NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Midostaurin for treating advanced systemic mastocytosis

The Department of Health and Social Care 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: November 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 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: 27 November 2020

Second appraisal committee meeting: TBC

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

1 Recommendations

1.1 Midostaurin is not recommended, within its marketing authorisation, for treating advanced systemic mastocytosis (aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasms and mast cell 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

There is no standard treatment for advanced systemic mastocytosis. Current treatments include interferon alpha, pegylated interferon alpha, cladribine, imatinib, and treatments usually used for acute myeloid leukaemia. Midostaurin aims to treat the disease and its symptoms.

Evidence suggests that midostaurin is more effective than current treatments, but the evidence is uncertain. This is because midostaurin has been compared indirectly with current treatments using evidence from 1 unpublished study. Also, it is unlikely that higher quality comparative evidence will become available.

Midostaurin meets NICE's criteria for a life-extending treatment at the end of life. However, the cost-effectiveness estimates are much higher than what NICE normally considers a cost-effective use of NHS resources for end of life treatments. So, midostaurin is not recommended for routine use in the NHS. Because more evidence is unlikely to become available to help with the uncertainty, midostaurin is also not recommended for use within the Cancer Drugs Fund.

2 Information about midostaurin

Marketing authorisation indication

2.1 Midostaurin (Rydapt, Novartis) is indicated 'as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of midostaurin is £5,609.94 for a 56-pack of 25 mg capsules (excluding VAT; British national formulary online, accessed September 2020), which equates to an annual cost of £146,359.33 at the standard dose of 100 mg twice daily. The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

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

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

- The 2 single-arm midostaurin clinical trials, D2201 and A2213, are sufficiently generalisable to NHS practice in England for decision making.
- The 3 subtypes of advanced systemic mastocytosis (aggressive systemic mastocytosis [ASM], systemic mastocytosis with associated haematological

neoplasms [SM-AHM] and mast cell leukaemia [MCL]) are usually clinically distinct.

- It is appropriate to pool the D2201 and A2213 studies to inform the comparative effectiveness estimate used in decision making.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, key issues summary, page 2), and took these into account in its decision making. It discussed the following issues in further detail which were outstanding after the technical engagement stage.

Treatment pathway and comparator

There is an unmet need for a disease-modifying treatment for advanced systemic mastocytosis

3.1 Mastocytosis is a rare group of heterogenous diseases characterised by excessive mast cells. It includes advanced systemic mastocytosis, a severe form of the disease with 3 diverse subtypes. ASM is typically the least severe subtype, followed by SM-AHN, then MCL which has a life expectancy of less than 1 year. The clinical experts advised that the treatment pathway for advanced systemic mastocytosis is complex. Treatment is individualised based on symptoms, and because of the diversity of the disease subtypes. There are no licensed, targeted or disease-modifying therapies to treat advanced systemic mastocytosis currently available for use in the NHS. The patient and clinical experts advised that the condition has a poor prognosis with current treatment options, particularly for SM-AHN or MCL. The patient experts also explained that the symptoms of advanced systemic mastocytosis have a major debilitating effect on their daily activities and quality of life. These include frequent and unexpected anaphylaxis, diarrhoea and vomiting. Available treatments do little to improve these symptoms and may cause additional side effects. The committee concluded that there is an unmet need for people with advanced systemic mastocytosis, and people with

the condition would welcome a disease-modifying treatment option like midostaurin.

A mixture of treatments used in current clinical management is the most appropriate comparator

3.2 The company's evidence submission compared midostaurin with how advanced systemic mastocytosis is currently treated in clinical practice (current clinical management). It used a composite comparator (a representative mixture of treatments currently used) including interferon alpha, cladribine, imatinib, pegylated interferon alpha and treatments that are typically used to treat acute myeloid leukaemia, such as azacitidine. The proportion of the composite comparator made up by each treatment was informed by opinions from 5 clinical experts. The committee recalled that there are no treatments licensed for advanced systemic mastocytosis in current NHS practice, and that treatment is highly individualised (see section 3.1). The clinical experts confirmed that the company's composite comparator is a reasonable representation of the treatments used in current NHS practice. The committee recognised that it would be difficult to identify a single treatment option to use as the comparator. It concluded that current clinical management, as defined by the company, was the appropriate comparator for decision making.

Clinical effectiveness evidence

The clinical effectiveness evidence for midostaurin is from 2 single-arm non-randomised trials

3.3 The clinical evidence for midostaurin came from D2201 and A2213, 2 non-randomised, open-label, single-arm clinical trials. Both trials included people with the 3 subtypes of advanced systemic mastocytosis (see section 3.1). D2201 was an international trial, including 4 patients from the UK, and A2213 was a US study. The median overall survival (OS) for advanced systemic mastocytosis from D2201 (December 2014 data, n=89) was 26.8 months. The median OS was shortest for MCL

(9.4 months), followed by SM-AHN (20.7 months), then ASM (51.1 months). The results of a more recent data cut were similar (August 2017; results are confidential and cannot be reported here). Median OS in the overall population in A2213 (n=26) was 40 months. The committee noted that most people in D2201 had stopped treatment with midostaurin within 1 year, with 19% of patients still having treatment at 3 years. The committee concluded that because D2201 and A2213 are single-arm trials, they do not provide evidence of the relative effectiveness of midostaurin compared with current treatment options. But it acknowledged that doing a phase 3 trial for advanced systemic mastocytosis would be difficult.

Comparative effectiveness evidence

The comparative evidence for midostaurin is highly uncertain, but estimates from Reiter et al. (2017) are suitable for decision making

3.4 The company's evidence submission did not include any studies that directly compared midostaurin with treatments currently used in NHS practice. The main comparative effectiveness evidence was from 2 non-randomised studies, Reiter et al. (2017) and CEREMAST. Reiter et al. pooled midostaurin time-to-event data from the D2201 and A2213 trials and compared it with outcomes from German registry data for treatment without midostaurin. The CEREMAST study compared outcomes from a midostaurin compassionate use programme in France with outcomes from French registry data for treatment without midostaurin. The company's preferred analyses used results from Reiter et al. The committee noted that the study was presented at a conference, but was otherwise unpublished, meaning it had received less scrutiny than if it had been fully peer reviewed. The company explained that it was not aware of planned publications by the study investigators, but that it had identified very little comparative effectiveness evidence because advanced systemic mastocytosis is rare. It had determined Reiter et al. to be the best evidence available. The clinical expert explained that the registry used in

Reiter et al. remains the main source of data used internationally. The ERG agreed with the company's conclusion that Reiter et al. was the best available source of comparative effectiveness evidence. But it highlighted its limitations, which included its small sample size and limited information about what treatments were used and study recruitment. It also noted the risk of bias present in all non-randomised evidence. The ERG also advised that there are potential limitations to pooling data from the D2201 and A2213 trials, because they have different study protocols and median follow-up durations. In response to technical engagement, a clinical expert advised that the A2213 study is likely to be less generalisable to NHS clinical practice than D2201. The committee agreed that there is limited evidence for midostaurin because the condition is rare, so data from the 2 studies could be pooled for decision making. It agreed that Reiter et al. was more robust than the CEREMAST study. The committee noted ongoing data collection by the European Competence Network on Mastocytosis registry and considered whether it might provide more robust evidence on outcomes with current treatments. A patient expert advised that although the registry has data for approximately 500 people with advanced systemic mastocytosis, some of them might already be having treatment with midostaurin, and the frequency of follow up is unclear. The committee concluded that the quality of comparative effectiveness evidence was poor, but in the absence of more robust evidence it would consider outcomes from Reiter et al. in its decision making. It agreed that it would interpret the resulting estimates (see section 3.5) with caution.

The propensity score matched HR suggests midostaurin is more effective than current clinical management, but this is uncertain

3.5 The comparative OS of midostaurin was by far the most important clinical factor affecting its cost effectiveness. In its evidence submission, the company considered several OS hazard ratios (HRs), based on Reiter et al. (2017), as options to inform the comparative effectiveness of midostaurin. Following technical engagement, the company updated

some of the HR analyses using a more recent D2201 data cut (containing 1 extra year of data). The committee noted that the company's preferred HR was from a multivariable regression analysis using pooled D2201 and A2213 data for midostaurin (0.52, 95% confidence interval [CI] 0.32 to 0.84). This analysis attempted to account for potential imbalances in patient characteristics between the midostaurin clinical trials and the German registry data from Reiter et al. The committee was concerned that the company's preferred HR was similar to the HR that did not adjust for imbalances (0.50, 95% CI 0.33 to 0.76). This suggested that the regression analysis might not have fully captured important observed or unobserved differences between the datasets. The committee considered that the propensity score matching analysis might provide a more unbiased estimate of the HR (0.64, 95% CI 0.33 to 1.24). The ERG advised that the propensity score matching analysis meant reducing the sample size (to achieve 2 groups of 'matched' pairs of patients), and it may be preferable to retain the bigger sample size used by the multivariable regression analysis. It also advised that like the regression analysis, the matching analysis cannot adjust for any unobserved imbalances in patient characteristics. The committee noted that in the propensity score matched analysis the number of patients was substantially lower, which led to a wider CI but suggested that the unadjusted patient groups were not well matched. It considered that, on balance, it would prefer an unbiased estimate of the HR with a wider CI, rather than a potentially biased estimate of the HR with a narrower CI. The committee concluded that from the available HRs to inform comparative survival, the propensity score matched HR was the most robust estimate to inform the economic model and decision making. The committee also concluded that, based on its preferred HR, midostaurin does appear to be clinically effective compared with current clinical management, but the estimate remains uncertain.

Economic model

The company's economic model is broadly acceptable for decision making

3.6 The company presented a partitioned survival model with 4 mutually exclusive health states: 2 progression-free survival (PFS) states (with either sustained response or lack or loss of response), progressed disease and death. The model used a lifetime time horizon. People entered the model in 1 of the 2 PFS states depending on the disease's initial response to treatment. They could move from PFS (sustained response) to PFS (lack or loss of response), informed by duration of response data. The company fitted parametric curves to D2201 time-to-event data to estimate transition probabilities, and applied HRs from Reiter et al. (see section 3.5) to estimate outcomes for current clinical management. The ERG advised that the parametric curves for midostaurin had been selected appropriately and appeared to be reasonable. The committee concluded that company's economic model was broadly acceptable for decision making.

The model should use 1 health state with a single utility value for progression-free survival

3.7 The company's model partitioned PFS by response status (see section 3.6), to allow the utility value with progression-free disease to differ depending on response to treatment. The company stated that this was supported by clinical advice that quality of life is affected by treatment response. The ERG recognised that PFS may be different for people whose disease responded and those whose disease did not, based on the trial data. However, it had concerns about the reliability of the response rate and duration data used by the company to partition the progression-free health state. It considered that the data were not appropriate for this purpose. The ERG also advised that it is inconsistent to partition PFS by response status without similarly partitioning OS, because the trial data

also suggested that OS was affected by treatment response. In response to technical engagement, the company provided a revised analysis using a single utility value for the progression-free health state. The committee recognised the limitations of the data for partitioning PFS and the inconsistency in not partitioning OS. It agreed that partitioning OS would increase the model's reliance on uncertain response data. Therefore, the committee concluded that the model should have 1 PFS health state, with a single utility value from the company's revised analysis.

The utility estimates might not capture the full effect of midostaurin on quality of life

3.8 The committee noted that the utility values used in the model had been derived from the single-arm D2201 trial, so it had not seen quality of life evidence from people having current clinical management. It recalled that advanced systemic mastocytosis often has a major debilitating effect on a person's life (see section 3.1). The patient experts advised that the quality of life improvement after starting treatment with midostaurin was rapid and substantial. One patient expert explained that they had beneficial effects after 1 week of starting treatment, and up to 10 hours of normal life per day after 1 month of treatment. The clinical experts also reiterated the large improvement in quality of life with midostaurin. They advised that there is very little comparator quality of life data available because midostaurin is increasingly being used before other treatments in other countries. The committee considered that, although it had not seen quality of life evidence directly related to current clinical management, it is likely that the utility estimates used in the model did not capture all of the benefits of midostaurin that had been described by the patient and clinical experts. It recalled its earlier conclusion that the response data were too uncertain to implement response-based utility values (see section 3.7), which might have been a way to include the quality of life benefits of midostaurin. The committee concluded that the incremental quality-adjusted life years (QALYs) estimated by the model may be conservative for midostaurin, and that it would consider this in its decision making.

A 3-year treatment benefit is suitable for decision making, although this might be optimistic

3.9 The company's base-case model applied the comparative effectiveness HR for the duration of the model (38 years), which assumed the benefit of starting treatment with midostaurin lasts for a person's lifetime. The ERG considered that a lifetime treatment benefit was unlikely to be plausible, and that the progression and survival rates with midostaurin would instead become equal to other treatments over time. In response to technical engagement, the company presented alternative analyses where the HR became 1 (no treatment effect) after 3, 5 and 10 years. The clinical experts advised that the longer a person has midostaurin, the more sustained disease response is. But they noted that disease response is often lost because of associated haematological malignancy instead of mastocytosis itself. They also advised that while there is no known resistance to midostaurin, its effect dissipates rapidly after stopping treatment, even if doses are only missed for a few days. The committee considered whether it was appropriate to include a lifetime treatment benefit in the model. It recalled that most people did not continue to have midostaurin in the long term (see section 3.3). The committee considered that it was implausible to retain the Reiter et al. (2017) HR for people who were no longer having midostaurin. It also noted that it had not seen long-term, robust comparative effectiveness evidence, so the duration of treatment benefit is highly uncertain. The committee considered that a 3-year midostaurin benefit duration is likely to be optimistic for people who stop having treatment before 3 years. But it considered it potentially pessimistic for the minority of people who remain on treatment beyond 3 years, to an unknown extent. On balance, the committee concluded that it would consider a 3-year treatment benefit duration for midostaurin in its decision making, even though this was likely to be optimistic.

End of life

Midostaurin is considered to be 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. The committee considered whether midostaurin meets both end of life criteria for people with advanced systemic mastocytosis. For the life expectancy criterion, the committee noted that Reiter et al. (2017), which it had accepted as a source of comparative effectiveness evidence (see section 3.4), reported a median survival with current clinical management of 19.5 months. The committee agreed that life expectancy was clearly lower than 24 months for people with MCL, but that this is less clear for advanced systemic mastocytosis overall. Some sources of evidence reported median survival estimates above 24 months, but the company explained that these studies often included people with indolent systemic mastocytosis, which is much less severe and has a longer life expectancy than advanced systematic mastocytosis. For the life extension criterion, the committee noted that Reiter et al. reported a median survival benefit of 21.9 months for midostaurin compared with current clinical management. It also noted that the economic model predicted a mean survival benefit far higher than the 3 months stipulated by the life extension criterion. The patient and clinical experts advised that there is increasing clinical experience and evidence, albeit non-randomised, suggesting that midostaurin improves life expectancy considerably. Therefore, the committee concluded that midostaurin could be considered a life-extending treatment at the end of life.

Cost-effectiveness estimates

All cost-effectiveness estimates are higher than £100,000 per QALY gained

3.11 The committee noted that the company's base-case probabilistic estimate of cost effectiveness in the overall, advanced systemic mastocytosis population was above £100,000 per QALY gained (all estimates are confidential, so exact values cannot be reported here). This is substantially higher than what is normally considered to be a cost-effective use of NHS resources (£50,000 per QALY gained for a life-extending treatment at the end of life). This was also the case for a subgroup analysis including only people with SM-AHN or MCL, which are the 2 more severe subtypes. The committee recalled its preferred assumptions for decision making:

- Using the Reiter et al. (2017) propensity score matched OS HR (see sections 3.4 and 3.5).
- Using a single PFS health state, with a single utility value from the company's revised analysis (see section 3.7).
- Assuming the treatment benefit of midostaurin lasts for 3 years, after which its progression and survival rates become equal to the comparator (see section 3.9).

With the preferred assumptions, the cost-effectiveness estimates for the overall population and the more severe subgroup (SM-AHN or MCL) remained higher than £100,000 per QALY gained. The committee considered that the estimates were uncertain because of limitations in the clinical and comparative effectiveness evidence (see sections 3.4, 0 and 3.9). It recalled its conclusion that the incremental QALY estimates from the model might not capture all of the quality of life benefits associated with midostaurin compared with current treatment options (see section 3.8). However, it agreed that the size of benefit that might have been missed would not be large enough to

reduce the cost-effectiveness estimate to a level that NICE considers cost effective, nor would it offset the other uncertainties. Therefore, midostaurin could not be recommended for routine use in the NHS.

Cancer Drugs Fund

Midostaurin is not recommended for use in the Cancer Drugs Fund

3.12 Having concluded that midostaurin could not be recommended for routine use, the committee then considered if it could be recommended for treating advanced systemic mastocytosis 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). The committee noted that the key uncertainty was the lack of availability of comparative effectiveness evidence. The committee was not aware of any planned future midostaurin or comparator studies that might resolve this uncertainty. Also, it understood that data to inform comparative effectiveness could not be collected as part of the Cancer Drugs Fund. The committee concluded that midostaurin is not recommended for use in the Cancer Drugs Fund.

Innovation

Midostaurin is an innovative treatment for advanced systemic mastocytosis

3.13 The company considered midostaurin to be innovative because there are currently no other licensed or targeted disease-modifying treatment options for people with advanced systemic mastocytosis. The patient and clinical experts emphasised the importance of alleviating debilitating symptoms and improving health-related quality of life, and the potential benefit from midostaurin in achieving this (see section 3.1). It recalled that the utility values used in the economic model might not capture all quality of life benefits associated with midostaurin, because there were no quality of life data from people having current clinical management (see section

3.8). However, it had taken this potential uncertainty into account in its decision making (see section 3.11). It concluded that while midostaurin may be innovative, this does not change the cost-effectiveness conclusion because the estimates are substantially higher than £50,000 per QALY gained.

Equalities considerations

There are no equalities issues relevant to the recommendation

3.14 No equalities issues were raised during scoping and technical engagement. No potential equality issues were identified in the company submission. The committee concluded that there were no equalities issues relevant to the recommendation.

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
November 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.

Zain Hussain and Verena Wolfram
Technical leads

Jamie Elvidge
Technical adviser

Gavin Kenny
Project manager

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