NICE National Institute for Health and Care Excellence

NICE guidance

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic 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 Ponatinib is recommended, within its marketing authorisation, as an option for treating chronic-, accelerated- or blast-phase chronic myeloid leukaemia in adults when:

- the disease is resistant to dasatinib or nilotinib or
- they cannot tolerate dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate or
- the T315I gene mutation is present.

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 tolerate dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate or
- the T315I gene mutation is present.

1.3 Ponatinib is recommended only if the company provides the drug with the discount agreed in the patient access scheme.

2 The technology

Table 1 Summary of ponatinib

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 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 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.'
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 about 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 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 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 CML

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. The committee heard from the patient expert that patients whose disease responds to ponatinib can live a 'normal' life, treatment can be maintained and the risk of side effects can be minimised by adjusting the dosage and frequency at which ponatinib is taken.

4.2 The committee considered the current guidance on CML. It noted that NICE technology appraisal guidance on dasatinib and nilotinib recommends dasatinib and nilotinib for Philadelphia-chromosome-positive (Ph+) chronic- or accelerated-phase CML in adults who cannot tolerate or whose disease is resistant to imatinib, and bosutinib (see NICE's technology appraisal guidance on bosutinib) for chronic-, accelerated- or blast-phase CML after at least 1 TKI when imatinib, nilotinib and dasatinib are not clinically appropriate. The committee noted that approximately 95% of people with CML have Ph+ disease. The committee considered the summary of product characteristics for ponatinib and it noted that ponatinib is indicated for use in adults with 'chronic-phase, accelerated-phase, or blast-phase chronic myeloid leukaemia 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'. The committee noted that this was the same population used in the scope issued by NICE, and was aware that any recommendations it made on the use of ponatinib would be within the marketing authorisation. The committee considered that in the current treatment pathway, ponatinib may be an option

when the TKIs imatinib, nilotinib and dasatinib are not clinically appropriate.

4.3 The committee heard from the clinical experts that ponatinib can have various severe side effects, and in particular there is an increased risk of severe cardiovascular occlusive events. However, both the clinical and patient experts explained that although some people will not be able to tolerate ponatinib because of toxicity, the most common side effects are generally tolerable in this patient population. The committee 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. It noted that for people with chronic-phase CML, the summary of product characteristics suggests stopping ponatinib if there has not been a complete haematological response by 3 months, and reducing the dose to 15 mg if there has been a major cytogenetic response.

4.4 The committee heard from the clinical experts that it was important to distinguish between resistance and intolerance. It heard that certain types of CML 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 associated side effects, despite their disease responding to the treatment (but these people may be able to tolerate a different TKI).

4.5 The committee heard from clinical experts that response to treatment is measured using a sensitive molecular assay, real-time quantitative polymerase chain reaction (RQ-PCR), and that a result of less than 10% at 3 months is considered to be an important milestone in predicting long-term survival. It heard that around 70% of people with newly diagnosed CML having imatinib will reach this milestone; this rises to 90% in people having a second-generation TKI (dasatinib, nilotinib or bosutinib). Some people may not reach this milestone because they cannot tolerate imatinib, rather than because their disease is resistant to treatment. Around 50% of people who cannot tolerate imatinib have an RQ-PCR of less than 10% 3 months after starting a second-generation TKI. The other 50% need further treatment with ponatinib or an allogeneic stem cell transplant.

Clinical management of Philadelphia-chromosome-

positive ALL

4.6 The committee considered the current guidance on ALL. It noted that NICE technology appraisal guidance on pegaspargase for treating acute lymphoblastic leukaemia recommends pegaspargase as part of antineoplastic combination therapy for newly diagnosed ALL in people of all ages. It noted that although there was no other NICE guidance currently available, and none specifically for people with Ph+ ALL, imatinib and dasatinib are available for people with Ph+ ALL and dasatinib was previously available for this indication through the Cancer Drugs Fund. It noted the population in both ponatinib's marketing authorisation and the NICE scope (section 4.2) and was aware that any recommendations it made on the use of ponatinib would be within the marketing authorisation. The committee concluded that it was appropriate to consider ponatinib as an option in adults with Ph+ ALL whose disease is resistant to, or who cannot tolerate, imatinib and dasatinib.

4.7 The committee heard from the clinical experts that before TKIs became available, Philadelphia-chromosome-positive (Ph+) ALL was considered the most severe form of leukaemia. The TKIs have changed the treatment pathway for people with ALL, who now have more tolerable treatment options than the previous standard of care (chemotherapy).

Clinical effectiveness in CML

4.8 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 II, 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 (offering placebo to patients who have not responded to previous treatment) which prevented the company from designing the trial as a randomised control trial design. The committee was aware that for some patients in the trial, the dosage was changed or treatment was stopped which led to uncertainties about the best dosing level, the duration of treatment, and the generalisability of the reported outcomes. The committee concluded that despite these uncertainties the evidence presented was sufficient for decision-making in

this case.

4.9 The committee considered the results of the PACE study for people with CML. For patients with chronic-phase CML, the primary outcome was the proportion of patients achieving major cytogenetic response (MCyR, defined as complete cytogenetic response or partial cytogenetic response) within 12 months of starting treatment. For patients with accelerated-phase and blast-phase CML, the primary outcome was the proportion of patients achieving a major haematologic response (MaHR, defined as complete haematologic response or no evidence of leukaemia, confirmed by blood analyses) within 6 months of starting treatment. Patients in the study had 1 to 4 TKIs (imatinib, dasatinib, nilotinib or bosutinib) and conventional therapy, before having ponatinib. For patients with chronic-phase CML, 56% of patients having ponatinib after 1 TKI achieved a MCyR at 12 months; this increased to 67% for patients having 2 previous TKIs, 45% for 3 TKIs and 58% for 4 TKIs. At 12 months overall survival was 94% and progression-free survival was 80%. For patients with accelerated-phase CML, 55% of patients having ponatinib after 1 TKI achieved a MaHR by 6 months; this increased to 61% for patients having 2 previous TKIs, 50% for 3 TKIs and 67% for 4 TKIs. At 12 months overall survival was 84% and progression-free survival was 55%. For patients with blast-phase CML, 31% achieved a MaHR by 6 months. Overall survival was 29% and progression-free survival was 19%.The committee also considered results at 4-year follow-up, provided as commercial in confidence by the company. The committee concluded that the PACE study demonstrated ponatinib to be an effective treatment for CML.

4.10 The committee discussed the matching adjusted indirect comparison carried out by the company to allow an indirect comparison of ponatinib with bosutinib. The approach was only used for patients with chronic-phase CML because theirs were the only data comprehensive enough 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 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. was representative of UK practice, and had been used in a recent Cancer Drugs Fund reconsideration of the NICE technology appraisal guidance on bosutinib for previously treated chronic myeloid leukaemia. The committee heard from the ERG that using the company's

weightings for patients in its analysis had made little difference to the results of the matching adjusted indirect comparison. 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. The committee noted that considerable overlap between the 2 populations is needed to prevent all the weighting being given to a few patients. It noted comments received during consultation highlighting evidence that ponatinib is more effective than dasatinib, nilotinib and bosutinib when compared with imatinib in newly diagnosed disease. The committee considered that despite the uncertainty about the matching adjusted indirect comparison, it could be used for decision-making in this case.

4.11 The committee considered the results of the PACE study in light of ponatinib's role in treating CML in people with the T315I gene mutation. For patients with chronic-phase CML, 70% achieved an MCyR by 12 months, overall survival was 92% and progression-free survival was 83%. For patients with accelerated-phase CML, 50% achieved an MaHR by 6 months. For patients with blast-phase CML, 29% achieved an MaHR by 6 months. Overall and progression-free survival was not reported. The committee noted that these results were at least as good as those as patients without the T315I gene mutation. The committee noted that although ponatinib is the only drug licensed for use in people with the T315I gene mutation, it generally works better than other treatments in people without the T315I gene mutation. The committee concluded that the clinical-effectiveness evidence for ponatinib in people with the T315I gene mutation showed it to be an effective treatment, and was sufficient for its decision-making.

4.12 The committee discussed the comparators listed in the scope issued by NICE. It noted that interferon alfa was included as a comparator in the company's submission for chronic-phase CML only, because it is rarely used to treat CML in the UK and there was no evidence for its effectiveness in accelerated- and blast-phase CML. The committee heard from the clinical and patient experts that best supportive care should not be considered as a relevant comparator because of its limited clinical effectiveness. The committee noted comments received during consultation which suggested that best supportive care should be considered as a comparator, because bosutinib may be ineffective at this stage of the disease and best supportive care would represent the only treatment

option. The committee heard from the clinical and patient experts that although allogeneic stem cell transplant can be curative, it is usually most suitable when there are no other treatment options. The committee also heard that allogeneic stem cell transplant would not be suitable for some people with chronic-phase CML because of either fitness or the availability of a suitable donor, and that there are substantial allogeneic stem cell transplant-associated risks. The committee concluded that bosutinib was the most appropriate comparator based on the current treatment pathway but noted that best supportive care would be the only option for some people, so it should also be a comparator.

Clinical effectiveness in Philadelphia-chromosome-positive ALL

4.13 The committee noted that the clinical evidence for ponatinib in Ph+ ALL came from the PACE study. The committee noted that because of the small number of patients in the Ph+ ALL subgroup (n=32), the results lacked statistical power. The committee heard from the ERG that patients in the study had received nilotinib, which is not representative of NHS practice. It heard from the clinical experts that because many patients in PACE had already had several ineffective treatments before the study, the results for ponatinib were less favourable than they may be in practice. The committee acknowledged the limitations of the evidence base in this population, but concluded that it was sufficient for its decision-making.

4.14 The committee considered the results of the PACE study. For patients with Ph+ ALL, 41% achieved the primary outcome (that is, a MaHR within 6 months of starting treatment). At 12 months, overall survival was 40% and progression-free survival was 7%. The primary outcome was not reported by line of therapy; the committee noted results at 4-year follow-up, provided as commercial in confidence by the company, which did report results by line of therapy but merged Ph+ ALL with blast-phase CML. The committee concluded that the results of the PACE study demonstrated that ponatinib is an effective treatment in Ph+ ALL patients.

4.15 The committee considered the comparators in the scope issued by NICE. It noted that because allogeneic stem cell transplant would only be considered after

ponatinib in those people for whom it is suitable, it was not a relevant comparator. The committee considered that for people for whom a transplant was suitable, the relevant comparators for ponatinib would be best supportive care and induction chemotherapy. However, it noted that chemotherapy would only be used to induce remission in people for whom an allogeneic stem cell transplant is suitable; for people who can have ponatinib but for whom an allogeneic stem cell transplant is unsuitable, the only other treatment option (and so the relevant comparator) was best supportive care.

4.16 The committee considered that, as for CML, ponatinib was at least as effective in treating Ph+ ALL in people without the T315I gene mutation as it was in people with the mutation (section 4.11). It considered the results from the PACE study in this population, and noted the results reported at 12 months which showed that 36% achieved a MaHR by 6 months. The committee noted that although ponatinib is the only drug that is 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 clinical-effectiveness evidence for ponatinib in people with the T315I gene mutation showed it to be an effective treatment, and was sufficient for its decision-making.

Cost effectiveness in CML

4.17 The committee discussed the cost-effectiveness evidence presented by the company and its critique by the ERG. It noted that because no studies were identified that were relevant to the decision problem, the company constructed a de novo model. During consultation, the company submitted a revised patient access scheme (PAS). 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 choice of standard error used for many parameters. It noted this but accepted the structure of the company's economic model and considered it appropriate for its decision-making.

4.18 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 compared with the baseline health state applied in the model matched those seen in Szabo et al. It accepted the approach taken by the company and considered it appropriate for its decision-making.

4.19 The committee considered the company's base-case deterministic incremental cost-effectiveness ratios (ICERs) for people with CML, using the revised PAS price for ponatinib and list prices for the comparators. The committee noted that these ICERs were different to those which would be used for decision-making. This was because of the confidential PASs in place for bosutinib, dasatinib and nilotinib. The ICERs for CML in this guidance all use the price for ponatinib including the revised PAS and list prices for the comparators.

4.20 The committee discussed the ERG's exploratory analyses on the deterministic ICERs in the company's original submission. 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 and Bayesian information criterion, but did not take into account clinical expert advice on the plausibility of the survival curves that it used in its base case. The company had provided additional analyses using the Guyot methodology in response to a clarification letter from the ERG. The committee concluded that the company had neither properly explored the effect of alternative parametric distributions nor justified its chosen distribution.

4.21 The committee considered the ERG's investigation of parameter uncertainty in the company's model. It heard that the choice of curves of best fit for survival functions and duration of response had a big effect on the ICER, and that the ERG had fitted additional combinations of curves to explore this uncertainty, resulting in a range of potential ICERs. The committee heard responses from the company about the appropriate curve for progression-free survival, and that the choice of log normal led to a clinically implausible result in which patients whose condition did not respond had better outcomes than those whose condition did respond. The committee noted that because of limited data there was considerable parameter uncertainty and no curve provided a definitive fit, including the

company's preferred exponential curve for progression-free survival. It therefore concluded that the ERG's fitting of alternative distributions was appropriate.

4.22 The committee considered the ERG's additional exploratory analyses and noted that the ICERs also increased when a 3-month stopping rule for bosutinib was applied in the chronic- and blast-phase CML models, to align it with ponatinib. The committee heard from the clinical experts that it would be reasonable to assume that the 3-month stopping rule would be used in clinical practice, as suggested in the summary of product characteristics (section 4.3), because clinicians would stop treatment with bosutinib or ponatinib as soon as possible if the disease were no longer responding to treatment. The committee concluded that a 3-month stopping rule should be applied to bosutinib in the models.

4.23 The committee considered ponatinib drug wastage in the chronic-phase CML model. It heard from the ERG that assuming drug wastage in the company model increased 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 of missed doses on maintaining treatment response. The clinical experts also stated that people whose disease responded to treatment would have 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 only a small effect on the ICER.

4.24 The committee considered the company's revised PAS discount and the ERG's exploratory ICERs, using the revised PAS for ponatinib and list price for comparators. It heard from the ERG that the ICERs could be anywhere within its exploratory range, and it was not possible to specify a likely value within it.

- For chronic-phase CML, the ICERs for ponatinib were:
  - compared with best supportive care: £18,246 to £27,667 per quality-adjusted life year (QALY) gained
  - compared with bosutinib: £19,680 to £37,381 per QALY gained
  - compared with allogeneic stem cell transplant: £18,279 to dominated (that is, ponatinib was both less effective and more costly than

transplant) per QALY gained.

The ERG considered it unlikely that the comparison with interferon alfa would not be cost effective, so did no additional analyses.

- For accelerated-phase CML, the ICERs for ponatinib were:
  - compared with best supportive care: £7,123 to £17,625 per QALY gained
  - compared with bosutinib: generally ponatinib was dominant (no further analyses were done)
  - compared with allogeneic stem cell transplant: dominant (that is, transplant was both less effective and more costly than ponatinib) to £61,896 per QALY gained.
- For blast-phase CML, the ICERs for ponatinib were:
  - compared with best supportive care: dominant
  - compared with bosutinib: £16,209 to £21,404 per QALY gained
  - compared with allogeneic stem cell transplant: £5,033 per QALY gained to dominant.

The committee noted that the ICERs for ponatinib compared with allogeneic stem cell transplant in accelerated-phase CML and ponatinib compared with bosutinib in blast-phase CML, using the revised PAS for ponatinib and list price for comparators mostly fell within a range usually considered to be a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained). For people with chronic-phase CML, even though some of the ICERs in the ERG's analyses using the revised PAS for ponatinib and list price for comparators for ponatinib compared with bosutinib were above £30,000 per QALY gained, the ICERs were mostly within the range usually considered to be cost effective. The committee then considered the inclusion of the comparators' confidential PAS discounts in the analysis. It noted that for chronic-phase CML, the range using the revised PAS for ponatinib and PAS price for comparators included values of less than £20,000 per QALY gained and, given the uncertainty of the true value within the range, it was possible that

ponatinib was a cost-effective option in these patients. It also considered the ICER range for ponatinib compared with best supportive care to be relevant, because without ponatinib best supportive care could be the only treatment option in patients whose condition did not respond to a second-generation TKI. The precise decision-making ICERs cannot be reported because of a confidential PAS for the comparators. The committee concluded that ponatinib was cost effective compared with best supportive care and potentially cost effective compared with bosutinib, so recommended ponatinib for chronic-phase CML as a cost-effective use of NHS resources.

Cost effectiveness in Philadelphia-chromosome-positive ALL

4.25 The committee discussed the company's de novo model for Ph+ ALL. The ICERs discussed in this population are those used in the committee's decision-making, because there were no confidential PASs for the comparators.

4.26 The committee understood that the ERG considered the company's model for ALL had underestimated the uncertainty around the ICER in the same way as its model for CML (that is, it did not adequately explore the effect of alternative distributions and values for its model parameters). The committee noted that the company had done indirect comparisons because of a lack of direct comparative evidence. The committee noted that the company's base-case ICERs for ponatinib were:

- compared with induction chemotherapy: £29,812 per QALY gained
- compared with best supportive care in people for whom allogeneic stem cell transplant is suitable: £26,319 per QALY gained
- compared with best supportive care in people for whom allogeneic stem cell transplant is unsuitable: £31,210 per QALY gained.

The committee concluded that there was sufficient evidence for its decision-making.

4.27 The committee considered the company's indirect comparison of ponatinib and best supportive care. It noted that the company's model resulted in different overall survival rates for patients in the ponatinib group compared with those in the best supportive care group. The committee understood that non-response in either treatment arm should give 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 were set at the same value for both ponatinib and best supportive care. In the first, the ERG used the overall survival figure for ponatinib, and in the second it used the overall survival figure for best supportive care. In the group for whom allogeneic stem cell transplant is suitable, ponatinib dominated induction chemotherapy (that is, it was less expensive and more effective) in both scenarios. In the same group of patients the ICERs dropped to £12,661 per QALY gained when using the overall survival figure for ponatinib, and £18,690 per QALY gained for ponatinib compared with best supportive care. In the group for whom allogeneic stem cell transplant is unsuitable, ponatinib dominated best supportive care in both scenarios. The committee concluded that assuming overall survival after non-response was the same for ponatinib and best supportive care, and using either overall survival value for ponatinib or best supportive care, adequately accounted for the uncertainty around this comparison in this case.

4.28 The committee also considered the choice of parametric distribution in the company's Ph+ ALL model. It heard from the ERG that it 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.

4.29 The committee considered the ICER range calculated by the ERG, taking into account the overall survival adjustment for people whose disease did not respond to ponatinib or best supportive care, assuming no half cycle correction of intervention cost, removal of immortality for a small subset of patients, (for group suitable for allogeneic stem cell transplant only) as well as the highest and lowest values from the combinations of alternative parametric distributions used by the ERG.

- In people for whom allogeneic stem cell transplant is suitable, the ICER for ponatinib compared with best supportive care was £7,156 to £29,995 per QALY gained; compared with induction therapy, the ICER was less than

£5,000 per QALY gained.

- In people for whom allogeneic stem cell transplant was unsuitable, ponatinib dominated best supportive care.

End-of-life considerations

4.30 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.

People with chronic-phase CML

4.31 The company's model estimated that patients' life expectancy is, on average, more than 4 years regardless of treatment. Therefore the committee concluded that the end-of-life criteria, which apply to people with a life expectancy of 2 years or less, were not satisfied for the population with chronic-phase CML.

People with accelerated-phase CML

4.32 The company's model estimated that, on average, patients having bosutinib would live for more than 6 years, those having allogeneic stem cell transplant would live for more than 3 years, and those having best supportive care would live for slightly less than 2 years. The committee noted that the company's model predicted a large extension to life for ponatinib compared with best supportive care of 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.

People with blast-phase CML

4.33 The company's model estimated that patients having bosutinib, allogeneic stem

cell transplant or best supportive care have a life expectancy of less than 2 years. The committee noted that in the model, ponatinib extends life by more than 3 months compared with all the comparators. The committee concluded that the end-of-life criteria were satisfied for people with blast-phase CML.

People with Ph+ ALL

4.34 The company's model estimated that patients having best supportive care 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 had an extension of life of more than 7 years. It also noted that the model predicted an extension of life of nearly 1 year for patients for whom allogeneic stem cell transplant is unsuitable and who were having ponatinib. The committee concluded that the end-of-life criteria were met for people with Ph+ ALL regardless of allogeneic stem cell transplantation suitability.

4.35 The committee considered that the ERG's exploratory ranges, taking into account the end-of-life conclusions it had made for each population. The committee concluded that the end-of-life criteria were not met for the chronic-phase CML population, but because the ERG's exploratory ICER ranges for ponatinib compared with bosutinib largely included values considered to be cost effective, and the values compared with best supportive care were cost effective (usually £20,000 to £30,000 per QALY gained), ponatinib could be considered a cost-effective use of NHS resources. The committee concluded that in those groups in whom the end-of-life criteria were met, the ICERs for ponatinib compared with its relevant comparator were less than £50,000 per QALY gained, so it recommended ponatinib for chronic-, accelerated- and blast-phase CML, and Ph+ ALL, as a cost-effective use of NHS resources.

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 chronic, accelerated or blast-phase chronic myeloid leukaemia, or Philadelphia-chromosome-positive acute lymphoblastic leukaemia, 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 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 Mark Tanner at mtanner@incyte.com.

6 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.

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

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