NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Midostaurin for untreated acute myeloid leukaemia

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using midostaurin 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: December 2017

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

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using midostaurin 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: 4 January 2018

Second appraisal committee meeting: 23 January 2018

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

1 Recommendations

1.1 Midostaurin is not recommended within its marketing authorisation (that is, with standard daunorubicin and cytarabine as induction and high-dose cytarabine as consolidation therapy, and alone after complete response as maintenance therapy) for treating newly diagnosed acute FLT3-mutation-positive myeloid leukaemia in adults.

1.2 This recommendation is not intended to affect treatment with midostaurin 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

Treatment for acute myeloid leukaemia is chemotherapy. Evidence from a randomised controlled trial shows that people taking midostaurin with chemotherapy live longer than people taking chemotherapy alone. However, the trial did not include people over 60 so the effectiveness of midostaurin in older people is uncertain.

There is also considerable uncertainty about the cost effectiveness of midostaurin because of problems with the economic model. These include not accounting properly for remission after relapse and including implausibly high long-term costs in some situations.

Midostaurin does not meet both of NICE's criteria for being a life-extending treatment at the end of life because people newly diagnosed with FLT-3-positive acute myeloid leukaemia normally have a life expectancy of more than 24 months. The most likely cost-effectiveness estimate of midostaurin plus chemotherapy compared with chemotherapy alone is more than £62,818 per quality-adjusted life year gained. This is

much higher than the range normally considered to be a cost-effective use of NHS resources, so midostaurin is not recommended.

Midostaurin is not suitable for use within the Cancer Drugs Fund because it does not have plausible potential to be cost effective at its current price and more clinical data collection would not address the uncertainties.

2 Information about midostaurin

Marketing authorisation indication	Midostaurin (Rydapt, Novartis) is indicated 'in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia who are FLT3 mutation-positive'.
Dosage in the marketing authorisation	The dose of midostaurin is 50 mg orally twice daily on days 8–21 of induction and consolidation chemotherapy cycles. For patients who have a complete response midostaurin is continued every day as single agent maintenance therapy until relapse, for up to 12 cycles of 28 days each.
Price	The price was submitted as commercial in confidence because it has not been confirmed by the Department of Health.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Novartis and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

New treatment option

People with FLT3-mutation-positive acute myeloid leukaemia would welcome a new treatment option

3.1 Acute myeloid leukaemia is a rapidly progressing form of leukaemia, often diagnosed following an emergency admission to hospital. The clinical experts explained that there are 2 main types of FLT3 mutation, ITD and TKD. The FLT3-ITD mutation is associated with poorer outcomes. The

committee understood that the marketing authorisation for midostaurin is for all adults with any type of FLT3-mutation-positive acute myeloid leukaemia. A patient expert stated that people with the disease have fatigue, weakness or breathlessness, memory loss, bruising, bleeding and frequent infections. Also, the diagnosis has a big emotional impact on them and their families and carers. The clinical experts explained that if the disease progresses, outcomes are likely to be poor. New treatments that could improve the chance of successfully inducing first remission would be welcomed. The committee concluded that people with untreated disease would welcome any new treatment that could improve survival, quality of life and induce remission, especially one that can be taken orally.

Clinical management

Treatment for acute myeloid leukaemia is chemotherapy

3.2 Current treatment for newly diagnosed acute myeloid leukaemia is intensive chemotherapy, for people who are fit enough to have it. The clinical experts explained that the aim of intensive chemotherapy is to induce complete remission, after which people would either have consolidation chemotherapy or a stem cell transplant. The committee understood that midostaurin would be used to treat FLT3-positive acute myeloid leukaemia when given with induction and consolidation chemotherapy, and then as maintenance monotherapy for up to 12 months. The committee concluded that established clinical management is chemotherapy (without midostaurin), and this is the relevant comparator for this appraisal.

Clinical evidence

The mean age of people in the trial is lower than in NHS clinical practice in England

3.3 The evidence for midostaurin came from RATIFY, a phase 3, multicentre, double-blind, randomised, placebo-controlled trial that included

717 patients with FLT3-positive acute myeloid leukaemia. It compared midostaurin with intensive chemotherapy (daunorubicin plus cytarabine), followed by midostaurin monotherapy (n=360) with chemotherapy alone (n=357). The ERG noted that RATIFY only included people aged 18 to 60 years, but that a significant proportion of people with acute myeloid leukaemia are over 60. A clinical expert said that it would not be unreasonable to assume that the results would be similar for people over 60. The clinical experts explained that a large proportion of patients aged 60 to 70 are eligible for treatment with intensive chemotherapy, and that it would increasingly be used for those over 70 as well. The committee understood that the marketing authorisation for midostaurin is not restricted to a particular age group. It concluded that RATIFY was relevant to clinical practice in England, but that the mean age of people likely to be eligible for midostaurin in England is higher than the mean age of people in the trial.

Clinical effectiveness results

Midostaurin increases overall and event-free survival compared with chemotherapy alone

3.4 The primary outcome measure in RATIFY was overall survival. Treatment with midostaurin plus chemotherapy increased overall survival compared with chemotherapy alone from 25.6 months to 74.7 months (hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.63 to 0.95, p=0.0078). Event-free survival was a secondary end point in RATIFY; the company defined an event as not achieving complete remission within 60 days of starting treatment, relapse from complete remission or death from any cause. Treatment with midostaurin plus chemotherapy increased event-free survival compared with chemotherapy alone from 3.0 months to 8.2 months (HR 0.78; 95% CI 0.66 to 0.93, p=0.002). The committee concluded that midostaurin plus chemotherapy was clinically effective compared with chemotherapy alone.

Adverse effects

Midostaurin is well tolerated

3.5 The committee noted that, although there was an increase in exfoliative dermatitis in the midostaurin group compared with the placebo group in RATIFY, the numbers of people who had other adverse effects were similar between the 2 groups. It concluded that midostaurin was generally well tolerated.

The company's economic model

The model is inflexible and people do not move from the relapsed state to remission

3.6 The company used a partitioned-survival economic model with 5 health states: acute myeloid leukaemia diagnosis and induction, complete remission, relapse, stem cell transplant and death. The complete remission health state was split into 3 further substates (consolidation, monotherapy and complete remission after stopping first-line treatment) and the stem cell transplant state was split into 3 tunnel states (treatment, recovery and post-stem cell transplant recovery). The company used data from RATIFY in the model, and assumed that after a period equal to the length of the trial, or 80 cycles (about 6.2 years), people surviving would be cured. The ERG noted that the model did not allow for the possibility of a person's disease responding to subsequent therapy other than stem cell transplant, if they had relapsed or refractory disease. People in the relapsed state did not move into the complete remission state, so they either moved into the stem cell transplant state or stayed in the relapsed state for a long time. The ERG noted that after about 10 years in the model, 15% of the people in the midostaurin group were in the relapsed health state, which was associated with high costs (about £60,000 per year) and low quality of life (0.53 QALYs per year). The clinical experts stated that they would expect about 10 to 15% of people whose disease relapsed to be in complete remission after subsequent therapy, and

people whose disease did not then respond to subsequent therapy were likely to live for a few months more. The committee agreed that in RATIFY, people whose disease relapsed after initial therapy lived for much longer than the clinical experts suggested they would in NHS clinical practice. In its exploratory analysis, the ERG added a new cured health state to the model, in which it assumed the same costs and benefits as the complete remission after first-line therapy health state. The ERG explored 3 analyses in which all people who were still alive entered the cured state either after 80 cycles (about 6.2 years), after 3 years or when they stopped initial therapy. The committee considered that neither the company's base case nor the ERG's exploratory analyses reflected the clinical experts' description of what they would see in clinical practice. The committee concluded that, of the analyses presented by the company and the ERG, surviving patients with relapsed disease entering a cured health state after 3 years was the most appropriate to overcome the model's restriction on people in the relapsed state and better reflect clinical practice in England.

The costs associated with complete remission after initial therapy and stem cell transplant recovery are implausible

3.7 In its base-case model, the company used the same routine care costs as used in the NICE technology appraisal for azacitidine (TA399) for people in complete remission after first-line therapy and stem cell transplant recovery. The ERG noted that people in the equivalent health states in TA399 had poorer health than the people expected to be in these health states in the current model, and it therefore considered that the costs (about £8,000 per year) were too high. The ERG explored 3 analyses in which it assumed there were no routine care costs in the first-line therapy and stem cell transplant recovery health states after the cure point (80 cycles or about 6.2 years), after 3 years, or after patients stopped treatment. The clinical experts stated that people whose disease was in complete remission would still need to attend hospital appointments for monitoring. They also stated that the main treatment goal was to enable a

stem cell transplant and that people whose disease was in complete remission after stem cell transplant were likely to be seen in hospital frequently, although this would lessen over time. The ERG noted that in RATIFY, 59.4% of people in the midostaurin group and 55.2% of people in the placebo group had a stem cell transplant. The clinical experts explained that they would expect more people to have a stem cell transplant in clinical practice because its use is increasing as older patients become fitter. The committee agreed that the routine care costs applied in the company's base-case model for people in the complete remission after first-line therapy and stem cell transplant recovery health states were too high. However, it considered that it was implausible that there would be no costs associated with monitoring these groups of people after a certain point, as in the ERG's exploratory analyses. The committee agreed that its preferred model was the ERG's exploratory analysis in which no health state costs were applied after the cure point for either people in complete remission after first-line therapy or for post-stem cell transplant recovery. It concluded that, of the options presented, this was the best one to overcome the model's over-estimation of long-term costs following a successful treatment outcome and better reflect clinical practice in England.

Survival after the cure point

The survival rate after the cure point is uncertain

3.8 In the model, the company assumed that people who were alive after cycle 80 (about 6.2 years) were cured and applied the same mortality rate that would be expected in the general population, adjusted for age and sex. The ERG noted a study by Martin et al. (2011), which suggested that the mortality rate for people who had a stem cell transplant was 4 to 9 times higher than for the general population for at least 25 years after the transplant. The clinical experts stated that they would expect mortality risk to increase following stem cell transplant, but that an overall 4-fold increase in mortality rate seemed high. The committee agreed that the

mortality rate for people whose disease had been 'cured', and especially for people who had a stem cell transplant, would likely be higher than the general population mortality rate. It concluded that, from the company's base case and the ERG's exploratory analyses, the most plausible was the lowest increase in mortality rate from the literature, that is, a 4-fold increase in mortality rate. However, the committee noted that changing the mortality rate beyond the cure point had a limited effect on the incremental cost-effectiveness ratio (ICER).

Duration of treatment

The length of treatment in the model should match the RATIFY trial

3.9 In the model, the company assumed that the maximum number of cycles of midostaurin monotherapy was 12, which is consistent with the RATIFY protocol and with the marketing authorisation. The ERG noted that a small number of people in RATIFY actually had up to 18 cycles of midostaurin monotherapy and it therefore increased the maximum cycle length in its base case to 18. The committee concluded that the data in the model should be taken from the trial, but noted that because of the small number of people who had more than 12 cycles, increasing the maximum cycle length to 18 had a limited effect on the ICER.

The company's original calculation of time on treatment is the most appropriate

3.10 In response to the ERG's clarification questions, the company changed the way it calculated the time on treatment in the model. This reduced the total amount of midostaurin that people had, and increased the amount of treatment received in the standard of care group. In its exploratory analysis, the ERG used the company's original calculation. At the committee meeting, the company stated that its original calculation was more appropriate. Therefore the committee concluded that this original calculation should be used in the model.

Utility values in the model

Age-adjusted utility values are appropriate

3.11 The company used utility values from literature sources, because information on health-related quality of life was not collected as part of RATIFY. It used utility values of 0.830 for the complete remission after first-line therapy state and 0.826 for the post-stem cell transplant recovery state. The ERG noted that the company had not adjusted these utility values in the model to account for health-related quality of life decreasing with age. In its base-case model, the ERG adjusted the utility values in these 2 health states for age, which the committee concluded was appropriate.

Including adverse effects of stem cell transplant in the model is appropriate

3.12 The company did not include reductions in utility values for adverse effects from initial treatment or subsequent treatment, including stem cell transplant. It suggested that because it had used utility values that were specific to treatment stage, the values would already include the impact of any adverse effects. The clinical experts highlighted that graft versus host disease, a potential adverse effect of stem cell transplant, would have a significant impact on quality of life. In its base case, the ERG included a reduction in utility values and an increase in costs to account for the effects of graft versus host disease. The committee concluded that adverse effects of stem cell transplant should be included in the model.

Cure point

The cure point used in the model is uncertain

3.13 The ERG noted that the company had used a cure point of about 6.2 years (80 cycles in the model) based on the length of RATIFY, and extrapolated the survival benefit of midostaurin over standard of care at this point over a lifetime. The ERG noted that this was an arbitrary assumption and explored analyses in which it changed the cure point to 5 years, resulting in a similar ICER, and 4 and 7 years, which increased

the ICER over the 6.2 year base case. The clinical experts stated that they would expect anyone whose disease was still in relapse after 5 years to be cured. The committee considered that it would prefer to use the latest point at which the data showed a levelling out effect because this was more logically a point of 'cure'. However it noted that at 7 years, the data from the trial were based on a very small number of people and were therefore unreliable. The committee concluded that there was uncertainty about the most plausible choice of cure point, but it was likely that the true ICER was higher than the company's and the ERG's base-case ICERs, because moving the cure point either earlier or later increased the ICER.

Mean age of the population in the model

The mean age of the population eligible for midostaurin is higher than the mean age of the population in the model

3.14 In the company's model, the mean age of the population on entry to the model was 45 years based on RATIFY, which excluded people over 60. The clinical experts explained that a large and increasing proportion of people aged 60 to 70 with FLT3-positive acute myeloid leukaemia would be eligible for intensive chemotherapy, and therefore eligible for midostaurin. They also suggested that 40 to 60% of people currently having intensive chemotherapy are over 60. The committee agreed that the mean age of people who would be eligible for midostaurin in NHS practice in England would likely be higher than 45 years. In its base case, the ERG used the mean age of 45. However, it presented 3 exploratory analyses in which it changed the mean age of the population on entry to the trial to 50, 55 and 60. Increasing the mean age significantly increased the ERG's base-case ICER. The ERG pointed out that this change only affected the life expectancy of people in the model and did not change treatment effectiveness. The committee concluded that it was likely the mean age of people eligible for midostaurin in England would be around 60. Therefore the true ICER was likely to be higher than the company's and ERG's base-case results.

The company's new analysis of the effect of midostaurin in older people is not appropriate to use in the model

3.15 In response to the ERG's critique of the mean age of people in RATIFY, the company did a new analysis of a single-arm phase 2 study of midostaurin, which included people with FLT3-positive acute myeloid leukaemia up to the age of 70. In the new analysis, the company used propensity score matching to compare people in the phase 2 study with historical controls. It also selectively used some of the ERG's amendments to the company's original base-case model:

- using complete response data uncensored for stem cell transplant
- reverting to its original calculation of time on treatment
- including adverse effects of stem cell transplant and
- using overall survival data from a later data cut.

The company claimed the new analysis showed that midostaurin was more effective in improving overall survival for people over 60 and incorporated the data into its model. In the company's new model, the mean age of the population on entry to the model was 65. The company applied overall survival data from the propensity score-matched analysis of the phase 2 study to people in the model who were over 60, and overall survival data based on RATIFY to people who were 60 or under. The ERG noted that people in the historical control groups that the company used in its analysis had a shorter life expectancy than people in the standard of care group in RATIFY. The clinical experts stated that survival rates for people with FLT3-positive acute myeloid leukaemia had improved in recent years. The committee noted that midostaurin appeared more effective in this analysis than in RATIFY, but agreed that this was likely because of the poor survival rates of people in the historical control groups. The committee also noted that this analysis was a non-randomised comparison that could be susceptible to confounding, and concluded that it should not be used in preference to the trial-based economic model with a simple and logical age adjustment.

Cost-effectiveness results

The ERG's changes to the company's base-case model increase the ICER

3.16 The company's deterministic base case showed that the ICER for midostaurin compared with standard of care was £33,672 per quality-adjusted life year (QALY) gained. The ERG corrected some errors in the company's base case, used data from a later data cut of RATIFY and used complete remission data without censoring for stem cell transplant, which lowered the ICER to £28,465 per QALY gained.

In its preferred base case, the ERG made 7 further adjustments to the company's base-case model:

- adding a new cured health state, which people entered after stopping initial treatment (see section 3.6)
- assuming no costs after people stopped initial treatment (see section 3.7)
- assuming that, after the cure point, people in the model had a mortality rate that was 4 times higher than that of the general population (see section 3.8)
- increasing the maximum number of cycles of maintenance therapy with midostaurin from 12 to 18 cycles (see section 3.9)
- using the company's original calculation of time on treatment (see section 3.10)
- adjusting utility values for age (see section 3.11) and
- including adverse effects of stem cell transplant (see section 3.12).

These changes resulted in an exploratory ICER of £62,810 per QALY gained for midostaurin compared with standard of care. After reviewing the ERG's base-case model, the company calculated a new base-case ICER of £27,754 per QALY gained. This was based on the company's original base case, but included some of the changes that were in the ERG's base case, and the new analysis of the phase 2 study. The committee recalled it had concluded that the analysis of the phase 2 study

should not be used in the economic model (see section 3.15). The committee noted that when the ERG incorporated the committee's preferred assumptions about the cured health state (people enter the cured state after 3 years; see section 3.6), ongoing routine care costs (no costs after the cure point; see section 3.7) and mean age of the population on entry to the model (60 years; see section 3.14) instead of the assumptions in the ERG's base case, the ICER was similar to the ERG's base-case ICER, at £62,818 per QALY gained. The committee also recalled that the ICER increased even further when the cure point was changed from 80 cycles to 4 or 7 years, which it agreed was plausible (see section 3.13).

Midostaurin is not recommended for routine use in the NHS

3.17 The committee concluded that the most plausible ICER for midostaurin compared with standard of care was likely to be much more than £62,818 per QALY gained, because the cure point could be different and the mean age of the population could be higher than 60. This was much higher than the range normally considered a cost-effective use of NHS resources. Therefore it could not recommend midostaurin for treating newly diagnosed acute myeloid leukaemia that is FLT3-positive.

Innovation

Midostaurin's benefits are captured in the cost-effectiveness analysis

3.18 The company considered midostaurin to be an innovative treatment. It highlighted that induction therapy for treating FLT3-positive acute myeloid leukaemia has not changed much in the past 30 years and that midostaurin is the first targeted tyrosine kinase inhibitor that inhibits FLT3 activity. A patient expert and the clinical experts explained that there was an unmet need for a targeted treatment to improve remission rates and overall survival. The committee concluded that midostaurin would be beneficial for patients, but it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

End of life

Midostaurin does not qualify as a life-extending treatment for people with a short life expectancy

3.19 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods. It noted that the results of RATIFY showed that midostaurin increased life expectancy compared with standard of care by more than 3 months. Therefore midostaurin met the criterion of extension to life of at least an additional 3 months. However, it noted that all the estimates of mean overall survival for people with acute myeloid leukaemia from the literature were over 24 months, except those in a study by Marnadie et al. (2013). It agreed that this study was not likely to be representative of the UK population because it was based on relatively old registry data from 1995 to 2002, and included people from countries where life expectancy is lower than in the UK. The committee noted that the median overall survival of people in the standard of care group in RATIFY was 26 months with a greater mean, and that this was a more relevant population because it only included people with FLT3-positive acute myeloid leukaemia. One of the clinical experts highlighted another study in people with FLT3-positive acute myeloid leukaemia (Knapper et al. 2017), which reported that median overall survival for people in the control group was more than 24 months. Therefore midostaurin did not meet the short life expectancy criterion of less than 24 months. The committee concluded that midostaurin did not meet all of NICE's criteria for being considered a life-extending treatment at the end of life.

Cancer Drugs Fund

Midostaurin is not suitable for the Cancer Drugs Fund

3.20 Having concluded that midostaurin was not recommended for routine use, the committee then considered if it could be recommended for treating

FLT3-positive acute myeloid leukaemia within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. The committee noted that the company did not make a case for midostaurin to be included in the Cancer Drugs Fund. It also considered that the most plausible ICER was much higher than the range normally considered to be a cost-effective use of NHS resources. The committee agreed that midostaurin did not have plausible potential to satisfy the criteria for routine use and that there were no clinical uncertainties that could be resolved through data collection within the Cancer Drugs Fund. It concluded that midostaurin did not meet the criteria to be included in the Cancer Drugs Fund.

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.

Andrew Stevens
Chair, appraisal committee
December 2017

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

Sally Doss
Technical Adviser

Stephanie Yates
Project Manager

ISBN: [to be added at publication]