National Institute for Health and Care Excellence

Single Technology Evaluation

Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia [ID1627]
Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Company, Brancaster Pharma Ltd	Acute myeloid leukaemia (AML) is an orphan disease with approximately 2,900 people diagnosed each year in the UK. Within the expected indication for histamine dihydrochloride and interleukin-2 (HDC/IL-2) this includes adult AML patients who have undergone intensive induction and consolidation treatment, are in first complete remission (CR1), are not considered suitable for allogeneic stem cell transplant and are 60 years old or less. From post-hoc analyses by Nilsson et al (2020), AML patients who derive the most benefit in terms of relapse prevention and overall survival are those in CR1, with a normal karyotype and less than 60 years old. Since there are no data from the pivotal phase 3 study by Brune et al (2006) on the genetic profiles of the patients, the data supporting which patient genetic subtypes are likely to benefit most is limited. NICE has already approved maintenance treatments for those AML patients with FLT3 mutations (TA523) and FLT3-ITD mutations (TA1013) and hence	Comment noted. Topic is currently scheduled as STA. NICE will follow standard process around routing

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		these patients may be excluded from treatment with HDC/IL-2 without further data. Considering all these different factors the treatable population for HDC/IL-2 is likely to be less than 100 patients per annum in England and with the proposed reasonable price will have a minimal budget impact. We therefore question the validity of going through the full NICE single technology appraisal process for such a small population of eligible patients. Other routes such as highly specialised technology evaluation or funding through the cancer drugs fund may be more appropriate.	
Wording	Company, Brancaster Pharma Ltd	Alternative wording: 'To appraise the clinical and cost effectiveness of histamine dihydrochloride with interleukin-2 immunotherapy within its marketing authorisation for maintenance treatment of acute myeloid leukaemia and in patients not considered suitable for allogeneic stem cell transplant'	Comment noted. NICE will aim to keep population as wide and inclusive as possible in line with anticipated marketing authorisation wording.
Timing Issues	Company, Brancaster Pharma Ltd	We anticipate that the marketing authorisation for HDC/IL-2 will be granted in [redacted] and hence would expect that NICE guidance will be published by the end of January 2026. Around 50% of AML patients under the age of 60 in CR1 relapse so there is still an unmet need to improve outcomes in this patient population. For this reason, the evaluation for HDC/IL-2 should be expedited.	Comment noted. NICE has scheduled this topic into the programme and aim to publish final guidance as soon as possible after receiving marketing authorisation.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Company, Brancaster Pharma Ltd	Further details about the unmet need for AML patients and the importance of relapse prevention should be included in the background information section such as: • Relapse is one of the main causes of death in patients with AML who achieve complete remission (CR) of the disease after chemotherapy • Approximately 50% of patients who reach first remission after induction and consolidation treatment will relapse within 12 months • Relapse prevention at CR1 is important as the CR rate after relapse with new cycles of chemotherapy is low, and whenever a second CR is achieved, the duration of the second relapse-free interval is usually considerably shorter than that of the first period, with a median survival after relapse of approximately 3-9 months (Breems et al., 2005; Klco et al., 2015; Ravandi et al., 2010; Walter et al., 2010). • The 5-year overall survival (OS) rate in relatively young AML patients, aged 50-65 years, is 31.4% (SEER 2022). • There is a clear unmet need for further treatment strategies to prevent relapse in patients with AML.	Comment noted. Unmet need and importance of relapse prevention added to scope. Further details are not usually included at this stage but details on the relapse with this technology can be included in the submission.
Population	Company, Brancaster Pharma Ltd	We believe the population should be more specifically defined as follows: People who have undergone intensive therapy with induction and consolidation treatment, who are not considered suitable for allogeneic stem cell transplant, who are in first remission and 60 years old or younger.	NICE will aim to keep population as wide and inclusive as possible in line with anticipated marketing authorisation wording.
Subgroups	Company, Brancaster Pharma Ltd	Post-hoc analyses of the original phase 3 patient population (Nilsson et al 2020) indicates that those who are not suitable for allogeneic stem cell transplant, have a normal karyotype, are in CR1 and are less than 60 years old showed significantly improved relapse prevention and overall survival.	NICE will aim to keep population as wide and inclusive as possible in line with anticipated

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		Consequently, the subgroup should include AML patients who are not suitable for allogeneic stem cell transplant, have normal karyotype, are in CR1 and are less than 60 years old. Due to the time at which patients were recruited to the phase 3 study (Brune et al 2006) there were no genetic profiling data collected and hence there is limited available comparative data to indicate which genetic subtypes within the normal karyotype subgroup are likely to respond best to HDC/IL-2 immunotherapy. There are already NICE approved maintenance treatments for AML patients with FLT3 mutations (TA523) and FLT3-ITD mutations (TA1013) and hence without further clinical data we would not consider HDC/IL-2 to be an alternative treatment option for those patients. Consequently, the normal karyotype subgroup for HDC/IL-2 should exclude patients with FLT3 and FLT3-ITD mutations where there is evidence of clinical and cost-effectiveness for other products.	marketing authorisation wording.
Comparators	Company, Brancaster Pharma Ltd	The comparator used in the pivotal phase 3 Brune et al study (2006) was best supportive care and hence we believe that this should be considered as the only comparator within this appraisal. The indication for HDC/IL-2 immunotherapy states that the efficacy is strongest for those patients who are 60 years old or less. The clinical evidence supporting the patients who are 60 years old or less should therefore be evaluated within the context of this appraisal for HDC/IL-2. The QUAZAR study evaluating the efficacy of oral azacitidine as a maintenance therapy in AML constituted the main evidence used in the NICE single technology appraisal (TA827) which approved the treatment for use on the NHS. The patient eligibility criteria for the QUAZAR study excluded those who were younger than 55 years and hence composes a different population of patients with a different prognosis as compared with the data supporting HDC/IL-2. For this reason, oral azacitidine is not a logical comparator. We believe that there is insufficient evidence from the QUAZAR study of patients	Comment noted. The list of comparators is intended to be broad. The appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical and cost-effectiveness

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		who had received oral azacitidine who are 60 years or less to make a valid comparison with HDC/IL-2. NICE has previously approved midostaurin as a maintenance treatment for AML patients with FLT3 mutations (TA523) and quizartinib for AML patients with FLT3-ITD mutations (TA1013). There is little evidence to support the use of HDC/IL-2 in these genetic subtypes where there are already effective and approved treatments. As a result, midostaurin and quizartinib should not be considered comparators for this appraisal. Using a similar rationale sorafenib should also not be considered a comparator. We are unaware of any comparative data or otherwise indicating that cytarabine alone or in combination with other antineoplastic agents has shown benefit as a maintenance treatment in patients with AML after induction and consolidation treatment. For this reason, cytarabine should not be considered a valid comparator in this appraisal.	evidence and current clinical practice. No action required.
Outcomes	Company, Brancaster Pharma Ltd	We propose that 'progression-free survival' might further be defined as 'leukaemia-free survival' or 'relapse-free survival'. In addition, for the evaluation of AML we considered whether 'remission rate' might be more appropriate than 'response rate'.	Comments noted. NICE has maintained progression free survival because it aligns with other scopes in this topic area. Outcomes are not an exhaustive list and if company feel it would be beneficial other outcomes can be included in their submission.

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Equality	Company, Brancaster Pharma Ltd	The licensed indication for HDC/IL-2 will state 'The efficacy of Histamine dihydrochloride 0.5 mg/0.5 mL solution for injection has not been fully demonstrated in patients older than age 60.' This clearly indicates that the evidence for the therapy is best supported in patients who are 60 years old or less and hence may exclude those who are older than 60 years.	Comments noted. NICE will appraise within the marketing authorisation and cannot make a recommendation outside the marketing authorisation, but will consider all evidence available
Other considerations	Company, Brancaster Pharma Ltd	We believe it is important that patients have the choice for effective and well tolerated alternative treatment options and would like to ensure that this is made clear in the scope and taken into consideration during the rest of the appraisal process. AML patients who are in CR1 after induction and consolidation treatment may have a choice of treatment options to prevent relapse and HDC/IL-2 is an effective, well-tolerated immunotherapy option with a finite treatment schedule. Patients should be made aware of this effective and well tolerated option to prevent relapse so that they can make an informed choice about which therapy suits them best. The published data for HDC/IL-2 in the above cohort of patients highlights that this treatment offers a therapy with a good evidence base for those in the cohort who are less than 60 years old, providing those patients with an important improvement in therapy choice.	Comments noted. No action required.
Questions for consultation	Company, Brancaster Pharma Ltd	Which treatments are considered to be established clinical practice in the NHS as maintenance therapy for people with acute myeloid leukaemia? No comment – covered above.	Comments noted. No action required.

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		Have all relevant comparators for histamine dihydrochloride with interleukin-2 for people with acute myeloid leukaemia who are in remission been included in the scope? Yes – covered above. Are the outcomes listed appropriate? Yes –covered above Are there any subgroups of people in whom histamine dihydrochloride with interleukin-2 is expected to be more clinically effective and cost effective or other groups that should be examined separately? Yes, the subgroup of AML patients in whom HDC/IL-2 has shown additional efficacy are those who are in CR1 after induction and consolidation treatment, have a normal karyotype and are less than 60 years old. Where do you consider histamine dihydrochloride with interleukin-2 will fit into the existing care pathway for acute myeloid leukemia? Based on the evidence we believe that HDC/IL-2 immunotherapy will be best suited as a maintenance treatment for adult AML patients who are in first remission (CR1) after induction and consolidation treatment, are not considered suitable for allogeneic stem cell transplant, have a normal karyotype, are 60 years or less and do not have a FLT3 or FLT3-ITD mutation. Do you consider that the use of histamine dihydrochloride with interleukin-2 can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? No data are available on the treatments that patients within the phase 3 study (Brune et al 2006) received after relapse. It is however intuitive that if you are reducing the number of patients relapsing with a treatment then you are likely	

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		to be reducing the number of patients offered allogeneic stem cell transplants or other treatments at relapse. It is reasonable to assume that an additional health-related benefit would be a reduction in the need for allogeneic stem cell transplant or other treatments at the time relapse. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. No data are available on this from the phase 3 study (Brune et al 2006) however the data from the sub-group analysis by Nilsson et al (2020) could be used to make estimations on what impact this could have on the reduction in the number of patients requiring transplants or other treatments at relapse. 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 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 histamine dihydrochloride with interleukin-2 is 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. No comment – covered above.	

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Additional comments on the draft scope	Company, Brancaster Pharma Ltd	No	

Comment 3 provisional stakeholders list

Section	Consultee/ Commentator	Comments [sic]	Action
	Company, Brancaster Pharma Ltd	No comment. We believe the provisional stakeholder list to be complete and appropriate.	No action required.

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

Jazz Pharma (comparator)