National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy

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
Appropriateness	Bristol Myers Squibb Pharmaceuticals	Yes, this topic is appropriate to refer to NICE for appraisal.	Thank you for your comment. No action required.
	Jazz Pharmaceuticals	No comment	No action required.
	Leukaemia Care	Yes. There is a need to increase survival in AML.	Thank you for your comment. No action required.
Wording	Bristol Myers Squibb Pharmaceuticals	The licensed indication for oral azacitidine in UK (Great Britain) is as follows: ***"…is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT)"***	Thank you for your comment. The remit has been kept brief. The population section has been updated to reflect the marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
		Therefore, BMS suggest including the following elements from the above indication within the remit: - *Induction therapy +/- consolidation therapy* - *Patients in CR/CRi who are not candidates for, or choose not to proceed to, HSCT*	
	Jazz Pharmaceuticals	No comment	No action required.
Timing Issues	Bristol Myers Squibb Pharmaceuticals	Given the lack of treatment options for maintenance therapy in patients with AML, there is a high unmet need for an effective standalone treatment option in the NHS	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. For more information please see https://www.nice.org.uk/guidance/proposed/gid-ta10775
	Jazz Pharmaceuticals	No comment	No action required.
	Leukaemia Care	Survival is poor for AML, especially with increasing patient age. The need for new treatments with the potential to extend survival is high.	Thank you for your comment. NICE aims to

Section	Consultee/ Commentator	Comments [sic]	Action
			provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. For more information please see https://www.nice.org.uk/guidance/proposed/gid-ta10775
Additional comments on the draft remit	Bristol Myers Squibb Pharmaceuticals	N/A	No action required.
	Jazz Pharmaceuticals	No comment	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bristol Myers Squibb Pharmaceuticals	The remission rate quoted in the background information is 'around 66%'. For further context, the European LeukemiaNet (ELN) 2017 recommendations cite a complete remission being achieved in[1]: - 60% to 80% of younger adults - 40% to 60% of older adults	Thank you for your comment. The background section of the scope has been updated to state that up

Section	Consultee/ Commentator	Comments [sic]	Action
		with intensive induction therapy. It also important to also note that even after achieving remission, relapse rates remain high and the 5-year overall survival rates are low, particularly for patients with adverse risk factors [2]. The description of maintenance therapy is accurate; however, we would also note that maintenance is not currently considered standard practice in AML treatment according to ELN 2017 recommendations[1]. A notable exception exists in the UK for a subgroup of patients that may be eligible for midostaurin, a chemotherapeutic agent indicated for patients with FLT3-mutation-positive AML. The use of this agent in maintenance is, however, fundamentally linked to both the specific mutation, and the induction and consolidation therapies administered to the patient[3]. BMS suggests adding that the decision for transplantation is based on multiple factors. The intended benefit - a reduction in relapse risk, is weighed-up against the risk of non-relapse mortality. The risk stratification of the AML, response to chemotherapy, patient fitness, donor source and patient choice are all important considerations[4].	to 80% of younger adults and up to 60% of older adults achieve complete remission and that outcomes are poor for people with adverse risk factors. The scope has been updated to reflect the reasons why stem cell transplantation may not be appropriate.
	Jazz Pharmaceuticals	No comment	No action required.
The technology/ intervention	Bristol Myers Squibb Pharmaceuticals	Please include that ***Oral azacitidine received notification of marketing authorisation from the MHRA on 1st July 2021*** for the following indication: *"..maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including*	Thank you for your comment. The scope has been updated to reflect that oral azacitidine received a marketing authorisation

Section	Consultee/ Commentator	Comments [sic]	Action
		those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT)" Please include some more detail relating to the mechanism of action; see below for suggested wording taken from the SmPC: ***"Azacitidine is a DNA methyltransferase inhibitor and epigenetic modifier. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates. Incorporation of azacitidine into the DNA of AML cells, modified epigenetic pathways through the inhibition of DNA methyltransferases, and reduction of DNA methylation. This led to alteration of gene expression, including re-expression of genes regulating tumour suppression, immune pathways, cell cycle, and cell differentiation. Incorporation of azacitidine into the RNA of AML cells, inhibited RNA methyltransferase, reduced RNA methylation, decreased RNA stability, and decreased protein synthesis"***	in the UK. The technology section has been updated to include additional details about oral azacitidine.
	Jazz Pharmaceuticals	No comment	No action required.
Population	Bristol Myers Squibb Pharmaceuticals	In line with the licensed indication please include: "…who are not eligible for**, including those who choose not to proceed to,** hematopoietic stem cell transplantation (HSCT)"	Thank you for your comment. The scope has been updated with the proposed addition.
	Jazz Pharmaceuticals	Patients on liposomal cytarabine daunorubicin, a population who were not included in the clinical trial, are they eligible for Onureg maintenance?	Thank you for your comment. The committee will consider the most appropriate population based on evidence presented to it

Section	Consultee/ Commentator	Comments [sic]	Action
			when making its recommendation for oral azacitidine.
	Leukaemia Care	The population is defined accurately.	Thank you for your comment. No action required.
Comparators	Bristol Myers Squibb Pharmaceuticals	BMS consider the relevant comparator for this appraisal to be 'established clinical management without oral azacitidine'. Maintenance therapy is not a standard AML treatment, however, most patients who are in CR/CRi and are not proceeding for a transplant undergo a 'watch-and-wait' strategy. This was reflected in the phase 3 QUAZAR study, where oral azacitidine was compared to placebo. Both treatment groups were also permitted to receive best standard of care [6]. We would therefore consider 'watch and wait' with supportive care to be the 'established clinical management without oral azacitidine'. BMS consider supportive care to be symptom and disease management without active therapy. BMS does not consider that midostaurin, indicated for patients with FLT-3-positive AML, is a relevant comparator to oral azacitidine. BMS sees the small overlap in clinical utilisation to be in FLT3-positive patients who have achieved CR/CRi after successfully receiving induction therapy that includes midostaurin. Those proceeding to maintenance therapy, and not eligible for, or choose not to proceed to HSCT would then have the choice to either receive midostaurin or oral azacitadine. Given the treating haematologist has selected induction therapy with midostaurin, BMS believes it to be clinically implausible that midostaurin would be discontinued following CR/CRi and the patient to be started on oral azacitadine maintenance therapy.	Thank you for your comment. The scope aims to be inclusive, so comparators are included even if only applicable to a small number of people. The committee can discuss the most appropriate comparators during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		The licence and NICE recommendation[3] both couple the use of midostaurin as maintenance therapy with its combination in induction and consolidation regimens for eligible patients. This precludes it from being an option as an independent maintenance therapy, and only reflects a maintenance option for a small subgroup of patients. Additionally, as patients in the midostaurin Phase 3 trial were randomised prior to induction rather than at the start of maintenance therapy, the midostaurin trial design does not allow for a direct comparison of outcomes in the maintenance period alone. Therefore, given BMS view of clinical implausibility, we propose removing midostaurin as a comparator.	
	Jazz Pharmaceuticals	Another comparison could be parenteral azacytidine e.g. subcutaneous comparison with oral as maintenance treatment.	Thank you for your comment. The comparators have been updated to reflect that some people may have subcutaneous azacitidine. The committee can decide the most appropriate comparators based on evidence presented to it.
	Leukaemia Care	There are no standard treatments for those who aren't already having midostaurin since they were newly diagnosed.	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Outcomes	Bristol Myers Squibb Pharmaceuticals	The proposed outcome measures capture the most important health outcomes of oral azacitidine	Thank you for your comment. No action required.
	Jazz Pharmaceuticals	No comment	No action required.
Economic analysis	Bristol Myers Squibb Pharmaceuticals	The proposed approach and wording are considered appropriate[5]. The lifetime horizon will be appropriate in the base case analysis.	Thank you for your comment. No action required.
	Jazz Pharmaceuticals	Cost effectiveness comparison with subcutaneous azacytidine as maintenance.	Thank you for your comment. The scope has been updated to reflect that some people may have subcutaneous azacitidine. The committee can decide the most appropriate comparisons based on evidence presented to it.
Equality	Bristol Myers Squibb Pharmaceuticals	No comment	No action required.
	Jazz Pharmaceuticals	No comment	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	Bristol Myers Squibb Pharmaceuticals	No comment	No action required.
	Jazz Pharmaceuticals	Cost effectiveness comparison with subcutaneous azacytidine as maintenance clinical comparison	Thank you for your comment. The scope has been updated to reflect that some people may have subcutaneous azacitidine. The committee can decide the most appropriate comparisons based on evidence presented to it.
Innovation	Bristol Myers Squibb Pharmaceuticals	Oral azacitidine was specifically developed for use as a maintenance therapy for patients who are in remission. The pharmacokinetic profile, combined with the dosing regimen, provides the opportunity to deliver azacitidine at a low systemic dose over a prolonged period. The oral route of administration may reduce the treatment burden of patients, with the potential to support persistence and compliance on treatment. Oral azacitidine has been investigated in the company sponsored phase 3 trial (QUAZAR), which demonstrated an increase in overall survival (primary endpoint) as compared to placebo. The QUAZAR trial will form the core data supporting this submission [6]. We expect that the health-related benefits	Thank you for your comment. The innovative nature of the technology will be considered by the committee based on evidence presented to it. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		associated with the use of this technology will be captured in the QALY calculation. Currently, there exists an unmet need for a standalone maintenance therapy for AML, as Midostaurin is the only treatment option currently recommended by NICE as a maintenance therapy [3,] which is indicated for the subgroup of FLT3 mutation positive patients. Additionally, it's licence and NICE recommendation couple its use in maintenance with induction and consolidation treatments, that preclude it being an option as an independent maintenance therapy. Many patients therefore do not have a treatment option available to them as a maintenance therapy. As AML maintenance is not currently an established standard of care for patients in remission, we believe that oral azacitidine would satisfy an unmet need for those patients in CR/CRi that are not candidates for, or who choose not to proceed with hematopoietic stem cell transplantation.	
	Jazz Pharmaceuticals	No comment	No action required.
	Leukaemia Care	This treatment has the potential to prevent relapse. A survey of acute leukaemia patients conducted by the Acute Leukaemia Advocates Network showed that those who relapse are among the patients who experience the worst quality of life. The impact of preventing relapse is unlikely to have been captured via the QALY calculations.	Thank you for your comment. The innovative nature of the technology will be considered by the committee based on evidence presented to it. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Questions for consultation	Bristol Myers Squibb Pharmaceuticals	***How should established clinical management without oral azacitidine be defined?*** For patients with AML in complete remission, who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT) established clinical management without oral azacitidine is 'watch and wait,' with best supportive care. ***Are the outcomes listed appropriate?*** The outcomes listed are appropriate ***Are there any subgroups of people in whom oral azacitidine is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** Based on the results of QUAZAR, oral azacitadine is expected to be an effective treatment for patients within the marketing authorisation (i.e. AML patients who achieved CR or CRi following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, HSCT) ***Where do you consider oral azacitidine will fit into the existing NICE pathway for blood and bone marrow cancers?*** Oral azacitidine should be considered as single agent for maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT)	
	Jazz Pharmaceuticals	No comment	No action required.
Additional comments on the draft scope	Bristol Myers Squibb Pharmaceuticals	N/A	No action required.
	Jazz Pharmaceuticals	No comment	No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Novartis Pharmaceuticals UK