NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ponatinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using ponatinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 06 March 2017

Second appraisal committee meeting: 16 March 2017

Details of membership of the appraisal committee are given in section 7.

1 Recommendations

1.1 Ponatinib is recommended as an option for treating chronic myeloid leukaemia (CML) in adults with:

- chronic phase CML
  - only when the T315I gene mutation is present
- accelerated phase or blast phase CML
  - when the disease is resistant to dasatinib or nilotinib or
  - when they cannot have dasatinib or nilotinib and for whom imatinib is not clinically appropriate or
  - when the T315I gene mutation is present and
- the company provides ponatinib with the discount agreed in the patient access scheme.

1.2 Ponatinib is recommended, within its marketing authorisation, as an option for treating Philadelphia chromosome positive acute lymphoblastic leukaemia in adults when:

- the disease is resistant to dasatinib or
- they cannot have dasatinib and for whom imatinib is not clinically appropriate or
- the T315I gene mutation is present and
- the company provides the drug with the discount agreed in the patient access scheme.

1.3 This guidance is not intended to affect the position of patients whose treatment with ponatinib 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 technology

Description of the technology	Ponatinib (Iclusig, Incyte Corporation) is a third-generation antineoplastic protein kinase inhibitor that acts on the breakpoint cluster region-Abelson oncogene that leads to chronic myeloid leukaemia and Philadelphia chromosome positive acute lymphoblastic leukaemia.
Marketing authorisation	Ponatinib has a marketing authorisation for 'adult patients with: • chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation • Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.'
Adverse reactions	The most common treatment-related adverse reactions associated with ponatinib include abdominal pain, constipation, nausea, skin rashes, and dry skin. Some patients experience more severe adverse reactions including vascular occlusive events, hypertension, and increased liver enzymes, which can require dose adjustment or treatment termination. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Once daily oral doses: 15 mg, 30 mg or 45 mg. Dose levels and dose adjustments are determined by time on treatment, treatment response, and adverse reactions to treatment. For full details on treatment discontinuation and dose reduction, see the summary of product characteristics.

Price	Ponatinib is available at a cost of £5,050 for 60 15-mg tablets, or 30 45-mg tablets (excluding VAT; 'British national formulary' [BNF] online, accessed January 2017). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of ponatinib 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 (section 7) considered evidence submitted by Incyte and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

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

Clinical management of chronic myeloid leukaemia

4.1 The committee considered the views of the patient expert on their experience of ponatinib as a treatment for CML. It heard that people whose disease had not responded to initial treatment with a tyrosine kinase inhibitor (TKI) would value ponatinib as an option to control their condition. It heard that there are substantial risks associated with allogeneic stem cell transplant, including fertility problems, which is an important issue for patients considering becoming parents. The committee heard from a patient expert that patients whose disease responds to

ponatinib can live a 'normal' life, and that treatment can be maintained and the risk of side effects minimised by adjusting the dosage and frequency with which ponatinib is taken.

4.2 The committee heard from experts that people who receive ponatinib can have a number of severe side effects, and in particular there is an increased risk of severe cardiovascular occlusive events. It heard from experts and patients that some people will not be able to tolerate ponatinib because of toxicity, but that the most common side effects are generally tolerable in this patient population. It heard that side effects are likely related to drug dosage, and that their risk could be reduced by lowering the dose and frequency of treatment. The committee noted that the company's summary of product characteristics suggests considering discontinuation of ponatinib if a complete haematologic response has not occurred by 3 months, and that it provides guidance on dose reduction.

4.3 The committee heard from experts that it was important to distinguish between resistance and intolerance. It heard that certain CMLs can be resistant to treatment with a particular TKI resulting in non-response, and would be unlikely to respond to treatment with similar TKIs. On the other hand, some people may be unable to tolerate treatment with a particular TKI because of the adverse effects of treatment, despite their disease responding to the treatment. But these people may be able to tolerate treatment with a different TKI.

4.4 The committee heard from experts that reduction in tumour load at 3 months is an important milestone in chronic phase CML, and that this milestone would be met in around 20% to 30% of patients. Of those who did not, around 50% would respond to another TKI, and the rest would have ponatinib, bosutinib or allogeneic stem cell transplant.

4.5 The committee heard from clinical and patient experts that best supportive care (BSC) should not be considered as a comparator for ponatinib. It

also heard that although allogeneic stem cell transplant can be curative, it is a treatment option for people with chronic phase CML that is usually most suitable when all other treatment options have been exhausted. The committee heard that allogeneic stem cell transplant would not be suitable for some people with chronic phase CML either because of fitness or the availability of a suitable donor.

4.6 The committee considered the current clinical pathway for chronic myeloid leukaemia. It noted that dasatinib and nilotinib are recommended as an option for patients whose disease is resistant or intolerant to imatinib; and bosutinib is recommended as an option after prior treatment with 1 or more tyrosine kinase inhibitor when it is not clinically appropriate to treat with imatinib, nilotinib and dasatinib. The committee considered the place of ponatinib in the current pathway was as a treatment option when imatinib, nilotinib and dasatinib are not clinically appropriate, and therefore bosutinib was the most appropriate comparator.

4.7 The committee heard from experts that people with accelerated phase CML are a heterogeneous population, and that for some of them, their disease would respond to a first-generation TKI. It heard that a 3-month cytogenetic response was a reliable measure of effectiveness in these patients. The committee heard from experts that blast phase CML was the most acute phase of CML and that, depending on response to treatment, life expectancy would be less than 6 months. In blast phase CML, clinicians would want them to have the most clinically appropriate TKI available as soon as possible, and it would be unlikely that they would have the time to offer an alternative TKI therapy if the initial TKI used was not effective.

4.8 The committee heard from experts that clinical practice in England is changing because of new treatments like ponatinib and that treatment for CML would be tailored to the needs of the patients. It heard that the recent availability of generic imatinib was likely to lead to pressure for

using of this drug as initial treatment because of its lower cost. It also heard, that people who were intolerant to or whose disease was unresponsive to imatinib, would wish to stop therapy as early as possible, resulting in a push for immediate use of a new-generation TKI, such as ponatinib. The committee concluded that bosutinib was the most appropriate comparator.

Clinical management of Philadelphia chromosome positive acute lymphoblastic leukaemia

4.9 The committee heard from experts that before TKIs became available, ALL was considered the most severe form of leukaemia. The introduction of TKIs has changed the treatment pathway for people with ALL, who now have more tolerable treatment options compared with chemotherapy, which was previously considered standard of care. The committee concluded that for the populations in whom alternative TKIs are available, TKIs would be considered the most appropriate comparator to ponatinib, and BSC would only be considered an appropriate comparator when there was no alternative treatment. The committee noted that ponatinib is the only drug that is specifically licensed for the treatment of the T315I mutation. The committee also noted that because allogeneic stem cell transplant would only be considered after treatment with ponatinib in those people for whom it is suitable it was not a relevant comparator in this appraisal.

Clinical effectiveness in chronic myeloid leukaemia

4.10 The committee considered the clinical evidence presented by the company. It noted that the clinical evidence for ponatinib in CML came from the PACE study. This is a phase 2, single arm, open label, non-comparative study involving 66 sites across 12 countries, including 5 from the UK. The committee noted concerns about the lack of a comparator in the PACE study, but was aware of the ethical considerations which

prevented the company from designing the trial as a randomised control trial. The committee noted that the dosage levels were changed for some patients in the PACE trial and some patients had their treatment terminated which led to uncertainty around the optimal dosing level for ponatinib, and the duration of treatment, and the generalisability of the reported outcomes as a result. The committee concluded that the evidence presented was sufficient for decision-making in this case.

4.11 The committee discussed the matching adjusted indirect comparison carried out by the company to allow an indirect comparison with bosutinib. The approach was only used for patients with chronic phase CML because only in these patients was the data comprehensive, to allow the matching technique to be used. The committee discussed the appropriateness of the approach used by the company. It noted the concerns of the ERG (evidence review group) that individual patient data from the PACE trial were matched with aggregate data from Khoury et al. (2012). It heard from the clinical experts that Khoury et al. (2012) was representative of UK practice, and had been used in a recent Cancer Drugs Fund reconsideration of the NICE technology appraisal on bosutinib. The committee heard from the ERG that using the company's weightings for patients in their analysis had made little difference to the results. It heard from the company that none of the other comparators provided similar data relevant to this evaluation. It also heard that there were limitations in this approach, including that it involved several assumptions to allow for matching patient characteristics across a range of covariates and to account for unobserved heterogeneity. It noted that considerable overlap between the 2 populations is needed to prevent all the weighting being given to a few patients. The committee considered that despite the uncertainty about the matching adjusted indirect comparison, it could be used for decision-making in this case.

4.12 The committee considered ponatinib's role in treating CML in people with the T315I gene mutation. The committee noted that although ponatinib is the only drug that is specifically licensed for the T315I gene mutation, it is generally also more effective than other treatments in those people who do not have the T315I gene mutation. The committee concluded that the evidence on the clinical-effectiveness of ponatinib in people with the T315I gene mutation was sufficient for decision-making.

Clinical effectiveness in Philadelphia chromosome positive acute lymphoblastic leukaemia

4.13 The committee noted that the clinical evidence for ponatinib in Ph+ ALL came from the PACE study.

4.14 The committee noted that because the number of patients in the Ph+ ALL subgroup in the PACE study was small (n=32) the results in these patients lacked statistical power. The committee heard from the ERG that patients in the PACE study had nilotinib, which is not representative of practice in the NHS. It heard from experts that because many of the patients in PACE had taken multiple treatments that had not worked before entry to the study, the results were less favourable for ponatinib than they would be in practice. The committee acknowledged the limitations of the evidence base in this population, but concluded that it was sufficient for decision-making.

4.15 The committee considered ponatinib's role in treating ALL in people with the T315I gene mutation. The committee noted that although ponatinib is the only drug that is specifically licensed for the T315I gene mutation, it is generally also more effective than other treatments in those people who do not have the T315I gene mutation. The committee concluded that the evidence on the clinical-effectiveness of ponatinib in people with the T315I gene mutation was sufficient for decision-making.

Cost effectiveness in chronic myeloid leukaemia

4.16 The committee discussed the cost-effectiveness evidence presented by the company and its critique by the ERG. The committee discussed the limitations in the company's model. It heard from the ERG that the probabilistic sensitivity analyses done by the company were not robust because of the inappropriate characterisation of uncertainty in the curves, lack of correlation and the arbitrary selection of the size of the standard error used for many parameters. It accepted the structure of the economic model by the company and considered it appropriate for decision-making.

4.17 The PACE trial did not collect quality of life data. The company therefore used the values reported in Szabo et al. (2010), and applied utility decrements to set them to the UK population norm. The committee noted that this approach meant that neither the absolute, nor relative, differences in the health states to the baseline health state applied in the model matched those observed in Szabo. It accepted the approach taken by the company and considered it appropriate for decision making.

4.18 The committee considered the company's base-case deterministic incremental cost-effectiveness ratios (ICERs) for people with CML using the patient access scheme (PAS) price for ponatinib and the list price for its comparators. The committee noted that these ICERs were different to those which were used for decision-making. This was because of the confidential PASs currently in place for bosutinib, dasatinib and nilotinib. The ICERs stated in this document for CML all refer to ICERs calculated using the PAS price for ponatinib and list price for comparators.

Table 1 Company's and ERGs base-case ICERs for people with chronic myeloid leukaemia: ponatinib patient access scheme and comparator list prices

Treatment	Deterministic ICER per QALY gained Ponatinib vs comparator (ERG base case)
Chronic phase chronic myeloid leukaemia	
Best supportive care	£15,200 (£18,246 – £27,667)
Bosutinib	£18,213 (£19,986 – £52,121)
Interferon alfa	£6395 (probability of ponatinib not being cost effective judged low, and no further analyses conducted)
Allogeneic stem cell transplant	£4042 (£18,279 – Dominated)
Accelerated phase chronic myeloid leukaemia	
Best supportive care	£14,750 (£7475 – £18,005)
Allogeneic stem cell transplant	£13,279 (Dominating – £63,701)
Bosutinib	Dominant (ponatinib typically dominant, further analyses not conducted by ERG)
Blast phase chronic myeloid leukaemia	
Bosutinib	£17,601 (£17,066 – £22,512)
Best supportive care	Dominant (ponatinib typically dominant, further analyses not conducted by ERG)
Allogeneic stem cell transplant	Dominant (£4,004 – Dominated)
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.	

4.19 The committee discussed the ERG's exploratory analyses on the company's deterministic ICERs. It heard from the ERG that the parametric distributions fitted where individual patient data were unavailable were inappropriate, and that the company had not explored the effect of alternative distributions on the ICER. The committee noted that the company chose its parametric distributions based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC), but did not take into account clinical expert advice on the plausibility of the curves that were selected for its base case. The committee also noted that when the ERG used a selection of alternative curves considered plausible, the ICER for:

- ponatinib compared with bosutinib varied from £13,747 to £43,344 per quality-adjusted life year (QALY) gained in the population with chronic phase CML
- ponatinib compared with BSC ranged from £7,479 to £15,861 per QALY gained in the population with accelerated phase CML
- ponatinib compared with bosutinib ranged from £11,184 to £18,808 per QALY gained in population with blast phase CML.

The committee noted that particularly for the population with chronic phase CML, the ICERs for ponatinib compared with bosutinib were above the range which is normally considered cost effective even using the comparator list price. The committee heard from the ERG that the ICERs could be anywhere within its exploratory base-case range, and it was not possible to specify a likely value within it. The committee concluded that the company had not properly explored the effect of alternative parametric distributions nor had it justified its chosen distribution for the base case in its submission.

4.20 The committee considered the ERG's additional exploratory analyses and noted that when a 3-month stopping rule for bosutinib was applied in chronic phase and blast phase CML models to align it with ponatinib, this also increased the ICERs. The committee heard from clinical experts that it would be reasonable to assume that the 3-month stopping rule would be used in clinical practice as clinicians would stop a patient's treatment with bosutinib or ponatinib as soon as possible if the disease was no longer responding to treatment. The committee concluded that a 3-month stopping rule should be applied to bosutinib in the models.

4.21 The committee considered ponatinib drug wastage in the chronic phase CML model. It heard from the ERG that assuming drug wastage, that is, no vial sharing between patients in this model resulted in an increase in the ICER. The committee heard from experts that drug wastage would be

rare in people with chronic phase CML because they are generally well-informed about their disease and are aware of the seriousness of the effect missed doses on maintaining the treatment response. The clinical experts also stated that people whose disease responded to treatment would get prescriptions for several months but would be monitored during that period to ensure a response was being maintained. However, the committee considered that zero wastage is unlikely for any drug and that some allowance should have been made in the model for this, although it noted that this had a small effect up the ICER.

4.22 The committee considered the half-cycle correction used in the company's model. The committee noted that the ERG had removed this correction in its exploratory analyses and the resulting ICER increased slightly. The committee heard from experts that assuming a half-cycle correction would be appropriate because patients usually get a 1 month prescription at the beginning of treatment and would have their treatment reviewed at the end of that month. The committee concluded that because clinicians actively monitor the treatment of patients with chronic phase CML and might alter a dose within a 3-month period, it was appropriate for the company's model to take into account a half-cycle correction.

4.23 The committee considered the cost effectiveness of ponatinib in people with CML who have the T315I gene mutation. The committee noted that no separate cost-effectiveness evidence was provided for this population. However, the committee understood that because ponatinib is the first TKI specifically licensed for T315I mutation positive CML, the most relevant comparator for this population is BSC only. The committee noted that the ICERs for ponatinib compared with BSC fell within the range normally considered to be a cost effective. Therefore the committee concluded that ponatinib for treating T315I mutation positive chronic, accelerated or blast phase CML could be recommended as a cost-effective use of NHS resources. The committee considered the ERG's exploratory base case

ICER. It noted that the ICERs for ponatinib compared with allogeneic stem cell transplant and bosutinib in those with acute and blast phase CML, respectively, fell within a range usually considered to be a cost effective use of NHS resources (£20,000 to £30,000 per QALY). It noted that for chronic phase-CML the ERG's range of exploratory base case ICERs for ponatinib compared to bosutinib exceeded that which is usually considered to be cost effective. The committee looked at the impact of the inclusion of comparator PAS discounts for bosutinib, dasatinib and nilotinib, on the ERG's exploratory base case ICER values. It noted that in acute and blast phase-CML the ICERs for ponatinib compared with allogeneic stem cell transplant and bosutinib in those with acute and blast phase-CML, respectively, could still considered to be cost effective. For chronic phase-CML, the range of ICERs for ponatinib compared with bosutinib presented by the ERG, taking the bosutinib PAS into account, continued to exceed the range that is usually considered to be cost effective.

Cost effectiveness in Philadelphia chromosome positive acute lymphoblastic leukaemia

4.24 The committee discussed the company's model for Philadelphia chromosome positive (Ph+) ALL. The ICERs discussed in this population are those used in decision making by the committee since there were no comparator PASs.

4.25 The committee understood that the ERG considered the company's ALL model had underestimated the uncertainty around the ICER in the same way as for its CML model, because it did not adequately explore the effect of alternative distributions and values for its model parameters. The committee noted that the in the absence of direct comparative evidence the company had done indirect comparisons. The committee noted that the company's base-case ICER for ponatinib compared with induction chemotherapy using the PAS price for ponatinib was £31,123 per QALY

gained in patients for whom allogeneic stem cell transplant is suitable, and £33,954 per QALY gained in patients for whom allogeneic stem cell transplant is unsuitable. The committee concluded that there was sufficient evidence for decision-making.

4.26 The committee considered the company's indirect comparison of ponatinib and BSC. It noted that the company's model resulted in different overall-survival rates for patients in the ponatinib group compared with those in the BSC group. The committee understood that non-response in either treatment arm should result in the same overall-survival results. The committee noted that to account for this discrepancy, the ERG did 2 separate scenario analyses in which the overall survival rates was set at the same value for both ponatinib and BSC. In the first the ERG used the overall survival figure for ponatinib, and in the second the overall survival figure for BSC. In the group for whom allogeneic stem cell transplant is suitable, this resulted in a drop in the base-case ICER of £31,123 to ponatinib dominating induction chemotherapy (that is, less expensive and more effective) for both scenarios and to £12,983 and £18,959 per QALY for ponatinib compared with BSC respectively. The committee concluded that assuming overall survival after non-response was the same for ponatinib and BSC and vice versa adequately accounted for the uncertainty around this comparison in this case.

4.27 The committee also considered the choice of parametric distribution in the company's ALL model. It heard from the ERG that they explored a range of alternative parametric distributions which affected the ICER in both directions. The committee concluded that there was some uncertainty about which parametric distributions were most plausible and clinically appropriate.

4.28 The committee considered the uncertainty of the ICER calculated by the ERG taking into account the overall-survival adjustment for people whose disease did not respond to ponatinib or BSC, as well as the highest and

lowest values from the alternative parametric distributions used by the ERG. The committee noted that for people with Ph+ ALL for whom allogeneic stem cell transplant is suitable, the ICER for ponatinib compared with BSC ranged between £7,892 and £31,696 per QALY gained (also taking into account minor adjustments made by the ERG). The committee noted that in people with Ph+ ALL for whom allogeneic stem cell transplant was unsuitable, ponatinib dominated BSC.

End-of-life considerations

4.29 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.

- For people with chronic phase CML:
  - the company's model estimated that patients' life expectancy is more than 4 years regardless of treatment;
  - therefore the committee concluded that the end-of-life criteria, which applies to those with a life expectancy of 2 years or less, were not satisfied for the population with chronic phase CML.
- For people with accelerated phase CML:
  - the company's model estimates that, on average, those patients having bosutinib would live for more than 6 years; those that have allogeneic stem cell transplant would live for more than 3 years, and those who have BSC would live for slightly less than 2 years;
  - the committee noted that the company's model predicts a large extension to life for ponatinib compared with BSC; more than 6 years;
  - the committee concluded that the end-of-life criteria were met for people with accelerated phase CML for whom allogeneic stem cell transplant or bosutinib are not appropriate.

- For people with blast phase CML:
  - the company's model estimates that patients having bosutinib, allogeneic stem cell transplant or BSC have a life expectancy of less than 2 years;
  - the committee noted that in the model, ponatinib extends life compared with all the comparators by more than 3 months;
  - the committee concluded that the end-of-life criteria were satisfied for people with blast phase CML.
- For people with Ph+ ALL:
  - the company's model estimates that patients having BSC only had a life expectancy of less than 6 months
  - the committee noted that the model predicted that patients for whom allogeneic stem cell transplant is suitable and who were having ponatinib, an extension of life of more than 7 years
  - the committee noted that the model predicted for patients for whom allogeneic stem cell transplant is unsuitable and who were having ponatinib, an extension of life of nearly 1 year
  - the committee concluded that the end-of-life criteria were applicable to the population of people with Ph+ ALL regardless of eligibility for allogeneic stem cell transplantation.

4.30 The committee considered that the ERG's exploratory base-case ranges taking into account the end-of-life conclusions it had made for each population. The committee concluded that because the end of life criteria were not met for the chronic phase-CML population, and because the ERG's exploratory base case ICER ranges for ponatinib compared with bosutinib were above what is usually considered to be cost effective, ponatinib could not be considered a cost effective use of NHS resources, except for in cases where the T315I mutation is present. The committee further concluded in those groups who met the end of life criteria the range of ICERs for ponatinib compared with its relevant comparator were

below £50,000 per QALY. The committee concluded that ponatinib could be recommended for people with acute and blast phase-CML, and Ph+ ALL regardless of their suitability for stem cell transplantation and T315I mutation status.

Cancer Drugs Fund consideration

4.31 The committee was aware of the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England. Under the new arrangements, drugs may be given a conditional recommendation by NICE and made available to NHS patients through the Cancer Drugs Fund. Such a drug will remain available within the Cancer Drugs Fund, normally for up to 2 years, while more data are collected. The committee was aware that in considering this, the following criteria must be met:

- the ICERs have the plausible potential for satisfying the criteria for routine use
- it is possible that the clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS
- it is possible that the data will be able to inform a subsequent update of the guidance (normally within 24 months).

4.32 The committee concluded that the ICERs for ponatinib compared with bosutinib in the chronic phase-CML population were outside the range normally considered to be cost effective (£20,000 to £30,000 per QALY), but that in cases where the T315I mutation is present the ICER for ponatinib compared with best supportive care could be considered a cost effective use of NHS resources. It also concluded that the ICERs for ponatinib compared with the relevant comparator in the acute and blast phase -CML and Ph+ ALL populations were cost effective under the end of life criteria (up to £50,000 per QALY). The committee therefore concluded that ponatinib should not be included in the Cancer Drugs Fund.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia	Section
Key conclusion		
Ponatinib is recommended as an option for treating chronic myeloid leukaemia (CML) in adults with: • chronic phase CML – only when the T315I gene mutation is present • accelerated phase or blast phase CML – When the disease is resistant to dasatinib or nilotinib, or – if they cannot have dasatinib or nilotinib, and for whom imatinib is not clinically appropriate, or – when the T315I gene mutation is present and • the company provides ponatinib with the discount agreed in the patient access scheme		1.1
Ponatinib is recommended, within its marketing authorisation, as an option for treating Philadelphia chromosome positive acute lymphoblastic leukaemia in adults when: • the disease is resistant to dasatinib, or • they cannot have dasatinib and for whom imatinib is not clinically appropriate, or • the T315I gene mutation is present, and • the company provides the drug with the discount agreed in the patient access scheme.		1.2
The committee considered that best supportive care is rarely an appropriate treatment or comparator in patients suitable for ponatinib.		4.5

It concluded that bosutinib is the most appropriate comparator. It considered that while allogenic stem cell transplant was an appropriate treatment for this population it was most likely to be used after ponatinib; either as a final treatment option after to control symptoms, or after ponatinib had stabilised the condition to allow for allogenic stem cell transplant.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee heard that depending on how far their disease had progressed, prognosis could be poor in these patients, and it was important to get them on an effective treatment immediately. It understood that allogenic stem cell transplant had significant risks and side effects, and there was issues around availability of suitable donors, that made it a treatment option that was not suitable for all patients.	4.1 4.5 4.9
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee concluded that ponatinib was the only treatment licensed for the treatment of T315I gene mutation. It heard that even in patients who did not have the T315I mutation ponatinib offers advantages over bosutinib.	4.12 4.15

What is the position of the treatment in the pathway of care for the condition?	The committee considered bosutinib was the most appropriate comparator in the treatment pathway. The committee understood that the treatment pathway was changing and that the introduction of generic imatinib could cause further disruption	4.6 4.8
Adverse reactions	The committee heard from experts that people who receive ponatinib can have a number of severe side effects, and in particular there is an increased risk of severe cardiovascular events. It heard that some patients will not be able to tolerate ponatinib due to toxicity, but that the most common side effects are generally tolerable in this patient population. It heard that side effects are positively related to dosage of the drug, and that their risk could be reduced by lowering the dosage and frequency of treatment	4.1 4.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The key clinical evidence was the PACE trial. The committee noted that this was a non-comparative study, and that, in the absence of comparative evidence, the company had made an indirect comparison with bosutinib. The committee considered the limitations in both the evidence and company's chosen technique to make an indirect comparison but considered both appropriate for decision making.	4.10 4.11 4.13

Relevance to general clinical practice in the NHS	The committee concluded that evidence from the PACE trial and Khoury et al. (2012), for matching, was relevant to clinical practice in the NHS.	4.10 4.11
Uncertainties generated by the evidence	The evidence was limited and had the potential for biases. In the Ph+ ALL group, and in some of the CML subgroups patient numbers were small, and lacked statistical power. The key uncertainties in the evidence related to optimal dosing, duration of treatment, and in the results from the MAIC.	4.10 4.14
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that ponatinib offered a more effective treatment option to best supportive care, and offered some treatment benefits over bosutinib. It considered allogeneic stem cell transplant, as a later stage, and one not suitable for all patients. The committee was mindful that the clinical evidence was limited.	4.1 4.5 4.9 4.10 4.14

Evidence for cost effectiveness		
Availability and nature of evidence	The committee concluded that the clinical evidence presented by the company was limited but sufficient to inform the economic model	4.16 4.17
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee agreed with the modelling approach undertaken by the company, and its choice of economic inputs. However it was clear that the company had taken an arbitrary approach in its selection of curves of best fit, and had not explored the impact of uncertainties in its selection in probabilistic sensitivity analyses.	4.16 4.25
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?	The PACE trial did not collect quality of life data. The company used the values reported in Szabo et al. (2010), and applied utility decrements to set them to the UK population norm. The committee noted that this approach meant that neither the absolute, nor relative, differences in the health states to the baseline health state applied in the model matched those observed in Szabo.	4.17

Are there specific groups of people for whom the technology is particularly cost effective?	No	
What are the key drivers of cost effectiveness?	The key driver of cost effectiveness in all the models was the choice of distribution for measures of survival and treatment response.	4.19, 4.27, 4.27

Most likely cost-effectiveness estimate (given as an ICER)	The committee recognised that there was considerable uncertainty in the value of the ICER, and therefore its most likely value fell within a range. The committee concluded that because the end of life criteria were not met for the chronic phase-CML population, and because the ERG's exploratory base case ICER ranges for ponatinib compared with bosutinib were above what is usually considered to be cost effective, ponatinib could not be considered a cost effective use of NHS resources, except for in cases where the T315I mutation is present. The committee further concluded in those groups who met the end of life criteria the range of ICERs for ponatinib compared with its relevant comparator were below £50,000 per QALY. The committee concluded that ponatinib could be recommended for people with acute and blast phase-CML, and Ph+ ALL regardless of their suitability for stem cell transplantation and T315I mutation status.	Table 1, 4.19 4.23 4.28 4.30
Additional factors taken into account		
End-of-life considerations	The committee concluded that the end of life criteria had been met in patients with accelerated and blast phase CML, and Ph+ ALL.	4.29

Equalities considerations and social value judgements	No equality issues were raised during the appraisal.	N/A

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 accelerated or blast phase CML, or Ph+ ALL, or chronic phase-CML with the T315I gene mutation, and the doctor responsible for their care thinks that ponatinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Incyte corporation have agreed that ponatinib 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 [NICE to add details at time of publication]

6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executivewill decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Eugene Milne
Chair, appraisal committee
January 2017

7 Appraisal committee members and NICE project team

Appraisal committee members

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.

The technology appraisal committees are standing advisory committees of NICE.

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.

Neil Hewitt
Technical Lead

Richard Diaz
Technical Adviser

Stephanie Yates
Project Manager

ISBN: [to be added at publication]