National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Midostaurin for untreated acute myeloid leukaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Leukaemia CARE	Leukaemia CARE feels it appropriate to refer this topic to NICE appraisal.	Comment noted. No action required.
	Novartis Pharmaceuticals	Yes.	Comment noted. No action required.
Timing Issues	Leukaemia CARE	Acute myeloid leukaemia (AML) makes up about 33% of all leukaemia cases in the UK and is fatal if not treated. Prognosis following an AML diagnosis is poor, particularly in older adults. On average, 27% of those diagnosed will survive for five years or more after they have received treatment. This drops to just 5% survival for patients who over the age of 65. Because it is heterogeneous, AML is a disease that is unlikely to respond in a consistent pattern to non-targeted therapy. The existing cytarabine based regimens used to treat AML demonstrate limited efficacy. Patients that present the FLT3 mutation are associated with a particularly poor prognosis and there are limited treatment options for AML that specifically target the mutation. As such, there is an urgent need for new, effective treatment	Comment noted. No action required.

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		options that specifically target this mutation if patient outcomes are to be improved.	
	Novartis Pharmaceuticals	There is currently no approved FLT3 specific treatment in the NHS. Patients diagnosed with a FLT3 mutation have a poorer prognosis than those without the mutation. Median survival of FLT3 mutant AML after first relapse (median age of 55), has been reported to be <5 months (Ravandi et al, 2010 and Levis et al, 2011) FLT3 patients also have shorter remission durations (e.g. decreased disease-free survival [DFS] in patients with a complete response) (National Comprehensive Cancer Network, 2016). This presents a high unmet need for an effective treatment option for people with mutation-positive AML. With a maximum treatment duration of 18 months (1-2 induction cycles, 4 consolidation cycles and 12 cycles of maintenance) and with average treatment duration of 6 months, patients demonstrated up to 60 months of remission with the inclusion of midostaurin. This data is available from the CSR. Note in particular that NCCN guidelines recommend FLT3-ITD patients to be considered and enrolled in clinical trials when this option exists (National Comprehensive Cancer Network, 2016). <u>References:</u>	Comment noted. No action required.

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		Ravandi F, Kantarjian H, Faderl S, et al. Outcome of patients with FLT3-mutated acute myeloid leukemia in first relapse. Leuk Res. 2010;34(6):752–756. Levis M, Ravandi F, Wang ES, et al. Results from a randomized trial of salvage chemotherapy followed by lestaurtinib for patients with FLT3 mutant AML in first relapse. Blood. 2011;117(12):3294–3301. National Comprehensive Cancer Network 2016. NCCN Clinical Practice Guidelines in Oncology for Acute Myeloid Leukemia.	

Comment 2: the draft scope

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Background information	Leukaemia CARE	As the draft scope indicates, AML is a rapidly developing and aggressive disease that has a poor prognosis. As such, reference should be made to the emotional impact the disease has on patients, their carers and family. Feelings of shock, fear, anger, denial and isolation are usual following a cancer diagnosis and can have a profound impact on the emotional and physical wellbeing of both the patient, and their loved ones.	Comment noted. The background section of the scope is intended to provide a broad overview of the disease and its associated management. No action required.
	Novartis Pharmaceuticals	No comments.	No action required.

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The technology/ intervention	Novartis Pharmaceuticals	The Novartis brand name for midostaurin is Rydapt.	Comment noted. The scope has been updated with this brand name.
Population	Novartis Pharmaceuticals	Please can the population be amended from 'People with untreated, FLT3 mutation-positive acute myeloid leukaemia' to 'Adult patients with untreated FLT3 mutation-positive acute myeloid leukaemia' This is in keeping with the Azacitidine NICE scope. Please can the population be amended to additionally add patients 'who are fit for intensive chemotherapy'.	Comment noted. The population section of the scope has been kept broad. Any final recommendation for the drug will be within its marketing authorisation. No action required.
Comparators	Leukaemia CARE	As the scope document alludes to, there are few options that can be considered comparative to midostaurin for patients in this setting. Existing appropriate comparators are the induction and maintenance therapies currently used in clinical practice.	Comment noted. No action required.
	Novartis Pharmaceuticals	Standard treatment currently used in the NHS is 10+3 cytarabine/daunorubicin induction chemotherapy, followed by high dose cytarabine consolidation. This can be described as standard of care. Novartis will be planning a within trial cost-effectiveness analysis which will include the standard treatment of cytarabine/daunorubicin induction chemotherapy, followed by high dose cytarabine consolidation as a comparator.	Comment noted. The company is expected to justify the choice of treatments representing standard of care in its submission to NICE.

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		Azacitidine is not recommended in the UK for patients with AML with more than 30% bone marrow blasts in adults of 65 years or older who are not eligible for haematopoietic stem cell transplant. As midostaurin is suitable for patients who are receiving and are fit for intensive chemotherapy, Novartis agrees with the exclusion of azacitidine from the list of comparators.	
Outcomes	Novartis Pharmaceuticals	Novartis would like clarification of the outcomes to align with the midostaurin clinical trial programme as well as the outcomes listed in the scope for azacitidine. The following are suggested: - The term 'event-free survival' could be changed to progression-free survival for consistency with other relevant NICE TA scope outcomes (e.g. azacitidine – TA399) - 'Time to disease progression' could be included for consistency with other relevant NICE TA scope outcomes - Complete remission - Time to relapse - Overall survival	Comment noted. Additional specific outcomes may be considered as part of the full appraisal.
Economic analysis	Novartis Pharmaceuticals	Time Horizon: Lifetime should be the base case. Other option: 5 (or trial) years, 10 years. Perspective: NHS Discounting: 3.5% Model structure: Dynamic Markov model. Patient level data will be used for transitions to CR, OS, and DFS/EFS. Stem cell transplantation will also be included as a health state.	Comment noted. No action required.

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		Extrapolation: For the partitions, several extrapolation options will be provided (PH, individual models, piecewise). For the other health states, an option will be provided to use the clinical trial data or to input a transition rate. Utility: The team is running a TTO vignette study with the health states that will be used in the model.	
Equality and Diversity	Novartis Pharmaceuticals	No comments.	No action required.
Other considerations	Novartis Pharmaceuticals	No comments.	No action required.
Innovation	Leukaemia CARE	In a disease area where there is a poor prognosis, there has been little advancement in treatment in the last few decades. Patients in this setting (with the FLT3 mutation) are more likely to relapse after receiving this treatment and are considered high risk AML patients. In a setting where initial treatment is unlikely to be successful due to this particular mutation, midostaurin represents an effective, tolerable treatment option that offers a deepened response and survival benefit (when used in combination with induction therapy). Furthermore, it has shown potential to bridge some patients to transplant (the only curative treatment option for AML). For patients with FLT3 mutations, transplant would currently be an unlikely treatment option, as the desired response needed for a transplant is difficult to reach using existing treatment options. As such, midostaurin can be considered an innovative treatment option.	Comment noted. The innovative nature of midostaurin will be taken into account in the committee's discussion. No action required.

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	Novartis Pharmaceuticals	With a maximum treatment duration of 18 months (1-2 induction cycles, 4 consolidation cycles and 12 cycles of maintenance) and with average treatment duration of 6 months, patients demonstrated up to 60 months of remission with the inclusion of midostaurin. This data is available from the CSR.	Comment noted. The company is encouraged to describe the innovative nature of midostaurin in its submission to NICE. No action required.
Questions for consultation	Novartis Pharmaceuticals	***Have all relevant comparators for midostaurin been included in the scope?*** Yes. ***Are there specific chemotherapy regimens that are considered to represent established clinical management in the NHS for untreated, FLT3 mutation-positive acute myeloid leukaemia?*** Yes. Standard treatment currently used in the NHS is 10+3 cytarabine/daunorubicin induction chemotherapy, followed by high dose cytarabine consolidation chemotherapy. ***What is the role of stem cell transplant in the management of untreated, FLT3 mutation-positive acute myeloid leukaemia?*** The role of stem cell transplant (SCT) is to provide a long-term cure in those patients fit enough to receive SCT and in whom have achieved remission after standard high dose chemotherapy.	Comment noted. The company is expected to justify the choice of treatments representing standard of care in its submission to NICE. If the evidence allows, a scenario analysis will be considered where stem cell transplant is included as a subsequent treatment for people who are fit enough to undergo the

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		Is the FLT3 mutation routinely tested for in clinical practice? Yes, 83% of AML patients undergo FLT-3 mutation testing in clinical practice (Kantar Health Market Research, 2015). Testing for FLT3 mutation is currently purely prognostic in that a positive test informs the clinician that the patient will quickly relapse after standard chemotherapy compared to the full AML population. Midostaurin will give clinicians an opportunity to proactively treat FLT3-mutated patients in order to improve their outcomes towards those of the total AML population. Further, a proportion of AML patients have mutations in the FLT3 gene associated with worse prognostic implications. Therefore, all patients with a diagnosis of AML receive FLT3 mutation testing as part of the standard prognostic test battery post-diagnosis and pre-treatment planning. ***Are the outcomes listed appropriate?*** Novartis would like clarification of the outcomes to align with the midostaurin clinical trial programme as well as the outcomes listed in the scope for azacitidine. The following are suggested:	procedure and whose disease remitted after standard high-dose chemotherapy with or without midostaurin. The economic modelling should include the costs associated with diagnostic testing for FLT3 mutation in people with acute myeloid leukaemia who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals. Additional specific outcomes may be considered as part of the full appraisal.

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		- The term 'event-free survival' could be changed to progression-free survival for consistency with other relevant NICE TA scope outcomes (e.g. azacitidine – TA399) - 'Time to disease progression' could be included for consistency with other relevant NICE TA scope outcomes - Complete remission - Time to relapse - Overall survival ***Are there any subgroups of people in whom midostaurin is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** The benefit of midostaurin is observed in all patients with FLT3 mutation-positive AML. (Stone, ASH, 2015). ***Where do you consider midostaurin will fit into the existing NICE pathway, Blood and bone marrow cancers?*** Midostaurin should be considered as a first-line combination treatment with standard induction and consolidation chemotherapy for adults with FLT3 mutation-positive AML. Midostaurin should be considered as a single agent for maintenance therapy. ***NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know***	Thank you for your responses.

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		if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which midostaurin will be licensed;*** • ***could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*** • ***could have any adverse impact on people with a particular disability or disabilities.*** ***Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*** No comments. ***Do you consider midostaurin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?*** No comments. ***Do you consider that the use of midostaurin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?***	

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		No comments. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)	