NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using gilteritinib 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?

Issue date: January 2020

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 document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using gilteritinib 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: 5 February 2020

Second appraisal committee meeting: To be confirmed.

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Gilteritinib is not recommended, within its marketing authorisation, for treating relapsed or refractory FLT3-mutation-positive acute myeloid leukaemia in adults.

1.2 This recommendation is not intended to affect treatment with gilteritinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Relapsed or refractory FLT3-mutation-positive acute myeloid leukaemia is usually treated with salvage chemotherapy (a type of chemotherapy offered when a first course of chemotherapy has not worked, or the disease has come back after treatment). Gilteritinib is an alternative treatment taken as an oral tablet at home, which is an important quality-of-life benefit for patients.

The clinical evidence shows that people having gilteritinib live longer compared with people having salvage chemotherapy. However, there is uncertainty about long-term survival, particularly after stem cell transplant. This makes the cost-effectiveness results uncertain.

The most likely cost-effectiveness results show that gilteritinib is above the level normally considered a cost-effective use of NHS resources. Therefore, gilteritinib is not recommended for routine use in the NHS.

2 Information about gilteritinib

Marketing authorisation indication

2.1 Gilteritinib (Xospata, Astellas Pharma) is indicated 'as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation'.

Dosage in the marketing authorisation

2.2 The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) once daily. Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs. The summary of product characteristics states that response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response. In the absence of a response after 4 weeks of treatment, the dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted.

Price

2.3 The list price for gilteritinib is £14,188 per 28-day pack (company submission). Multiple courses of treatment will be used. The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Astellas Pharma, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee noted that several issues were resolved during the technical engagement stage, and agreed that:

- The utility values from Ara and Brazier are more plausible (see technical report, issue 6, page 27).
- Utility for progression should not be double counted by including both a lower utility value for the 'post-event' health state and including progression as an adverse event (see technical report, issue 6, page 27).
- Follow-up outpatient appointment costs should be included after the 3-year cure point (see technical report, issue 7, page 29).
- Relapse and progression costs should not be included for 'cured' patients (see technical report, issue 7, page 29).
- It is appropriate to assume 3.3 FLT3 tests are needed to identify 1 person with FLT3 mutation in the model. This means that more than 3 patients would need to be tested to identify 1 patient with FLT3-mutation-positive disease because it occurs in around 30% of patients (see technical report, issue 7, page 29).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 36), and took these into account in its decision making. It discussed the following issues (issues 1, 2, 3, 4, 5, 7 and 8), which were outstanding after the technical engagement stage.

New treatment option

People with relapsed or refractory acute myeloid leukaemia would welcome a new treatment option

3.1 Acute myeloid leukaemia (AML) is a rapidly progressing form of leukaemia, often diagnosed after an emergency admission to hospital. The FLT3 mutation is associated with poorer outcomes, such as a higher risk of relapse. Current treatment for relapsed or refractory AML is with salvage chemotherapy, which is administered as an inpatient treatment and is associated with side effects and debilitating complications. Gilteritinib is an oral tablet that is self-managed and can be taken at home. Patient experts explained that it would improve their quality of life if they could avoid the disruption and loss of autonomy associated with

inpatient treatment. They explained that the potential for improved quality of life is important to them, as well as the potential for improved survival. The committee concluded that people with relapsed or refractory AML would welcome a new treatment that improves survival and quality of life, particularly one that is taken orally at home.

Comparators

Best supportive care is a relevant comparator but the evidence presented to support its relative efficacy is not reliable

3.2 The clinical evidence came from ADMIRAL, an open-label, randomised trial which compared gilteritinib with the investigator's choice of salvage chemotherapy. The comparator arm included:

- low-dose cytarabine (LoDAC)
- azacitidine, mitoxantrone, etoposide and cytarabine (MEC)
- fludarabine, idarubicin, granulocyte-colony stimulating factor and high-dose cytarabine (FLAG-IDA).

The primary outcome measure in ADMIRAL was overall survival. Treatment with gilteritinib increased median overall survival compared with salvage chemotherapy from 5.6 months to 9.3 months (hazard ratio 0.64; 95% confidence interval 0.49 to 0.83, $p<0.001$). Best supportive care was not included as a comparator in ADMIRAL. The clinical experts noted that, in clinical practice, most people would have salvage chemotherapy. But they added that best supportive care is a relevant option in a small proportion of patients who choose not to have salvage chemotherapy because of toxicity and lack of fitness for treatment. Stakeholders at technical engagement considered that best supportive care could be a relevant option for 10% to 20% of patients in this population. The company included a blended comparator of salvage chemotherapy based on ADMIRAL in its economic model results. It did not include best supportive care as a comparator in its original base-case results. However it did include it as a separate comparator in a scenario analysis by

applying a hazard ratio of 2.86 to gilteritinib overall survival, informed by a naive indirect comparison. This was because there was no direct evidence comparing gilteritinib with best supportive care. The ERG had concerns about the methods, assumptions and sources used to inform the company's indirect comparison for best supportive care, including:

- the indirect comparison assumes that LoDAC is equivalent to salvage chemotherapy
- the source of the values used in the calculation of the hazard ratio between gilteritinib and best supportive care was unclear
- proportional hazards are assumed, which may not be appropriate because it is not clear whether the assumption was assessed.

The committee noted the ERG's concerns about the methods of including best supportive care and did not consider that the indirect comparison was reliable. After technical engagement, the company updated its analysis to include best supportive care in the blended comparator. This reduced the cost-effectiveness estimates. The ERG noted that the company's analysis assumed the characteristics of people receiving best supportive care are the same as for people receiving salvage chemotherapy, for example the stem cell transplant rate, which it considered was implausible. The committee agreed that the company's method of including best supportive care in the blended comparator was not appropriate. The committee concluded that best supportive care was a relevant comparator as well as salvage chemotherapy. But it agreed that the indirect evidence that had been presented to it to support the efficacy of best supportive care relative to gilteritinib in the relevant population was not reliable.

Prior midostaurin use

The proportion of people who would have received midostaurin in clinical practice in England may be higher than the proportion in ADMIRAL

3.3 NICE technology appraisal guidance on midostaurin (another FLT3 inhibitor) recommends it for use in the NHS for newly diagnosed acute FLT3-mutation-positive AML. In ADMIRAL, 13% of the gilteritinib group and 11.3% of the salvage chemotherapy groups had received prior FLT3 inhibitors. If, in clinical practice in England, the proportion of people who have received prior midostaurin is higher than in ADMIRAL, the efficacy of gilteritinib may be different to that seen in the trial. The company presented a subgroup analysis of people in ADMIRAL who had had prior FLT3 inhibitors, such as midostaurin. The results showed that, for patients with no prior FLT3 inhibitor (n=325), gilteritinib statistically significantly improved overall survival (hazard ratio 0.620; 95% confidence interval 0.470 to 0.818). For the 46 patients with prior use of an FLT3 inhibitor, the treatment difference was not statistically significant (hazard ratio 0.705; 95% confidence interval 0.346 to 1.438). However, this subgroup analysis only included a small number of patients and may be unreliable. The clinical experts confirmed that they would give gilteritinib after midostaurin in clinical practice. They stated that gilteritinib is a more potent FLT3 inhibitor and they did not believe that prior exposure to midostaurin would affect response to gilteritinib, although this is uncertain. The clinical expert estimated that there were about 600 people a year in England who have relapsed or refractory FLT3-positive AML. Comments from technical engagement suggested that around 50% to 60% of patients with newly diagnosed FLT3-positive AML may have midostaurin. The committee concluded that currently the proportion of people with relapsed or refractory disease who may have received prior midostaurin in clinical practice in England is higher than the proportion in ADMIRAL.

Cure assumptions

A 3-year cure point is plausible and no evidence was presented for a 2-year cure point

3.4 In its original model, the company assumed that all patients who were alive at 3 years were 'cured', regardless of whether their disease had progressed or they had had a stem cell transplant. After 3 years, survival was modelled using an uplifted general population mortality rate (standardised mortality ratio of 2.0). The 3-year cure assumption was based on NICE's appraisal of midostaurin for untreated FLT3-mutation-positive AML, published literature, and clinical advice given to the company. The company did not present any evidence from ADMIRAL to support the cure assumption. The clinical expert suggested that most relapses would be within 12 months. The ERG noted that the Kaplan–Meier curves from ADMIRAL did not show a plateau, which would have suggested a cure. At technical engagement, stakeholders agreed that it was clinically plausible to assume that patients alive after 3 years were cured. However, after technical engagement the company updated its model to include a 2-year cure point, instead of 3 years. The committee noted that the company had not provided any evidence or a clear rationale as to why it had changed the cure point. The committee concluded that a 3-year cure point was plausible and that it had not been presented with evidence for a 2-year cure point.

Gilteritinib effectiveness after HSCT

Data from ADMIRAL should be used to model post-stem cell transplant overall survival

3.5 In the company's model, post-stem cell transplant overall survival was based on a Gompertz curve fitted to data from a study by Evers et al. (2018). The company did not use ADMIRAL data for this group of patients from the company submission and the model because there was limited follow up and a small sample size. However, patients in the Evers study

did not all have FLT3 mutations so were not directly comparable to the population who would be eligible for gilteritinib in clinical practice. The company also highlighted data from a study by Ustun et al., which it used in a scenario analysis. This study included people with FLT3-positive AML but most people in the study did not have relapsed or refractory disease. The ERG highlighted the company's model's predictions and the proportion of patients alive at the end of the final data cut off from ADMIRAL. It said that, because of these, to meet the 3-year cure rate from the company's original model, the majority of surviving (censored) patients in the ADMIRAL gilteritinib-treated stem cell transplant group would need to be considered 'cured'. The ERG considered that the ADMIRAL trial was the most relevant data source, and did an analysis using ADMIRAL data to inform overall survival for people who had a stem cell transplant, which it included in its base case. The ERG pooled both treatment groups from ADMIRAL and fitted a lognormal parametric curve to the data until the 3-year cure point. At technical engagement, stakeholders agreed that the ADMIRAL data should be considered. The committee considered that the ADMIRAL trial was the most appropriate because it included the population relevant to this appraisal.

Gilteritinib maintenance therapy

ADMIRAL data should be used to model post-stem cell transplant overall survival, so this issue is not relevant

3.6 To model overall survival for the post-stem cell transplant group, the company applied a hazard ratio to the Gompertz model (see section 3.5) to reflect an additional survival benefit associated with gilteritinib maintenance therapy after stem cell transplant. The company derived the hazard ratio from an indirect comparison using data from Evers 2018. The company acknowledged that the results from ADMIRAL do not show a favourable effect of gilteritinib after stem cell transplant. However it noted that there were small patient numbers and high levels of censoring. The company believed that, if the patients with salvage chemotherapy were

followed up for longer, a benefit of gilteritinib maintenance therapy would be seen. The ERG considered that the company's approach was inconsistent. The company did not use ADMIRAL data to model post-stem cell transplant overall survival but it did use it, with the data from Evers, to calculate the hazard ratio for the additional benefit of gilteritinib. The ERG did an analysis using a hazard ratio of 1 to indicate no additional benefit of maintenance therapy, which it included in its base case. The clinical experts and other stakeholders at technical engagement confirmed that gilteritinib would be used as maintenance therapy after stem cell transplant in clinical practice, although there is little evidence to support this practice. The committee concluded that ADMIRAL data should be used to model post-stem cell transplant overall survival so agreed that the additional benefit of maintenance therapy included by the company was not relevant.

Costs

Wastage of 14 days' supply of gilteritinib should be accounted for

3.7 In its original model, the company did not include wastage for gilteritinib. The ERG considered that tablets could be wasted in clinical practice, for example, if patients died or their disease progressed while they were on treatment. The ERG did an exploratory analysis to include 14 days' supply of wastage for all patients who died before the 3-year cure point. After technical engagement, the company updated its model to include wastage for 7 days' supply of gilteritinib. The clinical expert explained that normally a 28-day pack would be given to each patient at a time. Therefore, the committee considered that it was reasonable to assume 14 days' supply of gilteritinib may be wasted if someone died before the 3-year cure point. The committee noted that this did not have a large impact on the cost-effectiveness results.

Drug costs should be applied in each cycle of the model

3.8 The company included the costs of gilteritinib and chemotherapy as one-off costs in the first cycle of the model. The ERG noted that this was an unconventional approach that meant:

- discounting could not be applied properly
- gilteritinib treatment duration was underestimated because some patients were still having gilteritinib at data cut off and this was not accounted for
- treatment duration was not linked to progression.

The ERG stated that, if the drug costs had been applied in each cycle, the incremental cost-effectiveness ratio (ICER) would likely increase although it did not know by how much. The committee agreed that drug costs should have been applied in each cycle.

Quality of life and costs associated with administration

The benefit of taking an oral tablet at home compared with having chemotherapy in hospital should be captured in the model

3.9 At technical engagement, the clinical expert highlighted that a potential benefit of gilteritinib is that it is an oral treatment that does not need to be administered in hospital, whereas salvage chemotherapy requires an inpatient stay. The ERG noted that the difference in costs between the 2 treatments was reflected in the administration costs included in the model. However, the ERG noted that the model did not assume any difference in quality of life between the 2 treatments to account for the different methods of administration. After technical engagement, the company updated its model to include a disutility value of -0.044 for high-intensity chemotherapy, which was sourced from a study by Wehler et al. (2018), because it was difficult to collect patient-reported outcomes from people in the salvage chemotherapy group in ADMIRAL. The company also updated some of the hospital costs to reflect this issue. The clinical and patient experts explained that the benefit of taking an oral tablet at home

compared with having chemotherapy in hospital would be important to patients. The committee accepted the company's disutility value of -0.044 for high-intensity chemotherapy but noted that it did not have a large impact on the cost-effectiveness results. The committee was concerned that the potential quality-of-life benefits of oral gilteritinib, with less time in hospital, compared with inpatient chemotherapy with frequent debilitating complications, had not been adequately addressed.

End of life

Gilteritinib meets the criteria to be considered as a life-extending treatment at the end of life

3.10 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. Median overall survival in the salvage chemotherapy group of ADMIRAL was 5.6 months. The clinical expert stated that median survival is around 2 to 3 months in this patient population, and the ERG's base case showed that modelled survival in the salvage chemotherapy and the best supportive care group was less than 2 years. Although the company's updated base case predicted that the mean overall survival in the blended comparator group was over 2 years, the committee agreed that this was likely to be because of the method the company used to model gilteritinib effectiveness after stem cell transplant (see section 3.5). Therefore, the committee concluded that the short life expectancy criterion was met. Both the company's and the ERG's base-case economic models showed that gilteritinib extended mean overall survival by over 3 months more than with salvage chemotherapy (in the ERG's model, 2.34 years more than best supportive care and 0.98 years more than salvage chemotherapy). ADMIRAL showed a median overall survival gain of 3.7 months for gilteritinib compared with salvage chemotherapy. The committee concluded that the extension to life criterion was also met, and that when its preferred

assumptions were applied in the model, gilteritinib met the criteria to be considered as a life-extending treatment at the end of life.

Cost-effectiveness results

The company's updated base-case ICER is below £50,000 per QALY gained

3.11 The company's original base-case ICER, with corrections made by the ERG, was £54,844 per quality-adjusted life year (QALY) gained, compared with salvage chemotherapy. All analyses include the patient access scheme for gilteritinib. In response to technical engagement, the company:

- updated the dispensing fee for gilteritinib
- included best supportive care in the weighted comparator at 25% (see section 3.2)
- changed the cure point from 3 years to 2 years (see section 3.4)
- included gilteritinib wastage of 7 days' supply (see section 3.7)
- included a disutility for high-intensity chemotherapy and updated some hospital costs (see section 3.9)
- updated utility values and costs in line with the technical team's preferred assumptions.

This resulted in an updated base-case ICER of £43,346 per QALY gained, compared with the weighted comparator. The committee noted that it did not consider that the evidence presented for the relative efficacy of best supportive care was reliable and that the company did not provide any evidence for changing the cure point from 3 years to 2 years. It also noted that the company's updated base-case ICER did not include all of the committee's preferred assumptions because it did not use ADMIRAL data to model post-stem cell transplant overall survival (see section 3.5) and it did not include gilteritinib wastage of 14 days' supply (see section 3.7).

The most plausible ICER is above £98,000 per QALY gained

3.12 The ERG amended the company's original base-case model to use ADMIRAL data for post-stem cell transplant overall survival. It also included the technical team's preferred assumptions for utility values and costs, and gilteritinib wastage of 14 days' supply. It included a 3-year cure point and did not include best supportive care as a comparator. This resulted in an ICER of £102,085 per QALY gained compared with salvage chemotherapy. After technical engagement, including the updated gilteritinib dispensing fee and the disutility for high-intensity chemotherapy (see section 3.9), the ICER was £98,498 per QALY gained. When the ERG included the confidential patient access scheme discount for azacitidine, the ICER increased. The ICER is confidential and cannot be reported here. The committee concluded that this was the most plausible ICER because it included its preferred assumptions. However it noted that best supportive care as a comparator was not accounted for in this ICER. The committee also noted that some uncertainty remained in the cost-effectiveness results, because the drug costs were applied as a one-off cost in the first cycle of the model (see section 3.8). The committee concluded that the most plausible ICER was above £98,000 per QALY gained.

Gilteritinib is not recommended as a cost-effective use of NHS resources

3.13 The committee concluded that the most plausible ICER was above the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life. It therefore concluded it would not recommend gilteritinib for relapsed or refractory FLT3-mutation-positive AML.

Cancer Drugs Fund

Gilteritinib does not meet the criteria to be considered for inclusion in the Cancer Drugs Fund

3.14 Having concluded that gilteritinib could not be recommended for routine use, the committee then considered if it could be recommended for treating gilteritinib within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). It discussed the following issues:

- The company did not express an interest in gilteritinib being considered for funding through the Cancer Drugs Fund.
- The modelling of overall survival data after stem cell transplant was uncertain. The committee noted that additional data on overall survival after stem cell transplant could potentially resolve this uncertainty, but that it was unclear where this data could come from.
- The company stated that no further data cuts are expected from ADMIRAL.
- There is not plausible potential to satisfy the criteria for routine use because the committee's preferred ICER was over £90,000 per QALY gained.

The committee concluded that gilteritinib did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

Other factors

There are no equality issues relevant to the recommendations

3.15 No equality or social value judgement issues were identified.

The benefits of gilteritinib can be captured in the cost-effectiveness analysis

3.16 The company, professional organisations and clinical experts considered that gilteritinib was innovative because it would be the first oral

monotherapy targeted for relapsed or refractory FLT3-positive AML. The committee agreed that these were important benefits of gilteritinib, but it concluded that it had not been presented with evidence of any additional benefits that could not be captured in the measurement of QALYs.

4 Proposed date for review of guidance

4.1 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 executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
January 2020

5 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.

Kirsty Pitt
Technical lead

Alexandra Filby
Technical adviser

Gemma Barnacle
Project manager

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