NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Asciminib for treating chronic myeloid leukaemia after 2 or more tyrosine kinase inhibitors

1 Recommendations

1.1 Asciminib is recommended, within its marketing authorisation, as an option for treating chronic-phase Philadelphia chromosome-positive chronic myeloid leukaemia without a T315I mutation after 2 or more tyrosine kinase inhibitors in adults. It is recommended only if the company provides asciminib according to the commercial arrangement (see section 2).

Why the committee made these recommendations

Usual treatment for chronic-phase Philadelphia chromosome-positive chronic myeloid leukaemia without a known T315I mutation after 2 or more tyrosine kinase inhibitors is tyrosine kinase inhibitors such as bosutinib, ponatinib, dasatinib or nilotinib. Although an allogeneic stem cell transplant can be a cure, it is not an option for many people. Asciminib is another tyrosine kinase inhibitor.

Clinical trial evidence shows that asciminib works better than bosutinib in people without a T315I mutation who have had 2 or more tyrosine kinase inhibitors, but it is uncertain how much longer people having asciminib live. It is unclear how well asciminib works compared with the other tyrosine kinase inhibitors when compared indirectly. This makes the clinical and cost-effectiveness results uncertain.

Despite the uncertainties, the cost-effectiveness estimates are likely to be within the range NICE considers an acceptable use of NHS resources. So, asciminib is recommended.

Issue date: June 2022

2 Information about asciminib

Marketing authorisation indication

2.1 Asciminib (Scemblix, Novartis) is indicated for the 'treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia (Ph + CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors, and without a known T315I mutation'.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for asciminib.

Price

2.3 The list price for asciminib is £4,050.37 for a 60-tablet pack of 40-mg tablets (excluding VAT; company submission).

The company has a commercial arrangement (simple discount patient access scheme). This makes asciminib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Novartis, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical need and treatment pathway

Chronic myeloid leukaemia has a substantial impact on quality of life

3.1 Symptoms of chronic myeloid leukaemia (CML) include weight loss, loss of appetite, splenomegaly (increased spleen size), skin rash, anaemia, sweating, drowsiness, abdominal fullness, sleep disturbances, muscle

soreness, muscle cramping and memory loss. As well as physical symptoms, the patient experts explained that being diagnosed with CML can have a major psychological impact. They described how the physical symptoms and the psychological impact of CML, as well as the side effects of current tyrosine kinase inhibitors (TKIs), can affect everyday life. They explained that this can have a considerable impact on family life, education and work, with many people diagnosed with CML having to stop work or reduce their hours. The committee concluded that CML has a substantial impact on the quality of life of patients, and their families and carers.

People with CML who have had 2 or more TKIs would welcome a new treatment option

3.2 The clinical experts explained that decisions about which TKI to prescribe are individual and depend on many factors, including comorbidities, age and resistance to a previously tried TKI. A dose reduction would be tried for people whose disease was responding to treatment but who could not tolerate it. They confirmed most people with CML have imatinib as first-line treatment, with dasatinib or nilotinib also available as first-line options. At second line or later, the choice of TKI depends on tolerance to treatment and resistance to previous TKIs. If a person was not able to tolerate a previous TKI, the choice of treatment is a TKI that is tolerable and effective, allowing them to remain on that treatment long term. If the disease is resistant, the choice of treatment depends on the potency of the TKIs that have been tried previously. If the disease is resistant to the less-potent first-generation TKI, imatinib, then a more potent TKI such as nilotinib, dasatinib or bosutinib may be tried. If the disease is resistant to a more potent TKI or the T315I mutation is present, ponatinib may be an option. The clinical and patient experts explained that ponatinib is associated with potentially serious adverse events that may have a substantial effect on quality of life for some people. They considered that although most CML responds to first-line TKI therapy, there remains an unmet need for CML that is resistant to existing TKIs and for people who

cannot tolerate them. They advised the main aim of treatment is to balance clinical effectiveness with side effects, and that many people have tried at least 2 previous TKIs. Although allogeneic stem cell transplant is potentially curative, it is only an option for a minority of people and is associated with a considerable risk of mortality and long-term issues with graft-versus-host disease. The NHS England Cancer Drugs Fund clinical lead confirmed that the treatment pathway is complicated and individualised. They explained there is a benefit to having alternative treatment options that are effective and tolerated. The committee recognised that people who are not eligible for allogeneic stem cell transplant and who cannot tolerate current TKIs or whose disease is resistant to them have limited treatment options. It also noted that asciminib works by inhibiting breakpoint cluster region protein-ABL1 and therefore may have a different mechanism of action compared with other TKIs. It concluded that asciminib would be an important option for people with chronic-phase Philadelphia chromosome-positive CML who have had 2 or more TKIs and do not have a T315I mutation.

Bosutinib and ponatinib are the main comparators

3.3 The clinical experts explained that the choice of TKI at third line and later varies on a case-by-case basis. They confirmed that once the 3 primary TKIs (imatinib, dasatinib and nilotinib) have been tried and are no longer tolerable, or the disease becomes resistant, the choice will normally be between bosutinib and ponatinib. The committee recognised that most people will have imatinib as their first-line treatment and therefore it is not an appropriate comparator. It also noted that nilotinib and dasatinib are most commonly used earlier in the treatment pathway than at asciminib's proposed positioning (see section 3.2). The committee was aware that most people having third-line and later treatment would have bosutinib. But ponatinib would be appropriate for people whose disease is resistant to bosutinib. It therefore concluded that although all of the TKIs except for imatinib are potential comparators, bosutinib and ponatinib are the main comparators for asciminib.

Clinical evidence

Asciminib is clinically effective compared with bosutinib, but the survival benefit is unclear

3.4 The clinical-effectiveness evidence was based on ASCEMBL: a randomised, controlled, open-label trial that compared asciminib with bosutinib. ASCEMBL included people with chronic-phase Philadelphia chromosome-positive CML after 2 or more TKIs and who did not have a T315I mutation. The primary outcome was major molecular response rate at 24 weeks. Secondary outcomes included complete cytogenic response, time to treatment discontinuation (TTD), progression-free survival and overall survival. The company also reported some of the outcomes at 48 and 60 weeks. Major molecular response and complete cytogenic response were higher in the asciminib arm than in the bosutinib arm at each reported time point. At 24 weeks, 25.48% of people in the asciminib arm had a major molecular response compared with 13.16% in the bosutinib arm. At 24 weeks, 40.78% of people in the asciminib arm had a complete cytogenic response, compared with 24.19% in the bosutinib arm. The results for all outcomes at 48 weeks and 60 weeks are considered confidential by the company, so they cannot be reported here. The committee noted that data for overall survival and progression-free survival from ASCEMBL was immature, so the survival benefit of asciminib was unclear. It concluded that asciminib is clinically effective compared with bosutinib for molecular and cytogenic response rates, but that the difference in survival outcomes is unclear.

The company did indirect treatment comparisons

3.5 Because ASCEMBL compared asciminib with bosutinib, there is no head-to-head evidence for asciminib against the remaining comparators. The company provided a series of unanchored matching-adjusted indirect comparisons (MAICs) to compare the TTD of asciminib with those of ponatinib, nilotinib and dasatinib. It explained that an unanchored MAIC was needed because the studies included did not share a common

comparator arm. At technical engagement, the ERG highlighted concerns with the company MAICs. These included comparator studies being excluded inappropriately, a lack of comparison with Haematological Malignancy Research Network (HMRN) data, adjustment for limited variables, and limited reporting of survival outcomes and relative estimates of effectiveness. At technical engagement, the ERG also requested MAICs for major molecular response outcomes, and for the MAICs to be compared with the HMRN data. In response, the company explained that it was not possible to adjust for all variables. It said that the survival data in ASCEMBL was too immature to support a comparison of survival data with other published studies. The company did provide further information about why certain trials were excluded from the MAICs. These included the small sizes of the trials, inappropriate comparators, different populations, and lack of baseline data for the relevant subpopulations. It also provided MAICs for major molecular response, and comparing outcomes for asciminib and bosutinib from ASCEMBL with outcomes for dasatinib, nilotinib and bosutinib from the HMRN data.

The indirect treatment comparisons are appropriate but should be interpreted with caution

3.6 The company noted that the comparison with HMRN data had several limitations, including non-randomisation, but that the results supported the original MAIC using the clinical trial comparator data. The committee noted that no MAIC for ponatinib was done because of the limited number of people who had ponatinib in the HMRN data. The ERG accepted that the trials in the company's MAIC analyses were likely to be the only trials for which a robust MAIC could be done. However, it had concerns about the differences between naive, unanchored and anchored analyses of TTD and the inconsistency between results for TTD and major molecular response. The ERG explained that this suggests that TTD is not an appropriate surrogate for survival outcomes. The ERG preferred the MAIC of major molecular response for the comparison of asciminib with other TKIs from the HMRN data. It thought that the MAIC analyses against

HMRN showed no clear evidence of any difference between asciminib and dasatinib or nilotinib. The committee recognised the uncertainty in the MAIC analyses, in particular the use of TTD, there being only 1 study per comparator, and the limited set of variables adjusted for. It concluded that the MAICs comparing asciminib with ponatinib, nilotinib and dasatinib were appropriate, but that the results should be interpreted with caution.

Economic model

The surrogate survival model structure is most appropriate

3.7 The company's economic model used a cumulative survival approach to estimate survival based on TTD. The company explained that this is because survival data from ASCEMBL is immature (see section 3.4). The cumulative survival model uses TTD parametric curves for each arm. Total survival time is estimated as the sum of treatment-specific TTD and a fixed, treatment-independent survival period post-discontinuation, which includes fixed periods in the accelerated phase and blast phase. The committee noted this model structure was used for decision making in NICE's technology appraisal guidance on bosutinib for previously treated chronic myeloid leukaemia (TA401). At clarification, the ERG asked the company to provide a surrogate survival modelling approach using a response-based model. This was broadly based on the model used in NICE's technology appraisal guidance on ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (TA451). Using the surrogate survival model, duration of progression-free survival is modelled as a function of cytogenic and haematological response. People are grouped into different response categories and assumed to follow response-dependent progression-free survival curves based on patient-level data digitised from TA451. The ERG was concerned with the cumulative survival model because it used TTD as a surrogate for survival outcomes. It explained that treatment decisions that impact TTD may be subjective, and therefore there are concerns about the validity of comparing TTD across trials. It also explained that there is a lack of

evidence to link TTD with survival outcomes. Therefore, it was concerned that TTD was confounded as a clinical outcome and less suitable for modelling. The company explained that using TTD as a surrogate for survival was validated by a clinician. It considered TTD a good surrogate outcome for survival because when people continue treatment it shows that they are able to tolerate it and that their condition is responding. The clinical experts agreed, but explained that previous surrogates used for survival in CML have been cytogenic or molecular response. They advised that both modelling approaches would be reasonable. The ERG preferred to use cytogenic or molecular response as a surrogate for survival based on the model used in TA451. It explained that this approach is supported by literature, and cytogenic or molecular response has clearer value as a clinical outcome than TTD. The ERG highlighted that this approach is not without limitations and explained that the progression-free survival curves used to estimate overall survival came from a second-line population and therefore may be an optimistic estimate in a third-line population. The committee recognised that because of the nature of the condition, there is currently no direct trial data to suggest a survival benefit for asciminib, and therefore a surrogate outcome must be used to estimate survival. It recognised the limitations of both approaches but was reassured that the cost-effectiveness results were broadly similar for both model types. It considered that a response-based approach using cytogenic or molecular response to estimate survival was more clinically appropriate and less subjective than using TTD. It therefore concluded that the surrogate survival model structure is the most appropriate for decision making.

Survival for 10.1 years after stopping treatment is clinically plausible

3.8 In the company-preferred cumulative survival model (see section 3.7), there is a fixed, treatment-independent survival period after stopping treatment. In its original submission, the company assumed 7 years survival after stopping treatment, based on estimates of mean overall survival from TA401. The ERG preferred a longer survival after stopping

treatment because the company survival estimate was in people who did not have a stem cell transplant or TKIs after imatinib was stopped. It was also concerned that the subsequent treatments used in TA401 no longer represent current NHS clinical practice. It therefore believed that the company estimate of 7 years survival after stopping treatment was pessimistic given changes in the treatment pathway and improvements in care. The ERG also highlighted that the mean survival from the HMRN data is likely to be greater than 7 years, and median survival in PACE, a single-arm, phase 2 clinical trial of ponatinib, is likely to be greater than 5 years. The ERG provided an alternative scenario of 10.1 years survival after stopping treatment. It explained that this was generated by extrapolating evidence from the PACE trial, assuming a mean overall survival of 167 months and a mean TTD of 46.3 months. It then subtracted the mean TTD from overall survival, resulting in an estimated post-discontinuation survival of 120.7 months (10.1 years). The clinical experts agreed with the ERG that a survival of 10.1 years after stopping treatment is a reasonable assumption. The committee noted that this assumption only applies to the company's cumulative survival model. It concluded that in the cumulative survival model, an assumption of 10.1 years survival after stopping treatment is clinically plausible.

End of life

Asciminib does not meet the end of life criteria

3.9 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The life expectancy of people with chronic-phase Philadelphia chromosome-positive CML after 2 or more TKIs who do not have a T315I mutation is estimated to be substantially greater than 2 years. And the evidence for a survival benefit is uncertain. Therefore, the committee concluded that asciminib does not meet the end of life criteria.

Cost-effectiveness results

The company's updated base case reflects the committee's preferred assumptions except for the model structure

3.10 The company used the cumulative survival approach in its base case. The committee preferred the surrogate survival model, using cytogenic or molecular response as a surrogate outcome to estimate survival. It noted that apart from the model structure (see section 3.7) its preferred assumptions aligned with the updated company base case:

- Removing retreatment with the same drug.
- Using the log-logistic curve to extrapolate TTD.
- Using Niederwieser (2021) for stem cell transplant survival outcomes.
- Using a multiplicative approach to adjust utilities for age.
- Ponatinib comparator dosing based on people having a major cytogenic response is assumed to reduce to a 15-mg dose and the cost is halved. People in chronic phase without a major cytogenic response and all people whose disease has progressed to the accelerated and blast phases are assumed to have the higher 45-mg or 30-mg dose. All dose reductions occur at 12 months.

An acceptable ICER would be within the range normally considered a cost-effective use of NHS resources

3.11 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted that although its preferred assumptions aligned with the company base case, it favoured a different model structure. It recognised the uncertainty with the model structure, but was reassured that the cost-effectiveness results were

broadly similar for the 2 different model structures. Therefore, the committee agreed that an acceptable ICER for asciminib would be between £20,000 and £30,000 per QALY gained.

The ICERs are below £30,000 per QALY gained for asciminib compared with bosutinib, nilotinib and dasatinib

3.12 There are confidential discounts for asciminib, bosutinib, nilotinib and dasatinib so the exact ICERs are confidential and cannot be reported here. Using the confidential discounts, the company base case ICERs were below £30,000 per QALY gained for all 3 comparisons. Using the committee's preferred model structure and all confidential discounts, the ICERs were below £30,000 per QALY gained for all 3 comparisons. The committee also considered scenario analyses varying the effectiveness of the comparator treatments, for which the ICERs were still all below £30,000 per QALY gained. Overall, the committee concluded that asciminib was a cost-effective treatment option compared with bosutinib, nilotinib and dasatinib.

Asciminib is cost saving compared with ponatinib

3.13 Using the confidential discounts, the company base case resulted in asciminib having an overall lower cost of treatment and a small loss in QALYs when compared with ponatinib. When an ICER for a technology is less effective and less costly than its comparator, the rule of accepting ICERs below a given threshold is reversed. So, the higher the ICER, the more cost effective a treatment becomes. The committee-preferred ICER, including all confidential discounts, resulted in asciminib still being associated with cost savings per QALY lost with an ICER above £30,000 saved per QALY lost. Overall, the committee concluded that asciminib was a cost-saving treatment option and was cost effective compared with ponatinib.

Other factors

3.14 No equality or social value judgement issues were identified.

Conclusion

Asciminib is recommended for routine commissioning

3.15 Using the committee's preferred assumptions (see section 3.10) and including all commercial arrangements resulted in an ICER below £30,000 per QALY gained for each pairwise comparison of asciminib with bosutinib, nilotinib and dasatinib. The ICER for asciminib compared with ponatinib showed that asciminib is associated with sufficiently high cost savings per QALY lost. The exact ICERs are confidential and cannot be reported here. The committee acknowledged uncertainty with the model structure, but was reassured that the cost-effectiveness results were broadly similar for the 2 different model structures (see section 3.7). Based on the evidence presented, the committee concluded that, with the discount agreed in the commercial arrangement, the most plausible ICERs were within the range that NICE normally considers an acceptable use of NHS resources. Therefore, it recommended asciminib as an option for treating chronic-phase Philadelphia chromosome-positive CML after 2 or more TKIs in adults without a T315I mutation.

4 Implementation

4.1 Section 7 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. Because asciminib has been available through the early access to medicines scheme, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication..

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft

recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. Asciminib will be available in England through a post early access to medicines scheme (EAMS+) arrangement with registered sites until the company has commercial stock available. At this point, interim CDF funding will begin for all eligible patients before the drug moves into routine commissioning. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have 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 2 months of the first publication of the final appraisal document.

4.4 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-phase Philadelphia chromosome-positive CML after 2 or more TKIs and does not have a T315I mutation, and the doctor responsible for their care thinks that asciminib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Richard Nicholas
Chair, appraisal committee
May 2022

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.

Nigel Gumbleton
Technical lead

Alex Filby

Technical adviser

Kate Moore

Project manager

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