaches to modelling overall survival for bosutinib between the company's approach and the ERG's cumulative

survival method (see sections 4.10 and 4.11) as applied to chronic, accelerated and blast phase CML. It was aware of comments from clinical experts whose opinion was that they would not expect a lasting effect if any tyrosine kinase inhibitor was stopped. The committee further reasoned that, if a treatment was continuing to have an effect, then a clinician would be extremely unlikely to stop treatment, particularly at the last line of treatment. Therefore, the committee felt that the opportunity for a benefit to last beyond treatment would be very limited in clinical practice. However, the committee noted that 2 arguments supporting a benefit of bosutinib beyond the end of treatment had been received during consultation. Firstly, the CMLSG, although casting doubt on post-treatment gains for tyrosine kinase inhibitors as a rule, did suggest that there might be a reduced disease load at the point of stopping bosutinib relative to disease load at the start of bosutinib treatment. The committee acknowledged this argument and considered it was plausible that there could be some post-treatment benefit if disease load decreased from baseline, but noted the lack of evidence for whether this was the case for people who stopped bosutinib in Study 200. Secondly, the company suggested that there might be a persistent molecular response after stopping treatment. The company supported its position with evidence from 4 non-comparative studies in which complete molecular response duration after first-line imatinib was assessed. The committee noted the ERG's concerns about the applicability of the first-line imatinib studies to third-line bosutinib, in particular:

- The complete molecular response rates in the first-line studies of 58.0% in 1 and 100% in the other 3 were markedly different from the 11.4% of the Study 200 third-line cohort.
- The reasons for stopping a tyrosine kinase inhibitor were different. In 2 of the first-line studies, stopping was actually pre-planned.

The committee considered that these were legitimate concerns and, as such, the studies could not be used as evidence of a lasting effect for bosutinib. The committee considered an exploratory analysis done by the company, which determined that there would need to be 17 months of post-treatment survival benefit with bosutinib relative to best supportive care for the incremental cost-effectiveness ratio (ICER) using the cumulative survival approach to be under

£30,000 per quality-adjusted life year (QALY) gained. The committee considered that, because 50% of people in Study 200 stopped bosutinib because of disease progression or lack of efficacy (so would not be expected to have post-treatment benefit), 17 months was likely to be an underestimate of the post-treatment benefit needed for the ICER to be within the range in which a technology would normally be considered a cost-effective use of NHS resources (within £20,000 to £30,000 per QALY gained). The committee concluded that, despite the lack of evidence, on balance it was appropriate to take into account some limited potential for post-treatment benefit when considering the cost-effectiveness results, but this potential should not be over-emphasised in light of the 50% of people in Study 200 who stopped bosutinib because of lack of efficacy or progression. It agreed that, on the presented evidence, any benefit could more reasonably be argued to be 1 or 2 months rather than 17 months.

4.15 The committee noted that, in the company's model after treatment with bosutinib, in all phases people received hydroxycarbamide, and that in the stem cell transplant arm people received stem cell transplant at the same point in the treatment pathway as bosutinib. It heard from the clinical experts, the patient experts (see section 4.3) and the CMLSG during consultation, that people would be likely to try all tyrosine kinase inhibitor options before stem cell transplant. The committee noted that the ERG had modelled a sequence in which people received a stem cell transplant after stopping bosutinib because it suggested that people who were eligible for stem cell transplant but who received bosutinib would receive a stem cell transplant rather than hydroxycarbamide after stopping bosutinib. The committee considered the company's comments on bosutinib and stem cell transplantation received during consultation. These related to the use of the Oehler et al. (2007) study to provide the estimate of overall survival for stem cell transplant. The committee was aware of comments from the ERG that, because the committee agreed that bosutinib was unlikely to be used as a second-line treatment, the Oehler study (in which patients had only received imatinib before stem cell transplant) might be less relevant than the Jabbour (2011) study, which the company preferred. In addition, the committee noted that the ERG agreed with the company that the Oehler study might overestimate the effect of stem cell transplant. However the committee remained concerned that the Jabbour study was a small study (16 patients) and that the overall survival estimate was therefore associated with

considerable uncertainty. The committee noted a comment from the CMLSG that there is very little published evidence and therefore evaluating the clinical effectiveness of stem cell transplantation is very difficult. The committee accepted that there was not a more accurate estimate available. The committee concluded that the likely effect of stem cell transplant would be between the estimates in the Jabbour (2011) and Oehler studies noting that, if the Jabbour estimate was applied using the ERG's sequence assumption and the cumulative survival method, this resulted in an ICER of £38,000 per QALY gained. The committee concluded that the appropriate intervention when stem cell transplant is an option is bosutinib followed by stem cell transplant.

4.16 The committee discussed the potential duration of treatment for people with chronic phase CML and whether it was plausible for people to continue to take bosutinib until transformation (the worst-case scenario presented by the ERG). The committee heard from the company that it considered a scenario in which all people received bosutinib until transformation inappropriate and implausible. It accepted that a proportion of people might take bosutinib after a lack of efficacy (disease progression in terms of loss of response rather than transformation to next disease phase) but, for these people, the appropriate comparator would be a failed tyrosine kinase inhibitor rather than best supportive care. The committee agreed that a failed tyrosine kinase inhibitor might be an appropriate comparator in these circumstances but considered the additional analysis by the company in which bosutinib was compared with a failed tyrosine kinase inhibitor (resulting in an ICER of £38,700 per QALY gained) included the implausible assumption that overall survival with a failed tyrosine kinase inhibitor was worse than with best supportive care. Furthermore the ICER of £38,700 per QALY gained resulted from using a surrogate estimate of overall survival on bosutinib rather than the committee's preferred cumulative approach. The committee further noted comments from the CMLSG that, for people for whom there were active treatment options available (such as stem cell transplant), the decision to try these treatments would be made before transformation to the next phase of CML. The committee remained aware of the ERG's estimate of £135,000 per QALY gained for the ICER of bosutinib compared with best supportive care if bosutinib is continued until transformation. Although it

considered that the consultation comments about (1) not continuing bosutinib all the way to transformation and (2) taking into account the costs of another failed tyrosine kinase inhibitor would bring this estimate closer to the ERG's exploratory base case of £49,000 per QALY gained, it would not lower the ICER entirely to this value.

4.17 The committee discussed the company's comment, received during consultation, that interferon alfa had not been considered as a comparator in the incremental analysis. The committee noted consultation comments from the CMLSG that reinforced the committee's original conclusion that interferon alfa is rarely used in the NHS in England and Wales. Nevertheless, the committee considered the analyses provided by the company in its response to consultation in which 2 new estimates of the overall survival with interferon alfa were used. The committee noted the ERG's comment that the new overall survival estimates, 7 years and 10.45 years, were highly speculative, and asked the company for clarification on whether these estimates were intended to reflect a plausible estimate of the overall survival with interferon alfa. The committee heard from the company that its base case remained the same, and these values were exploratory to highlight the company's assertion that, in comparison with interferon alfa, bosutinib is cost effective. The committee noted that this analysis did not use the ERG's cumulative survival method to estimate the overall survival of the bosutinib strategy, and so had used a higher estimate of survival after stopping bosutinib than the committee considered was plausible (see sections 4.10 and 4.14). The committee noted comments from the ERG that, when interferon alfa is included in the incremental analysis with bosutinib and other comparators, it is either dominated by other more effective and less costly interventions and is ruled out for consideration (as in the company's base case) or, when it is compared with bosutinib, the ICER is greater than the ICER for hydroxycarbamide compared with bosutinib (as in the ERG's cumulative survival method). Taking these points together, the committee concluded that interferon alfa is not used in clinical practice and, even if it were, including this comparator in the incremental analysis would not strengthen the case for bosutinib being cost effective.

4.18 The committee discussed the most plausible ICER for bosutinib

compared with best supportive care (that is, hydroxycarbamide), noting its previous conclusion that it is appropriate to consider hydroxycarbamide as best supportive care (see section 4.1) for chronic phase CML. It noted that the company had provided sensitivity analyses of a decreased overall survival on bosutinib and increased overall survival on hydroxycarbamide, and doubled bosutinib treatment duration using the surrogate approach and, in all of these analyses, bosutinib had a large post-treatment benefit. The committee considered the company's concerns that the cumulative survival approach was insensitive to changes in efficacy because changing duration of treatment with bosutinib had a marginal effect on the ICER. The committee noted that the modelling approach was sensitive to mortality while taking bosutinib, quality of life, and adverse events leading to stopping treatment. However, critically, the committee agreed with the ERG that the ICER would be expected to change little with duration of treatment in a situation in which each year of treatment contributes approximately equal benefit at approximately equal cost. The committee considered that the cumulative survival approach (assuming 3.5 years of overall survival with hydroxycarbamide) was more plausible than the surrogate method for estimating survival with bosutinib, and that £43,000 per QALY gained was the most plausible base-case estimate presented by the company and the ERG for bosutinib in chronic phase CML. The committee noted that the ERG presented only deterministic results and that the probabilistic results presented by the company had been marginally greater than the deterministic results. The committee further recognised that the ERG estimate did not account for potential post-bosutinib benefit (which would be expected to lower the ICER somewhat) or account for a proportion of people continuing to take bosutinib after loss of complete cytogenetic response (which would be expected to increase the ICER rather more). The committee concluded that there was no clinical evidence available to determine the extent that these 2 factors would affect the most plausible available ICER (£43,000 per QALY gained) but estimated that a range of £40,000 to £50,000 per QALY gained would be appropriate for the purposes of its decision-making.

4.19 The committee noted that the company had submitted a revised base case for the accelerated and blast phase populations in its response to the appraisal consultation document. In it, the higher study utility values

from Study 200 for these populations were used rather than the lower utility values from IRIS to approximate the benefit of returning to a second chronic phase, which had not been included in the original base case. The committee accepted that the approach was appropriate because returning to a second chronic phase would be expected to improve quality of life. It noted that the results of the revised base case were £49,600 and £47,400 per QALY gained for accelerated phase CML and blast phase CML respectively compared with hydroxycarbamide. The committee also considered the company's scenario analysis in which the costs of post-bosutinib tyrosine kinase inhibitor treatments were taken into account by the company (reflecting the costs of people taking hydroxycarbamide and returning to a prior tyrosine kinase inhibitor after stopping bosutinib in Study 200), which increased the ICERs of bosutinib compared with hydroxycarbamide to £58,100 per QALY gained for accelerated phase CML and to £63,800 for blast phase CML. The committee also noted that, when the Study 200 utility values were used alongside the ERG cumulative survival approach, the ICERs for bosutinib compared with hydroxycarbamide were £58,000 per QALY gained for the accelerated phase population and £60,000 per QALY gained for the blast phase population. The committee concluded that the cumulative survival approach used by the ERG was more plausible than the company's extrapolation approach because it avoided the uncertainty about the effect of subsequent treatments in Study 200 on overall survival. It concluded therefore that the most plausible ICERs for accelerated phase CML and blast phase CML were £58,000 and £60,000 per QALY gained, and that these were similar to the company's estimates from its scenario analysis taking into account post-bosutinib costs from Study 200.

4.20 The committee considered whether bosutinib was innovative and noted the company's comments that bosutinib has efficacy in patients whose CML is resistant to other tyrosine kinase inhibitors and that it has a good tolerability profile. The committee considered that the mutations that cause resistance to tyrosine kinase inhibitors differ and that some mutations cause resistance to bosutinib. Overall, the committee concluded that bosutinib did not offer a step-change from the tyrosine kinase class of drugs and that there were no additional benefits with bosutinib that had not been included in the QALY.

4.21 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 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 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. The committee discussed whether end-of-life criteria applied to bosutinib.

4.22 The committee considered that the short life expectancy criterion only applied to accelerated phase and blast phase CML because the life expectancy of people with chronic phase CML is longer than 24 months, as indicated by the estimated overall survival of the chronic phase population in both the company's base case and the ERG's exploratory analyses. It therefore concluded that the end-of-life criteria did not apply to chronic phase CML. The committee considered the supplementary advice criteria for the accelerated and blast phase CML populations. Regarding the short life expectancy criterion, the committee was aware that the company's estimate of survival for people with accelerated phase CML was 16 months and was 6 months for blast phase CML. It accepted that these estimates were less than 24 months. The committee considered the extension-to-life criterion, taking into account its conclusions on the uncertainties relating to the lack of comparative evidence (see section 4.9). The committee considered that there was uncertainty in the company's estimates of an extension of 1.7 years and 1.2 years in accelerated phase CML and blast phase CML respectively but that, on balance, it was reasonable to conclude that bosutinib

extends life by at least 3 months compared with best supportive care. Regarding the size of the population, the committee noted the company's estimate that 80 new patients would be expected to be eligible for bosutinib each year, of whom 8 people might be in accelerated or blast phase, and considered this a small patient population. In summary, the committee concluded that, based on estimated data, the end-of-life criteria had been met for bosutinib. Nevertheless, it considered that the plausible ICERs for the accelerated phase and blast phase cohorts were high and associated with uncertainty. The committee concluded that, even allowing for the supplementary advice for life-extending treatments, the magnitude of additional weight that would need to be applied to the QALY gains for bosutinib taken in accelerated phase and blast phase CML was too great for bosutinib to be considered a cost-effective use of NHS resources.

4.23 The committee considered whether there were any equality issues relating to the appraisal of bosutinib for previously treated CML. It noted that age may be used as a proxy for performance status and therefore for suitability of a stem cell transplant. However, people would not be stopped from having a stem cell transplant because of their age but decisions would be made on the basis of performance status. The committee concluded that there were no issues relating to access to treatment for the groups protected under the equalities legislation and there was no need to change its recommendations.

Cancer Drugs Fund reconsideration

4.24 This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on bosutinib for previously treated chronic myeloid leukaemia. The committee considered the likely position of bosutinib in the treatment pathway for chronic, accelerated and blast phase CML. The clinical experts stated that most people who receive a first-line Bcr-Abl tyrosine kinase inhibitor during the chronic phase of CML will remain on life-long treatment and life expectancy would be anticipated to be 'normal'. The committee heard from a patient expert that, in his personal experience, another Bcr-Abl tyrosine kinase inhibitor had caused severe debilitation, but that bosutinib is well tolerated. With the availability of further Bcr-Abl tyrosine kinase inhibitors, the

committee heard from clinical experts that the use of hydroxycarbamide in the third-line setting was diminishing in clinical practice and stem cell transplantation was likely to be used even later in the care pathway than it is now. The committee discussed the appropriate comparators and noted that the treatment of CML was evolving. Molecular monitoring was viewed as a better indicator of whether the disease was responding than indicators previously used (cytogenetic response). The committee noted that there was a significant unmet need for patients who had first-line imatinib treatment but were known to have CML unlikely to respond to nilotinib. The committee considered that a better understanding of resistance mechanisms, such as tyrosine kinase domain mutations, enabled a move towards highly targeted treatment that takes into account both the disease biology and risk of adverse reactions in individual patients. The committee concluded that there was the potential for targeted and individualised treatment.

4.25 The committee discussed the most plausible ICER for bosutinib compared with best supportive care for chronic phase CML. It noted its previous conclusion that it is appropriate to consider hydroxycarbamide as best supportive care. The committee's preferred assumptions were:

- the use of the cumulative overall survival modelling approach
- the plausibility of 1–2 months of post-treatment benefit after treatment with bosutinib
- the overall survival that could be obtained when treated with best supportive care (hydroxycarbamide) of 3.5 years.

The company submitted a new cost-utility analysis incorporating:

- a revised patient access scheme that provides a simple discount to the list price of bosutinib (the level of the discount is commercial in confidence)
- the cumulative survival modelling approach
- an assumption of 3.5 years of overall survival when treated with best supportive care (hydroxycarbamide).

This analysis assumed no post-treatment benefit. The committee noted that

the ERG estimates of the ICER were slightly above those submitted by the company. The committee considered that there were 2 key assumptions that influenced the ICER. The first was the presence or absence of, and the magnitude of, any post-treatment benefit. It noted that it was difficult to determine such benefit, which depended on why people had stopped treatment and whether or not they were in remission at the time they stopped treatment. The committee considered the collection of further evidence to answer this question, but concluded that this was not possible because the post-treatment benefit was difficult to define accurately and therefore difficult to quantify. The committee agreed that a post-treatment benefit of 1–2 months was plausible. The second factor affecting the ICER was the duration of overall survival associated with best supportive care (hydroxycarbamide). The committee heard that this was highly dependent on the stage of the disease at which hydroxycarbamide was taken. It noted that a shorter projected survival duration with hydroxycarbamide would result in more favourable cost-effectiveness estimates and lower ICERs for bosutinib compared with best supportive care (that is, hydroxycarbamide). The committee concluded that defining an accurate figure would be very difficult and agreed that a maximum of 3.5 years was not unreasonable. Given the cost-effectiveness analyses including the revised patient access scheme, and taking into account the unmet need in this patient population, the committee concluded that the ICERs were within the ranges normally considered a cost-effective use of NHS resources.

4.26 The committee considered whether bosutinib was innovative. It noted the company's comments that bosutinib has efficacy in patients whose CML is resistant to other Bcr-Abl tyrosine kinase inhibitors and that it has a good tolerability profile. The committee considered that the mutations that cause resistance to Bcr-Abl tyrosine kinase inhibitors differ and that some mutations cause resistance to bosutinib. However, it noted that bosutinib might be considered moderately innovative in a setting in which more targeted and individualised treatment may become possible in the future. This is based on genetic mutational response and profiling of patients or on clinical grounds, given the preference not to use nilotinib in the presence of raised cardiovascular risk.

End-of-life considerations

4.27 The committee considered the advice about life-extending treatments for people with a short life expectancy in line with NICE's final Cancer Drugs Fund technology appraisal process and methods. It discussed whether the Cancer Drugs Fund end-of-life criteria applied to bosutinib, noting that the criterion that the treatment is licensed or otherwise indicated for small patient populations is not included. The committee considered that the short life expectancy criterion only applied to accelerated and blast phase CML because the life expectancy of people with chronic phase CML is longer than 24 months (as shown by the estimated overall survival of the chronic phase population in both the company's base case and the ERG's exploratory analyses). It therefore concluded that the end-of-life criteria did not apply to chronic phase CML. The committee accepted that the short life expectancy criterion was fulfilled for the accelerated and blast phases of CML. The committee considered the extension-to-life criterion and noted that it was reasonable to conclude that bosutinib extends life by at least 3 months compared with best supportive care. In summary, the committee concluded that, based on estimated data, the end-of-life criteria had been met for bosutinib in the accelerated and blast phases of CML. On balance, given the cost-effectiveness analyses including the revised patient access scheme, and taking into account the unmet need in this patient population, the committee recommended bosutinib as a cost-effective use of NHS resources for chronic, accelerated and blast phase Philadelphia chromosome positive CML in adults when they have previously had 1 or more tyrosine kinase inhibitor, and imatinib, nilotinib and dasatinib are not appropriate.

Equality issues

4.28 The committee considered whether there were any equality issues relating to the appraisal of bosutinib for people with previously treated CML. It noted that age may be used as a proxy for performance status and therefore for suitability for a stem cell transplantation. However, people would not be stopped from having a stem cell transplantation because of their age; decisions would be made on the basis of performance status. The committee concluded that there were no issues

relating to access to treatment for the groups protected under the equalities legislation, and there was no need to change its recommendations.

Summary of appraisal committee's key conclusions

TA401	Appraisal title: Bosutinib for previously treated chronic myeloid leukaemia	Section
Key conclusion (Cancer Drugs Fund reconsideration of TA299)		
Bosutinib is recommended, within its marketing authorisation, as an option for treating Philadelphia chromosome positive chronic myeloid leukaemia (CML) in adults, subject to the conditions in section 1.1.		1.1
There is a significant unmet need for patients who have first-line imatinib treatment but are known to have CML unlikely to respond to nilotinib. Increasingly, there is the potential for targeted and individualised treatment. Bosutinib offers an alternative treatment option for people who are intolerant of other Bcr-Abl tyrosine kinase inhibitors.		4.24
Because the life expectancy of people with chronic phase CML is longer than 24 months the committee concluded that the end-of-life criteria did not apply to chronic phase CML. However the short life expectancy and the extension-to-life criteria were met for bosutinib in the accelerated and blast phases of CML.		4.27
On balance, given the cost-effectiveness analyses including the revised patient access scheme and taking into account the unmet need in this patient population, the committee recommended bosutinib as a cost-effective use of NHS resources for treating Philadelphia chromosome positive CML.		4.25
Current practice (TA299)		

Clinical need of patients, including the availability of alternative treatments	The committee noted that some people whose CML does not respond to, or who are intolerant of, imatinib, nilotinib and dasatinib would benefit from an alternative tyrosine kinase inhibitor treatment option such as bosutinib. It also noted that stem cell transplant was an option for a minority of patients and would be likely to be used after all tyrosine kinase inhibitor options had failed. The committee considered that, within its marketing authorisation, bosutinib was likely to be predominantly used third line or later in clinical practice.	4.3
	Clinical experts stated that people whose CML responds but who switch tyrosine kinase inhibitors because of intolerance would maintain their response if they switch to a new tyrosine kinase inhibitor and that there is no cross intolerance between tyrosine kinase inhibitors. The committee noted that bosutinib offers a treatment option for people who are intolerant of other tyrosine kinase inhibitors at the expense of clinically manageable side effects and that people who are intolerant of other tyrosine kinase inhibitors may benefit from bosutinib.	4.4
The technology (TA299)		
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 from patient experts that successful treatment with a tyrosine kinase inhibitor can improve quality of life to a level similar to that before the onset of CML symptoms, and tyrosine kinase inhibitors are convenient because they can be taken at home. The committee noted that bosutinib offers a treatment option for people who are intolerant of other tyrosine kinase inhibitors at the expense of clinically manageable side effects, and that people who are intolerant of other tyrosine kinase inhibitors may benefit from bosutinib.	4.4

What is the position of the treatment in the pathway of care for the condition?	The committee considered that, within its marketing authorisation, bosutinib was likely to be predominantly used third line or later but would precede the use of stem cell transplantation in clinical practice.	4.3
Adverse reactions	The committee noted that the main side effects of bosutinib were rashes, and gastrointestinal and haematological side effects. The clinical experts said that bosutinib is a very selective inhibitor of Bcr-Abl and has fewer off-target effects because of its mechanism of action. They said that it is these off-target effects that may underpin some of the adverse effects seen with other tyrosine kinase inhibitors, such as haematological toxicity, rashes and pleural effusion. Overall, the clinical experts stated that bosutinib is well tolerated.	4.4
Evidence for clinical effectiveness (TA299)		
Availability, nature and quality of evidence	The committee noted that marketing authorisation was granted on the basis of evidence presented in Study 200. It concluded that, although there were limitations to Study 200 because it was a single-arm study and only a small proportion of people met the licensed indication for bosutinib, it provided the only evidence for bosutinib relevant to the decision problem on which to base their decision. The committee concluded that the quality of the available data for the comparators was limited and that there was great uncertainty about how comparable the data were to Study 200. It also concluded that, although there were indicative data on the survival of patients receiving bosutinib and the comparator treatments, the relative treatment effect between bosutinib and the comparators was subject to uncertainty.	4.5

	The committee accepted that here were no further data available for bosutinib or the comparator treatments and accepted that these were the only data on which it could base its decision.	4.9
Relevance to general clinical practice in the NHS	Study 200 was a single-arm study in which only a small proportion of people met the licensed indication for bosutinib but it provided the only evidence for bosutinib on which the committee could base its the decision.	4.5
	In Study 200, some people had received additional treatments after stopping bosutinib. There was uncertainty about whether treatment duration with bosutinib in Study 200, in which people could receive further active treatments, would reflect treatment duration with bosutinib when taken as the last-line tyrosine kinase inhibitor in clinical practice.	4.8
Uncertainties generated by the evidence	There was uncertainty about whether treatment duration with bosutinib in Study 200, in which people could receive further active treatments, would reflect treatment duration with bosutinib when taken as the last-line tyrosine kinase inhibitor in clinical practice. There was uncertainty about the overall survival estimates for bosutinib from Study 200 because treatments received by some of the study population after bosutinib may have affected survival.	4.8
	The available data for the comparators were limited and there was uncertainty about how comparable the data were to Study 200. Although there were indicative data on the survival of patients receiving bosutinib and the comparator treatments, the relative treatment effect between bosutinib and the comparators was subject to uncertainty.	4.9

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee concluded that, although it was plausible that subgroups of people whose CML was resistant to, or who were intolerant of, tyrosine kinase inhibitor treatment may respond differently to bosutinib, the available data from Study 200 did not suggest that there was a substantially different clinical effect between the subgroups to warrant considering them separately.	4.7
Estimate of the size of the clinical effectiveness including strength of supporting evidence	In Study 200, a proportion of people in all CML phases and in the unmet medical need cohort had a complete cytogenetic response. The committee concluded that bosutinib had shown efficacy in Study 200 in terms of haematological and cytogenetic response.	4.6
Evidence for cost effectiveness (TA299)		
Availability and nature of evidence	Data on survival of bosutinib and the comparator treatments and the relative treatment effect between bosutinib and the comparators was subject to uncertainty.	4.9
	The committee considered the extension-to-life criterion, taking into account its conclusions on the uncertainties relating to the lack of comparative evidence.	4.22
Uncertainties around and plausibility of assumptions and inputs in the economic model	The company's model resulted in the length of time a person received hydroxycarbamide after bosutinib in the bosutinib arm being greater than the overall survival with hydroxycarbamide in the hydroxycarbamide arm in all disease phases.	4.10

	For chronic phase CML, the overall survival estimate was made from a surrogate outcome. The resulting increased survival on hydroxycarbamide after bosutinib, which resulted from the company's surrogate outcome modelling approach, meant that the company ascribed a considerable post-treatment benefit to bosutinib in chronic phase CML. The committee agreed that the overall survival estimate, derived from both the company's surrogate outcome approach and the assumed substantial post-treatment effect of bosutinib after stopping it, needed careful interrogation. The committee considered that, with the evidence review group's (ERG's) cumulative survival approach, overall survival in the bosutinib arm was assumed to be dependent on the time on treatment with bosutinib and the estimate for survival on hydroxycarbamide after bosutinib. The committee concluded that the key to determining whether the company or the ERG's modelling assumptions were more likely to reflect survival with bosutinib in clinical practice were (1) the overall survival estimates for bosutinib and hydroxycarbamide after bosutinib and (2) whether a post-treatment benefit would be expected with bosutinib.	4.11

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?	None.	–
Are there specific groups of people for whom the technology is particularly cost effective?	Not applicable.	–
What are the key drivers of cost effectiveness?	The committee concluded that the key to determining whether the company's or the ERG's modelling assumptions were more likely to reflect survival with bosutinib in clinical practice were (1) the overall survival estimates for bosutinib and hydroxycarbamide after bosutinib and (2) whether a post-treatment benefit would be expected with bosutinib.	4.11

	The committee remained aware of the ERG's estimate of £135,000 per quality-adjusted life year (QALY) gained for the incremental cost-effectiveness ratio (ICER) of bosutinib compared with best supportive care if bosutinib is continued until transformation. Although it considered that the consultation comments about (1) not continuing bosutinib all the way to transformation and (2) taking into account the costs of another failed tyrosine kinase inhibitor would bring this estimate closer to the ERG's exploratory base case of £49,000 per QALY gained, it would by not lower the ICER entirely to this value.	4.16
Most likely cost-effectiveness estimate (given as an ICER) (TA299)	For chronic phase CML the most plausible available ICER was £43,000 per QALY gained but taking into account the limited potential for post-bosutinib benefit and a proportion of people taking bosutinib after loss of complete cytogenetic response an estimated range of £40,000 to £50,000 per QALY gained was appropriate for the purposes of its decision-making.	4.18
	For accelerated phase CML and blast phase CML, the most plausible ICERs were £58,000 per QALY gained and £60,000 per QALY gained respectively.	4.19
Additional factors taken into account (TA299)		
Patient access schemes (PPRS)	The company for bosutinib agreed a patient access scheme with the Department of Health. The size of the discount is commercial in confidence.	2

End-of-life considerations	The committee concluded that, based on estimated data, the end-of-life criteria had been met for bosutinib. Nevertheless, it considered that the plausible ICERs for the accelerated phase and blast phase cohorts were high and associated with uncertainty. The committee concluded that, even allowing for the supplementary advice for committee for life-extending treatments, the magnitude of additional weight that would need to be applied to the QALY gains for bosutinib taken in accelerated phase and blast phase CML would be too great for bosutinib to be considered a cost-effective use of NHS resources.	4.22
Equalities considerations and social value judgements	The committee concluded that there were no equality issues relating to access to treatment for the groups protected under the equalities legislation and there was no need to change its recommendations.	4.23
Cancer Drugs Fund reconsideration of TA299	Bosutinib is recommended, within its marketing authorisation, as an option for treating Philadelphia chromosome positive CML in adults, subject to the conditions in section 1.1.	1.1
	There is a significant unmet need for patients who have first-line imatinib treatment but are known to have CML unlikely to respond to nilotinib. Increasingly, there is the potential for targeted and individualised treatment. Bosutinib offers an alternative treatment option for people who are intolerant of other Bcr-Abl tyrosine kinase inhibitors.	4.24
	Because the life expectancy of people with chronic phase CML is longer than 24 months the committee concluded that the end-of-life criteria did not apply to chronic phase CML. However the short life expectancy and the extension-to-life criteria were met for bosutinib in the accelerated and blast phases of CML.	4.27

	The company for bosutinib has agreed a revised patient access scheme with the Department of Health. The size of the discount is commercial in confidence. On balance, given the cost-effectiveness analyses including the revised patient access scheme and taking into account the unmet need in this patient population, the committee recommended bosutinib as a cost-effective use of NHS resources for treating Philadelphia chromosome positive CML.	4.25

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 bosutinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Pfizer have agreed that bosutinib 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 pfizerNICEaccount@pfizer.com.

6 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. 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 an associate director, a health technology analyst (who acts as technical lead for the appraisal) and a project manager.

TA299

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