National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [ID982]

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	-	-	-
Wording	Pfizer	[redacted] Please can the wording of the remit be amended so that it specifies *de novo* AML i.e. To appraise the clinical and cost effectiveness of gemtuzumab ozogamacin within its marketing authorisation for untreated *de novo* acute myeloid leukaemia	Comment noted. The scope has been kept broad so the term '*de novo*' has not been added. No action required.
	RCP	In the background section I think it would be more accurate to say that AML typically develops rapidly and is fatal unless treated.	Comment noted. The wording is in line with NICE writing style and

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			has been retained. No action required.
Timing Issues	Pfizer	It is important that clinicians in England and Wales are provided with suitable NICE Guidance on the use of gemtuzumab ozogamacin in clinical practice. [redacted]	Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10142. No action required.
	RCP	Moderate	Comment noted. No action required.
Additional comments on the draft remit	Pfizer	None	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pfizer	In order for the background information to be as accurate and complete as possible, Pfizer suggest the addition of the following points. Incidence of AML related to this remit	Comments noted. This section of the scope aims to provide a brief overview of the background for the

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		• The incidence of acute myeloid leukaemia in England is about 3,000 people per year[1] however not all patients are eligible for intensive chemotherapies, such as daunorubicin and cytarabine (DA). • SACT data (2014) indicate that approximately 45.5% of newly diagnosed AML patients are treated with an intensive chemotherapy, most commonly DA, in the induction phase and consolidation phase. • Therefore there are approximately 1,365 patients per year eligible for intensive chemotherapy which is the patient population that would be eligible for gemtuzumab ozogamacin in clinical practice. <u>Drugs used in AML in UK clinical practice</u> • As stated above, DA is the most commonly used intensive chemotherapy used in induction and consolidation phases. • Clinical expert advice states that mitoxantrone and etoposide are not used commonly in the UK for AML in either the induction or consolidation phases and hence cannot be considered as SOC. In AML 15 etoposide in combination with DA did not show benefits in health outcomes when compared to DA alone[2]. • FLAG-IDA (a combination of fludarabine, idarubicin, cytarabine and G-CSF) is mainly used in 1) patients who are classified as "poor risk" based on their cytogenetic profile and considered fit and 2) in young, fit patients where a rapid response is required. These groups represent a negligible proportion of the population and hence the majority of patients suitable for intensive chemotherapy will receive DA in UK clinical practice. Azacitidine is recommended by NICE in adults with AML with multilineage dysplasia (MDS). This type of AML occurs in patients with a prior history of MDS and is hence categorised as secondary AML.	appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal. No action required.
	Leukaemia Care	The background should include reference to AML deaths, 2516 (UK) or 2127 (England) per year.	Comments noted. Mortality statistics and

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		(Cancer Research UK, 2014. Acute myeloid leukaemia (AML) mortality statistics. Accessed May 2017.) Common symptoms experienced by AML patients also include fatigue, weakness or breathlessness, fever or night sweats, weight loss and bone, joint or muscle pain. A diagnosis of AML can also have a significant psychological impact. 51% of AML patients report feeling depressed or anxious more often since their diagnosis. (Leukaemia CARE, Patient Experience Survey 2016, currently unpublished).	list of symptoms have been updated in the background section.
	RCP	In the background section I think it would be more accurate to say that AML typically develops rapidly and is fatal unless treated.	Comment noted. The wording is in line with NICE writing style and has been retained. No action required.
The technology/ intervention	Pfizer	Yes the description is accurate.	Comment noted. No action required.
	RCP	Yes	Comment noted. No action required.
Population	Pfizer	Please can the defined population be amended so that it specifies de novo AML patients i.e. Adults with untreated *de novo* acute myeloid leukaemia. Please see the section below on "Questions for consultation; question 3" for our comments on subgroups in the population.	Comment noted. The scope has been kept broad so the term '*de novo*' has not been added. No action required.

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	RCP	Worthwhile highlighting that this assessment will relate to non-APL AML ie no comment is expected relating to acute promyelocytic leukaemia The specific population that this draft is written for is: adults with untreated AML who are eligible for intensive induction therapy. I don't know whether that should be stipulated up front or simply written into the report I think it will be important to try to consider the efficacy of gemtuzamab in different cytogenetic risk categories of AML. Data from UK NCRN group suggests increased impact in those with good risk and intermediate risk cytogenetics but not in those with high risk cytogenetic changes	Comments noted. The scope has been kept broad so the original wording has been retained. The proposed subgroups have been added to the 'Other considerations' section of the scope.
Comparators	Pfizer	UK expert clinical advice is that standard of care in the UK (outside of clinical trials) for patients with untreated AML is a combination regimen consisting of daunorubicin and cytarabine (DA). Therefore this combination should be considered as the main comparator for gemtuzumab ozogamacin (GO) in this appraisal.	Comment noted. The scope has been kept broad. Daunorubicin and cytarabine are included in the list of possible comparators.
	RCP	Comparators are reasonable, in the context of assessing adults who are eligible for intensive induction chemotherapy. Care will need to be taken if considering the impact of stem cell transplantation as part of standard of care, especially if cytogenetic risk groups are being separated. Stem cell transplant is not considered a standard of care in first remission for those with good risk genetic changes	Comments noted. No action required.
Outcomes	Pfizer	The outcomes listed are appropriate.	Comment noted. No action required.

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	RCP	Yes	Comment noted. No action required.
Economic analysis	Pfizer	A life-time horizon will be applied in the analysis.	Comment noted. No action required.
	RCP	5 year follow up is probably ideal in terms of survival	Comment noted. No action required.
Equality and Diversity	Pfizer	No equity issues have been identified.	Comment noted. No action required.
	RCP	No concerns	Comment noted. No action required.
Other considerations	Pfizer	In the UK the clinical pathway for patients treated in the first-line setting for AML may include stem-cell transplants for patients who are eligible and for whom it is appropriate based on their response to induction therapy, therefore the cost effectiveness evaluation will include a scenario that evaluates stem cell therapy as subsequent treatment.	Comment noted. No action required.
Innovation	Pfizer	Pfizer considers that gemtuzumab ozogamacin is a step-change in the management of AML as the approach to treating AML is to induce and sustain disease-free remission and current standard of care is limited in its ability to keep patients in remission. Gemtuzumab ozogamacin combined with standard induction chemotherapy delivers a more durable remission compared to chemotherapy alone with a median relapse free survival of 28.0 months compared to 11.4 months for patients on DA regimen (HR 0.526, P=0.0006)[3]. The overall economic costs of AML represent a major burden for example the costs associated with relapse and further rounds of	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its

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		chemotherapy are high therefore delaying preventing relapse and the associated costs represents a major benefit for the NHS. These benefits are acknowledged by the clinical community in the UK which is demonstrated by their continued use of gemtuzumab ozogamacin in the context of clinical trials in the UK. Clinical experts have continuously voiced their support for gemtuzumab ozogamacin access in the UK for patients with untreated AML.	product in its submission. No action required.
	RCP	Yes There has been very slow progress in improving therapy for patients with AML over the last 30 years, despite trials of many new agents and strategies. I do feel gemtuzumab has the potential to improve outcomes for patients with AML.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
Questions for consultation	Pfizer	1. How is gemtuzumab ozogamicin expected to be used in clinical practice? • Gemtuzumab ozogamicin has and continues to be investigated in clinical trials in the UK and worldwide. Patterns of use have changed over time as new data have become available. In addition clinical expert advice is that AML as a condition and the patient population require a treatment approach that is often tailored to an individual therefore it's important that clinicians are allowed flexibility with approved medicines to do this so that the best possible outcomes can be achieved for patients. • Following marketing authorisation Pfizer expects gemtuzumab ozogamicin to be used in clinical practice in line with its label (and as per the registration trial ALFA-0701[3]) for untreated patients with de novo AML as the benefit-risk profile would have been proven. The MA and hence NICE application will not cover secondary AML.	Comments noted. No action required.

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		Gemtuzumab ozogamicin would be offered in combination with DA in induction and consolidation with no maintenance phase. Specifically: o Induction: Gemtuzumab ozogamicin 3 mg/m2/day as a 2-hour IV infusion on Days 1, 4, and 7 in combination with DA o Consolidation: Gemtuzumab ozogamicin 3 mg/m2/day as a 2-hour IV infusion on Day 1 in combination with DA. 2. Have the comparators for gemtuzumab ozogamacin been defined appropriately in the scope? • The current scope has not identified any specific comparators for gemtuzumab ozogamicin. • However Pfizer understand from UK expert opinion that standard of care in the UK (outside of clinical trials) for patients with untreated AML who are eligible for intensive chemotherapy is a combination regimen consisting of daunorubicin and cytarabine (DA) which is used for induction and consolidation phases of treatment. Therefore this combination should be considered as the main comparator for gemtuzumab ozogamacin in this appraisal. Please note that there is no maintenance phase in the treatment approach of AML. • Stem cell transplant may be offered to people following induction and consolidation chemotherapy if they have achieved complete remission. Eligibility criteria include fitness, age and cytogenetics. Stem cell transplant is not a direct comparator to GO since it would be offered following induction and consolidation treatments in UK clinical practice. The use of transplant as a primary means of consolidation is not standard of care. 3. Are there any subgroups of people in whom gemtuzumab ozogamacin is expected to be more clinically effective and cost effective or other groups that should be examined separately?	Comments noted. The scope has been kept broad. Daunorubicin and cytarabine are included in the list of possible comparators. Comment noted. The proposed subgroups have been added to the

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		• Clinical data suggest that GO is more clinically effective in patients with favourable and intermediate cytogenetics. 4. Where do you consider gemtuzumab ozogamacin will fit into the existing NICE pathway, Blood and bone marrow cancers (2016)? Gemtuzumab ozogamacin would be used in patients with AML for induction and consolidation phases.	'Other considerations' section of the scope. Comment noted. No action required.
	NCRI-ACP-RCP	**How is gemtuzumab ozogamicin expected to be used in clinical practice?** • **Would gemtuzumab ozogamicin be used as part of induction, consolidation and/or maintenance regimens?** • **Would it be offered alone or in combination with other chemotherapy agents?** • **Would it be offered to patients with de novo and/or secondary acute myeloid leukaemia?** Mylotarg (GO) would be used as part of induction therapy rather than consolidation on maintenance. The evidence strongly is in favour of its use with other chemotherapy drugs that are used for remission induction therapy of AML in patients who are fit for intensive therapy. It would primarily be offered to patients with de novo AML but not exclusively so. The main body of evidence of efficacy is in patients who have good risk or standard risk cytogenetics with little evidence of benefit for patients with adverse risk cytogenetics. However, unfortunately for most patients with AML the cytogenetic results will not be known at diagnosis unless the patient has had a preceding myelodysplastic syndrome and cytogenetics have been previously analysed. Part of the problem here is that the cytogenetic analysis of AML samples in the UK may take up to 2 weeks. Rapid analysis of	Comments noted. No action required.

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		cytogenetics in AML is a pre requisite of targeting the use of GO for the right patient. **Have the comparators for gemtuzumab ozogamacin been defined appropriately in the scope?** • **Which treatments are considered to be established clinical practice in the NHS for previously untreated acute myeloid leukaemia, for the induction, consolidation and/or maintenance phases of treatment?** The standard therapy used in clinical practice outside of clinical trials in the combination of Daunorubicin and Cytarabine conventionally called DA which is normally given for 2 cycles of intensive induction chemotherapy. Alternatives that are being explored in the AML19 trial is the FLAG Ida combination combined with Mylotarg. The evidence is that Mylotarg can be safely combined with a number of different standard induction therapies for AML although DA is perhaps the most commonly used.regimen • **Are intensive or non-intensive chemotherapy regimens relevant comparators for gemtuzumab ozogamacin? Are there specific chemotherapy regimens that are considered to represent established clinical management in the NHS?** GO has only been combined with intensive therapies and there is really little evidence of benefit in combination with non intensive therapies such as Azacytidine.. Non intensive regimens are not a suitable comparator • **Would people with acute myeloid leukaemia be offered stem cell transplantation? If so, is it a relevant comparator for gemtuzumab ozogamacin?**	Comments noted. The scope has been kept broad. Daunorubicin and cytarabine are included in the list of possible comparators. Comment noted. No action required.

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		Some patients with AML treated with GO may go on to be offered stem cell transplantation and SCT is therefore part of a continuum of treatment for selected AML patients and is therefore not a comparator for GO therapy. • **Are the outcomes listed appropriate?** We believe the outcome measures listed are appropriate, EFS is the most important outcome measure as prevention of relapse is a key priority of AML therapy as salvage therapy is often unsuccessful and expensive and significantly adversely affects quality of life. • **Are there any subgroups of people in whom gemtuzumab ozogamacin is expected to be more clinically effective and cost effective or other groups that should be examined separately?** The sub groups of patients that most clearly benefit from GO as shown in the meta analysis are patients with standard risk and good risk AML as defined by cytogenetics, there is no evidence that the benefit is related to patients age or sex. Old and young patients who are fit for intensive therapy benefit. • **Do you consider gemtuzumab ozogamacin 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)?** The GO should be considered a standard part of the induction therapy of AML patients with good and standard risk cytogenetics, with the proviso given above about the frequent lack of availability of identifying these patients rapidl, due to delays in diagnostic cytogenetic analysis.	Comment noted. No action required. Comment noted. No action required. Comment noted. The proposed subgroups have been added to the 'Other considerations' section of the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
			Comment noted. No action required.
Additional comments on the draft scope	Pfizer	None	Comment noted. No action required.

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

None