National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804]

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
Appropriateness	NHS England	Yes	Thank you for your comment. No action required.
	Pfizer Ltd	No comments.	Thank you for your comment. No action required.
	Leukaemia CARE	Leukaemia CARE feels that it is appropriate for NICE to scope and appraise blinatumomab for the treatment of Philadelphia chromosome negative relapsed or refractory B-precursor ALL. Current treatment options for this patient population are limited and as such an increase in available therapies would only improve patient outcomes.	Thank you for your comment. This topic has now been referred to NICE by the Department of Health.
	National Cancer Research Institute (NCRI)	Yes. Our experts believe that it represents a major step forward in ALL therapy.	Thank you for your comment. No action

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	- Royal College of Physicians (RCP) - Association of Cancer Physicians (ACP)		required.
	Amgen	It would.	Thank you for your comment. No action required.
Wording	NHS England	Yes	Comment noted. No action required.
	Pfizer Ltd	Pfizer suggests clarification on the wording of the remit to note that the marketing authorisation is for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).	Comment noted. This topic has now been referred to NICE by the Department of Health. Please see the final wording of the remit in the scope.
	NCRI-RCP-ACP	Consideration should be given to include Ph positive ALL. There are data in Ph positive ALL and it is felt likely that the company will extend their licence.	Comment noted. Blinatumomab does not currently have a marketing authorisation in the UK for Philadelphia-chromosome-positive

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			relapsed or refractory B-cell ALL. NICE can only appraise a technology within its marketing authorisation.
	Amgen	The wording of the remit is accurate as the marketing authorisation for blinatumomab is; For the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)	Comment noted. No action required.
Timing Issues	NHS England	There is significant interest in access to this drug in this indication.	Comment noted. No action required.
	Pfizer Ltd	No comments.	Comment noted. No action required.
	Leukaemia CARE	Leukaemia CARE would agree that there is urgency to this appraisal due to the currently limited number of treatment options for relapsed or refractory ALL patients in this setting. There is currently no NICE treatment pathway for patients with ALL. Existing treatment for newly diagnosed ALL ranges from toxic chemotherapies to stem cell transplantation (if a match is found), with limited follow up options should these fail. As such, there is a distinct unmet need for additional, effective second line treatments in this already hard-to-treat haematological area.	Comment noted. No action required.
	NCRI-RCP-ACP	Urgent as there are no good alternative therapies for the group of patients	Comment noted. No action required. This

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		with relapsed / Refractory ALL. The life expectancy currently is 2-3 months. This new agent is available widely and used widely in many EU countries and in North America. British patients are well aware of its availability. UK played a major role in the trials to develop this agent so there is expertise with the agent within the UK.	topic has now been referred to NICE by the Department of Health.
Additional comments on the draft remit	NHS England	N/A	Comment noted. No action required.
	Pfizer Ltd	No comments.	Comment noted. No action required.
	Amgen	Given the unmet medical need that RR-ALL represents and the fact that blinatumomab was licensed in November 2015, it is urgent that this appraisal is conducted.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	NHS England	This is felt to be accurate and complete	Comment noted. No action required.
	Pfizer Ltd	Pfizer suggests that the final paragraph is amended to note relative proportions of patients treated with the comparators.	Comment noted. The background section of the scope has been

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		"In England and Wales, the majority of adults with r/r B-ALL are treated with combination chemotherapy regimen of fludarabine, cytarabine and granulocyte colony-stimulating factor, with or without idarubicin, followed by stem cell transplantation where a suitable donor can be found. A minority of patients would receive best supportive care (including palliative care)."	updated.
	Leukaemia CARE	The background information in the draft scope neglects to mention both the physical and psychological impact of the symptoms and diagnosis of ALL and the subsequent side effects of the few treatment options available. The draft scope stipulates that there are 536 people diagnosed with ALL in England each year. Around 43% of those diagnosed between 2011- 2013 were adults - the majority of those diagnosed would therefore be considered children and blinatumomab is not licenced for paediatric treatment. As stated, around 45% of patients will relapse or become refractory to initial treatment but of adults diagnosed, approximately 70% do not have the Philadelphia chromosome. As such, it could be estimated that it would only be approximately 70 - 75 patients who would be eligible to receive blinatumomab in this setting – and not all would receive treatment (considerably reducing the number of patients when considering economic modelling).	Comment noted. The background section is intended to provide a brief overview of the disease. Therefore no changes to the scope are required.
	NCRI-RCP-ACP	Overall adequate but: • Should make it initially clear that it only refers to B-ALL • Asparaginase used isn't 'crisastaspase' – this should be left as generic asparaginase • Should make it clear that the 5 year OS after relapse is less than 10%	Comment noted. The background section of the scope has been updated.

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	Amgen	Although the background information is accurate we feel mention should be made of • the lack of targeted agent • the fact that adult patients with R/R Ph (-) B-precursor ALL face imminent risk of death and, even with treatment, have a very poor prognosis with reported median overall survival (OS) in adult patients with R/R Ph (-) B-precursor ALL of less than 6 months; with ultimately, 94% of these patients dying from their disease, typically within a few months.	Comment noted. The background section is intended to provide a brief overview of the disease. Therefore no changes to the scope are required.
The technology/ intervention	NHS England	Yes	Comment noted. No action required.
	Pfizer Ltd	No comments.	Comment noted. No action required.
	NCRI-RCP-ACP	Should make it clear the technology is an antibody and that ALL cells invariably express CD19 Should mention that it is continuous IV Infusion for one month (short half-life of agent)	Comment noted. The technology section of the scope has been updated. The background section of the scope includes: “B-cell ALL is characterised by the presence of cytoplasmic immunoglobulins and CD10, CD19, CD22 and CD79a expression.”

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			The posology of the technology is not routinely included in a NICE technology appraisal scope.
	Amgen	No comment	Comment noted. No action required.
Population	NHS England	We note that in Mar 16 a licence extension was filed in the US to include treatment of paediatric and adolescent patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. We wonder if the scope should be widened to include this extension though would not wish to see the appraisal delayed.	Comment noted. NICE can only appraise a technology within its marketing authorisation and we have not been informed by the manufacturer that they are applying for a licence extension, therefore it would not be feasible to amend the population section of the scope to include the paediatric population.
	Pfizer Ltd	No comments.	Comment noted. No action required.
	NCRI-RCP-ACP	Yes	Following the scoping workshop, the other

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		Currently eligible adult patients with relapsed / refractory Ph- ALL should be looked at as being divided into 5 groups 1. Those treated on a modern protocol without allogeneic transplantation (likely to be young adults). 2. Those treated on an adult protocol with allogeneic transplantation in first remission 3. Elderly or frail patients treated on a palliative protocol from the outset 4. Those patients treated many years ago on an 'old style' protocol 5. Patients with disease that is refractory to first line therapy and so have not yet had the opportunity of progressing to transplant Patients in groups 1, 2 and 5 would clearly benefit from the availability of a novel agent such as Blinatumomab as a bridge to allogeneic transplantation as a definitive procedure. The timing of relapse for patients in group 2 is important; If they relapse within 12 months of their first transplant then it is unlikely that they could have a second transplant as consolidation of any response to blinatumomab. However, a late relapse would be a different scenario. Patients in group 3 are never going to be eligible for a definitive procedure and stand to gain much less in terms of life expectancy from the use of blinatumomab. As above, consideration should be given for the inclusion of Ph Positive ALL. There is a blind study for this population about the be published	considerations section of the scope has been updated with potential subgroups.

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	Amgen	No comment	Comment noted. No action required.
Comparators	NHS England	We feel that clofarabine should be included as a comparator followed by allogenic transplant where this has not already been received.	Comment noted. Following consultation comments, the comparators have been updated to include: clofarabine based combination chemotherapy
	Pfizer Ltd	No comments.	Comment noted. No action required.
	Leukaemia CARE	We would like to highlight there is no agreed standard of care for patients with acute lymphoblastic leukaemia (newly diagnosed or relapsed/refractory) and the best treatment option will often depend upon each patient's individual situation.	Comment noted. No action required.
	NCRI-RCP-ACP	FLAG-Ida is currently the most accepted standard of care despite being very toxic and having poor outcomes. It should also include other chemo regimens such as clofarabine-containing regimens -especially relevant to younger persons where clofarabine is standard of care for relapsed ALL.	Comment noted. Following consultation comments, the comparators have been updated to include: clofarabine based combination chemotherapy.

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	Amgen	The goal of therapy for adult patients with R/R Ph (-) B-precursor ALL is to achieve complete remission and proceed to allogeneic HSCT. Fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) based combination chemotherapy, with or without idarubicin is currently the most commonly used regimen for RR-ALL patients to induce a deep enough response to potentially attempted curative HSCT. As such it constitutes a relevant comparator for blinatumomab. In contract, Best supportive care would be used for patients for whom transplant would not be considered a viable options. We would not foresee blinatumomab to be used for those patients, as such we do not consider best supportive care as a relevant comparator.	Comment noted. Following consultation comments, the comparators have been updated to include: clofarabine based combination chemotherapy. Best supportive care may be an option when treatment with fludarabine, cytarabine and granulocyte colony-stimulating factor (GCSF) based combination chemotherapy, with or without idarubicin is considered inappropriate or contraindicated.
Outcomes	NHS England	Yes	Comment noted. No action required.
	Pfizer Ltd	No comments.	Comment noted. No action required.
	NCRI-RCP-ACP	MRD is not necessarily an important outcome measure	Comment noted. Following consultation

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		CR (complete remission) is the correct measure of response and the OS, remission duration etc are OK PFS is not used in leukaemia EFS would be more appropriate	comments, the outcomes have been updated to include event-free survival, relapse-free survival and complete remission.
	Amgen	The outcomes listed are all relevant and will be included, but it is important to note that progression free survival is traditionally named relapse free survival (RFS) in ALL. Furthermore since the aim of treatment is to induce the deepest remission possible to attempt HSCT, RFS is not a very informative outcome as opposed to treatment response rates (including minimal residual disease and hematologic responses)	Comment noted. Following consultation comments, the outcomes have been updated to include event-free survival, relapse-free survival and complete remission.
Economic analysis	NHS England	No comment	Comment noted. No action required.
	Pfizer Ltd	No comments.	Comment noted. No action required.
	Leukaemia CARE	As previous comments suggest, the number of people within this patient population (Philadelphia chromosome negative relapsed or refractory adult ALL patients) is very low – estimated to be around 70 - 75 annually. As such, we feel that it is important to identify this when considering blinatumomab as clinically and cost effective during the economic modelling process.	Comment noted. No action required.

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	Amgen	No comments	Comment noted. No action required.
Equality and Diversity	NHS England	No comment	Comment noted. No action required.
	Pfizer Ltd	No comments.	Comment noted. No action required.
	Leukaemia CARE	The Scottish Medicines Consortium (SMC) has recently appraised and approved blinatumomab for ALL patients in this setting and is therefore accessible to NHS patients in Scotland (who are eligible for the treatment). It is necessary for blinatumomab to be assessed (and approved) for patient access in England to avoid an inequitable situation (unequal access to the treatment throughout the UK). The All Wales Medicines Strategy Group (AWMSG) are also currently assessing blinatumomab in this setting.	Comment noted. No action required.
	NCRI-RCP-ACP	No concerns	Comment noted. No action required.
	Amgen	No comments	Comment noted. No action required.
Other considerations	NHS England	N/A	Comment noted. No action required.
	Pfizer Ltd	No comments.	Comment noted. No

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			action required.
Innovation	NHS England	N/A	Comment noted. No action required.
	Pfizer Ltd	No comments.	Comment noted. No action required.
	Leukaemia CARE	Blinatumomab is a novel therapeutic option that offers durable responses in a heavily pre-treated patient population where there is an urgent patient need for access to new, effective follow up treatments. Existing follow up treatments are toxic and not always preferable for patients who are usually extremely ill by this stage and have already received similar toxic treatments (that did not work). Blinatumomab has also proven to act as a bridge to stem cell transplant (considered the only “curative” treatment for ALL) which is a very welcome result in such a hard to treat disease area. Having an effective treatment available to patients who have not yet relapsed or are refractory to initial treatment would offer some piece of mind – knowing that should their treatment not work, there would be a secondary (effective) treatment option available to them. Finally, the administration of the treatment is done intravenously (via a pump) and includes treatment free intervals. This could lead to an improved quality of life for patients during their treatment. Overall, the introduction of blinatumomab would be considered an innovative treatment in this heavily pre-treated, difficult to treat patient population (with very limited available treatment options.)	Comment noted. No action required.

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	NCRI-RCP-ACP	This is a very innovative technology - some experts believe it represents a step change. ALL is an ultra orphan disease. Outcomes from relapsed / refractory disease are poor with life expectancies being measured in a few months for the vast majority of patients (only 7% survival in the UKALL12 data). The QALY may not capture the improved quality of life that patients have when treated on blinatumomab rather than FLAG-Ida. It also won't capture the benefits for family members when the patient is treated as an outpatient and is well. The QALY may also fail to capture the improved quality of life for the patient and for the family members if the patient survives.	Comment noted. No action required.
	Amgen	Blinatumomab is a novel single-agent immunotherapy that induces a rapid and durable response in a population of patients who have been heavily pre-treated with chemotherapy. Blinatumomab overcomes the limitations of traditional cytotoxic chemotherapy and represent a real step-change by enabling the patient's own immune system to target and eradicate malignant cells to achieve a durable remission or a quality transplant, which may translate to long-term survival for adult patients with R/R Ph (-) ALL. Indeed, with blinatumomab, more patients achieve complete remission (CR) or complete remission with partial haematologic response (CRh) when compared with standard-of-care chemotherapy (43% vs. 24%).Additionally, 82% of responders have no evidence of minimal residual disease (MRD-negative or MRD-) and 40% of responders go on to receive HSCT, which is	Comment noted. No action required.

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		currently the only potentially curative option for adult patients with R/R Ph (-) B-precursor ALL. For patients who would otherwise receive conventional chemotherapy, blinatumomab may allow them to spend more time at home with their family and less time as a hospital in-patient. Any improvement in a patients' treatment and quality of life will also have a wider impact on the lives of their family and friends. Delivery of blinatumomab would have less impact on a carers ability to work compared to delivery of conventional chemotherapy - where prolonged daily visits to hospital are required initially followed by a prolonged in-patient stay. The delivery of blinatumomab is likely to have be greater impact in comparison to supportive care. Although this group of patients often require regular hospital attendance and potential hospital admissions to treat the complications of ALL.	
Questions for consultation	NHS England	N/A	Comment noted. No action required.
	Pfizer Ltd	No comments.	Comment noted. No action required.
	Leukaemia CARE	Where do you consider blinatumomab will fit into the existing NICE pathway? There is no existing NICE pathway for patients with ALL.	Comment noted. No action required.
	NCRI-RCP-ACP	**Are people with relapsed or refractory B-precursor acute lymphoblastic leukaemia routinely tested for Philadelphia chromosome?** All patients with ALL are routinely tested for the Ph chromosome, both at diagnosis and relapse.	Comment noted. No action required.

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		Have all relevant comparators for blinatumomab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for Philadelphia-chromosome-negative relapsed or refractory B precursor acute lymphoblastic leukaemia? There are very little data on relevant comparators and using FLAG-Ida is reasonable for the UK. The following should also be considered: Clofarbine-containing regimens High dose methotrexate There is not currently a NICE pathway for patients with ALL **Are there any subgroups of people in whom blinatumomab is expected to be more clinically effective and cost effective or groups that should be examined separately?** Less effective when used later in the course of the disease Please identify the nature of the data which you understand to be available to enable the appraisal committee to take account of these benefits. Numerous phase 1 and 2 study publications in high ranking journals. Phase 3	Comment noted. Following consultation comments, the comparators have been updated to include: clofarabine based combination chemotherapy. Comment noted. No action required.

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		RCT data just presented in presidential session at European Haematology Association and being prepared for publication at present.	Comment noted. No action required.
Additional comments on the draft scope	NHS England	N/A	Comment noted. No action required.
	Pfizer Ltd	It will be important for the appraisal to account for the hospitalisation required for the administration of blinatumomab. As described in its SPC, hospitalisation is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and reinitiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended. Blinatumomab is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump over a period of up to 96 hours. The infusion bag must be changed at least every 96 hours by a health care professional for sterility reasons.	Comment noted. No action required.

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

Department of Health