National Institute for Health and Care Excellence

Single Technology Appraisal

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (MA review of TA554) [ID6290]

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	Anthony Nolan	Yes, we do believe this topic would be appropriate for a NICE appraisal.	Thank you for your comment. This appraisal has been scheduled into the work programme.
	Leukaemia Care	Yes	Thank you for your comment. This appraisal has been scheduled into the work programme.
	Novartis Pharmaceuticals	Novartis considers this topic appropriate to be referred to NICE, given the high unmet need faced by children with B-cell acute lymphoblastic leukaemia	Thank you for your comment. This appraisal has been scheduled into the work programme.

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Wording	Anthony Nolan		
	Leukaemia Care	Yes	Comment noted.
	Novartis Pharmaceuticals	Yes, the wording of the remit is appropriate	Comment noted.
Timing issues	Anthony Nolan	Very urgent, as no other CAR-T product is available for patients with B-ALL aged 25 years and under, and there are minimal opportunities for these patients to access CAR-T clinical trials and academic studies.	Thank you for your comment. This appraisal has been scheduled into the work programme.
	Leukaemia Care	Highly appropriate, especially with the recent setting up of new specialist CAR-T centres.	Thank you for your comment. This appraisal has been scheduled into the work programme.
	Novartis Pharmaceuticals	Tisagenlecleucel has been available via the Cancer Drugs Funds for children and young adults with B-cell acute lymphoblastic leukaemia since 2018. Now that the CDF period is ending and given the high unmet need, the re-evaluation of this technology for routine commissioning is relatively urgent.	Thank you for your comment. This appraisal has been scheduled into the work programme.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Anthony Nolan	The background section omits information on the expected survival after ALL relapse, we suggest this is added as it is important context.	Thank you for your comment. The background section has been updated to include survival rates after relapse.
	Leukaemia Care	N/A	No action needed.
	Novartis Pharmaceuticals	No comments	No action needed.
The technology/intervention	Anthony Nolan		
	Leukaemia Care	Yes	Comment noted. No action needed.
	Novartis Pharmaceuticals	No comments	No action needed.
Population	Anthony Nolan	The population of paediatric and young adult patients tisagenlecleucel is authorised for could also include patients with comorbidities which mean they are unable to undergo stem cell transplants, in addition to “B cell acute lymphoblastic leukaemia that is refractory, in relapse post transplant or in second or later relapse”.	Thank you for your comment. The population has not been changed in order to keep the population broad in the scope. The committee will consider if it is appropriate to make a recommendation for a narrower population and will only be able to make recommendations within the marketing

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			authorisation for this technology.
	Leukaemia Care	Yes	Comment noted. No action needed.
	Novartis Pharmaceuticals	The population is defined appropriately.	Comment noted.
Comparators	Anthony Nolan	Our understanding is that inotuzumab ozogamicin is only recommended for use in adults and so we would not be an appropriate comparator for the paediatric population. We also want to note that although allogeneic stem cell transplant is used in the same setting, not every patient will be suitable for or have access to an allogeneic stem cell donor.	Thank you for your comment. The comparators listed in the scope aims to be inclusive. The rationale for excluding any comparators from the evidence submission will be considered by the appraisal committee.
	Leukaemia Care	Inotuzumab is only indicated for adult patients aged 18 and over and therefore should not be used as a comparator for this treatment in the under 18's cohort. Furthermore, inotuzumab is often used earlier in the treatment pathway as a bridge to stem cell transplant. Therefore, this comparator is inappropriate for the 18-25 cohort as well as the under 18s and should not be applied to this appraisal of Tisagenlecleucel-T which would be used as in a later treatment line.	Thank you for your comment. The comparators listed in the scope aims to be inclusive. The rationale for excluding any comparators from the evidence submission will be considered by

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			the appraisal committee.
	Novartis Pharmaceuticals	The comparators of relevance to this submission reflect treatments currently licensed and used in the population of interest in this submission: patients under the age of 25 with B-cell acute lymphoblastic leukaemia (ALL) which is refractory, in relapse post-transplant, or in second or alter relapse. The relevant comparators are: • Blinatumomab • Fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy The following treatments listed in the draft scope are not comparators: • **Inotuzumab ozogamicin** is not licensed for use in patients under 18 and is only recommended by NICE in adult patients with ALL and as such does not form a relevant comparator in this appraisal. Inotuzumab ozogamicin is commonly used earlier in the treatment pathway (*i.e in primary refractory patients or following first relapse*), and typically as a bridge to SCT or CAR-T • **Stem Cell Transplantation (SCT)** is used as consolidation therapy following complete remission with prior treatment, such as blinatumomab or salvage chemotherapy, and does not constitute a standalone treatment option. As such, a comparison to SCT alone is not appropriate. The	Thank you for your comment. The comparators listed in the scope aims to be inclusive. The rationale for excluding any comparators from the evidence submission will be considered by the appraisal committee.

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		benefits of SCT are already implicitly captured for modelled comparator treatments: trial data informing treatment benefit include a proportion of patients who received SCT subsequent to complete remission. • **Tyrosine Kinase Inhibitors (TKIs)** are used in Philadelphia-chromosome-positive (Ph+ve) ALL. The proportion of patients with Ph+ve ALL within the eligible patient population for tisagenlecleucel constitute a small minority (<3%) and therefore TKIs are not considered to represent relevant comparators to this submission. Furthermore, given the eligibility criteria of the tisagenlecleucel clinical trials, patients had to have tried and failed two prior lines of TKI therapy, and previous feedback from UK clinical experts is that the use of a 3rd TKI does not constitute standard practice. • **Clofarabine** - clinical feedback received as part of both the original submission (TA554) and this submission indicated that FLAG-IDA is the predominantly used chemotherapy regimen in patients with relapsed disease, being associated with similar remission rates to clofarabine, with lower toxicity. As such, clofarabine does not represent standard NHS practice in this indication and is not considered a relevant comparator.	
Outcomes	Anthony Nolan	We welcome the inclusion of quality of life in the outcomes to be considered and strongly recommend that real-world evidence and patient-reported outcomes are considered to provide an indication of quality of life outcomes.	Comment noted. No action needed.
	Leukaemia Care	N/A	No action needed.
	Novartis Pharmaceuticals	No comments	No action needed.
Economic analysis	Anthony Nolan		No action needed.
	Leukaemia Care	N/A	No action needed.

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	Novartis Pharmaceuticals	The economic analysis will align with reference case stipulations as noted in the draft scope, however, non-reference case discounting of 1.5% will also be considered. As noted in the case for change consultation document for the NICE methods of health technology evaluation, "*NICE understands there is broad interest in potentially curative technologies including ATMPs, and a policy-level drive to support them"*. The report explored the use of a non-reference case discount of 1.5% for these technologies that have high upfront costs and long-term health benefits such as ATMPs and other one-off treatments. Furthermore, section 4.5.3 of the NICE health technology evaluations manual (2022), states that the "*committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects*" if certain criteria are met. Given, the innovative potential of Tisagenlecleucel, an ATMP and a one-off treatment, consideration of a non-reference case discount of 1.5% is justified.	Comment noted. Sections 4.5.1-4.5.2 of the NICE health technology evaluations: the manual outlines the approach to discounting. Further information is given in section 4.5.3, about the circumstances where non-reference case discounting may be considered by the Appraisal Committee. The Appraisal Committee will need to be confident that there is a highly plausible case for the maintenance of benefits overtime for using a non-reference case discount. Further, the Appraisal Committee will need to be satisfied that any irrecoverable costs associated with the technology (including, for example, its acquisition costs and

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			any associated service design or delivery costs) have been appropriately captured in the economic model or mitigated through commercial arrangements.
Equality	Anthony Nolan	As mentioned above, not every patient will be suitable for or have access to an allogeneic stem cell donor. If tisagenlecleucel were not to be routinely commissioned for this indication, patients without an allogeneic donor or for whom stem cell transplant would not be suitable would be particularly disadvantaged.	Thank you for your comment. The committee will consider any relevant equality issues when it makes recommendations.
	Leukaemia Care	Some patients, specifically from ethnic minority backgrounds, might be unable to have a stem cell transplant if a donor match cannot be found. A stem cell transplant might therefore not be an option for some patients for this reason, making this treatment an even more important option in this subgroup.	Thank you for your comment. The committee will consider any relevant equality issues when it makes recommendations.
	Novartis Pharmaceuticals	There is a high unmet need for a CAR-T in this population. Patients aged 26 years and over now have access to a CAR-T via the Cancer Drugs Fund (TA893). A routinely commissioned CAR-T treatment option is needed for children and young adults less than 26 years.	Thank you for your comment. This appraisal has been scheduled into the work programme. The committee will consider any relevant equality issues when it makes recommendations.

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Other considerations	Anthony Nolan	In economic analysis for this appraisal it would be pertinent to consider the secondary financial costs for patients and local health systems. Most patients only have to travel to receive tisagenlecleucel once in a specialist centre and can remain an outpatient at their local hospital for monitoring. Whereas for some comparators they might be required to travel far distances regularly for check-ups and will be in long-term inpatient care. In the current external economic environment, this cost to patients should also be considered as it can impact their mental and financial wellbeing and recovery.	Comment noted. Sections 4.4.1 of the NICE health technology evaluations: the manual outlines states “For the reference case, costs should relate to resources that are under the control of the NHS and PSS”. Sections 4.4.22-4.4.25 outlines the approach to non-NHS and PSS costs.
	Leukaemia Care	None	No action needed.
	Novartis Pharmaceuticals	No comments	No action needed.
Innovation	Anthony Nolan	We do consider this technology to be a step-change as there are currently no other potentially curative CAR-T products on the market for this particular age group and population. During the time that this treatment has been available on the CDF it has been very much welcomed by patients and their families, not only for its efficacy but also for the considerable quality of life benefits it offers. It will be useful to consider the degree of conditioning required prior to receiving tisagenlecleucel versus comparators such as stem cell transplant, as clinicians have noted this has an impact on quality of life due to potential long-term toxicity. This is particularly important as the population is very young, and the toxicity will impact them over a longer life course period.	Thank you for your comment. No action needed.

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		The Committee should also consider how quickly patients feel they are back to normal post-procedure when receiving either tisagenlecleucel or comparators, and what the impact is on their health and wellbeing during the period of therapeutic administration and recovery, which can vary by product.	
	Leukaemia Care	N/A	No action needed.
	Novartis Pharmaceuticals	As highlighted in TA554, the impact of r/r B-cell ALL is especially severe, affecting children, parents/caregivers and wider support networks. The burden of disease is exacerbated by the poor clinical outcomes, HRQoL and psychosocial outcomes associated with current treatment options for r/r B-cell ALL. With prognosis and treatment options deteriorating at each treatment line, there remains a critical unmet need for the routine commissioning of effective treatment options that offer substantial life extension and potential for cure thereby alleviating disease burden and improving quality of life of both patients and parents/caregivers. Following its reimbursement via the CDF, tisagenlecleucel has become an established treatment option as part of SOC, offering paediatric and young adult patients with r/r B-cell ALL the potential for a cure, as demonstrated by its proven effectiveness in achieving long-term remission and confirmed by clinical feedback received as part of this appraisal. The recommendation for routine commissioning of tisagenlecleucel in r/r B-cell ALL for patients aged up to 25 years would ensure that this patient population continues to benefit from access to curative options, as indicated by its established usage in current clinical practice.	Thank you for your comment. This appraisal has been scheduled into the work programme.
Questions for consultation	Anthony Nolan	N/A	No action needed.
	Leukaemia Care	N/A	No action needed.
	Novartis Pharmaceuticals	No additional comments	No action needed.
	Anthony Nolan	N/A	No action needed.
	Leukaemia Care	N/A	No action needed.

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Additional comments on the draft scope	Novartis Pharmaceuticals	No comments	No action needed.