National Institute for Health and Care Excellence

Health Technology Evaluation

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments [ID6325] 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	Gilead Sciences Ltd	Brexucabtagene autoleucel entered the managed access agreement (MAA) in February 2021 for the treatment of relapsed or refractory mantle cell lymphoma in adults who have previously had a Bruton's tyrosine kinase inhibitor (BTKi). This was under the understanding that the process and methodology for exiting the CDF would be substantially the same as that in place when signing the agreement, i.e. a 'Cancer Drugs Fund guidance review' by NICE under the technology appraisal process as set out in the NICE Guide to the process of technology appraisal – Process and methods (PMG19). Gilead relied upon the defined procedure which included the arrangements for how the technology would be assessed following completion of the MAA, when we agreed to the arrangements for participation in the CDF.	Thank you for your comments. Section 2.5 of the managed access agreement for brexucabtagene autoleucel states that the review 'will use the process and methods in place at the time the invitation to participate in the guidance review is issued'. These

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		As clearly mentioned in the MAA and NICE Guide, this exit process should be considered a reappraisal based on additional evidence listed in the data collection agreement, intended to answer the clinical uncertainty raised by the NICE Appraisal Committee. The 2018 Addendum to the NICE Technology Appraisal Methods Guide to support the new Cancer Drugs Fund arrangements, referred to "*a subsequent update of the guidance*" (paragraph 6.5.3) at the end of the MAA period. The current review of brexucabtagene autoleucel therefore forms the conclusion of the original appraisal rather than a de novo STA and to alter NICE's procedures retrospectively, applying substantially different methodology is inconsistent with standards of procedural fairness. Brexucabtagene autoleucel is a highly innovative therapy which arguably meets criteria for evaluation through the HST route, noting that: 1. The disease is very rare. Around 540 patients per year are diagnosed with MCL in England. However the number relapsed or refractory after 2 or more systemic treatments including a BTKi is much lower, around 90 per year. 2. The number eligible for treatment with this therapy is low Brexucabtagene autoleucel is available through the Cancer Drugs Fund (CDF) and is standard of care for eligible patients in the UK. Company data shows that [redacted] treatments were delivered to sites in the 12 months to September 2024. This may slightly overstate the number of treatments	methods are outlined in the NICE health technology evaluations: process and methods manual (2022). This topic has been selected as a single technology appraisal, as it was for the first evaluation of brexucabtagene autoleucel (TA677). The HST criteria have not substantially changed and hence it would not be appropriate to route via the HST process.

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		delivered, but the company believes [redacted] is an upper limit for the number of eligible patients per year. In addition, around 90 people per year, with relapsed or refractory B-cell acute lymphoblastic leukaemia who are 26 years and over are also eligible for treatment with brexucabtagene autoleucel. 3. The disease significantly shortens life expectancy. A United Kingdom real-world study of patients with progressive disease after second line ibrutinib, conducted before brexucabtagene autoleucel became available, found median life expectancy of only 1.4 months. Life expectancy was longer but still very limited for patients who received further therapies (median of 0.4 months for patients who did not receive third line treatment; 11.6 months for those who received some form of third line therapy). 4. There are no other satisfactory treatment options Brexucabtagene autoleucel is the recommended standard of care for eligible patients in the UK. Management options for patients who have failed a covalent BTK inhibitor and are unfit for, or have already received, CAR-T are poorly defined, and no standard of care is currently recognised.	
Wording	Gilead Sciences Ltd	**Current wording:** To appraise the clinical and cost effectiveness of brexucabtagene autoleucel within its marketing authorisation for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments. **Proposed wording:**	Thank you for your comments.

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		To appraise the clinical and cost effectiveness of brexucabtagene autoleucel within its marketing authorisation for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor. **Rationale:** To accurately describe the marketing authorisation.	The wording of the remit has been updated to better reflect the marketing authorisation.

Comment 2: the draft scope

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Background information	Gilead Sciences Ltd	**Current wording:** There were 543 new cases of mantle cell lymphoma diagnosed in England in 2021. Regional data from the north-east of England indicates that the 5-year survival rate for people with mantle cell lymphoma is 47.4%, and the median age at diagnosis is around 72 years. Mantle cell lymphoma is more common in men than women (3:1 ratio). **Proposed wording:** In England each year there are around 90 patients with mantle cell lymphoma (MCL) who relapse or are refractory to two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor. In the last 12 months around [redacted] patients received brexucabtagene autoleucel treatment.	Thank you for your comments. Thank you. Additional text has been added to the background section of the scope to highlight that each year there are around 90 patients with

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		Outcomes in these patients who have failed successive lines of treatment are historically very poor. With a large international retrospective cohort study (including UK patients) showing that patients who progressed with ibrutinib had a median survival of less than 3 months. In another UK real-world analysis, the median survival after progression on a BTKi at second line but without CAR-T was 1.4 months. **Rationale:** The current wording is misleading as it implies the relevant population is much larger than the number known to be treated (it refers to all MCL patients rather than the limited number of patients in the R/R post BTKi setting). Overall survival after two or more lines of systemic therapy is considerably lower than overall survival for patients presenting with MCL for the first time. **Current wording:** There is no accepted standard of care for treating relapsed or refractory mantle cell lymphoma in people who have received at least 2 previous lines of therapy. A range of chemotherapy regimens with rituximab are used such as, RBAC (rituximab, bendamustine and cytarabine), rituximab plus bendamustine, RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), RCVP (rituximab, cyclophosphamide, vincristine, and prednisolone) and single-agent cytarabine. **Proposed wording:** 2024 BSH guidelines recommend that eligible MCL patients who are relapsed or refractory (including stable disease) after anti-CD20 antibody-containing immunochemotherapy and BTKi should be offered brexucabtagene autoleucel (evidence rating 1A). Candidates for CAR-T treatment should be risk assessed prior to initiation of a BTKi, with targeted monitoring to minimise the risk of delay initiating brexucabtagene autoleucel and maximise the likelihood of successful	mantle cell lymphoma (MCL) who relapse or are refractory to two or more lines of systemic therapy. Brexucabtagene autoleucel has been available through the Cancer Drugs Fund rather than through standard commissioning. It is therefore not yet possible for it to be considered as part of

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		infusion. No standard of care is acknowledged for patients who are unfit for, or have already received, CAR-T; chemotherapy regimens with rituximab can be used but supporting data is limited. In the absence of CAR-T, there is no accepted standard of care for treating relapsed or refractory mantle cell lymphoma in people who have received at least 2 previous lines of therapy. A range of chemotherapy regimens with rituximab are used such as, RBAC (rituximab, bendamustine and cytarabine), rituximab plus bendamustine, RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), RCVP (rituximab, cyclophosphamide, vincristine, and prednisolone) and single agent cytarabine. **Rationale:** To reflect current (2024) UK clinical consensus and practice on standard of care which has changed since the previous brexucabtagene autoleucel submission. **Additional text proposed** NICE technology appraisal 677 recommends autologous anti-CD19-transduced CD3+ cells within the Cancer Drugs Fund as an option for treating relapsed or refractory mantle cell lymphoma in adults who have previously had a Bruton's tyrosine kinase inhibitor (BTKi). **Rationale:** To include all NICE technology appraisals that describe the current pathway **Current wording:** First-line treatment of mantle cell lymphoma may also include rituximab chemotherapy, and allogeneic haemopoietic stem-cell transplantation for fitter patients. Allogeneic haemopoietic stem-cell transplantation is a potentially curative treatment in patients for whom it is suitable	standard care. No change to scope required. As above. No change to scope required.

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		Proposed wording: Younger fit patients should receive a first-line induction regimen containing rituximab and high-dose cytarabine. Patients obtaining an objective response to induction therapy should be offered consolidation autologous stem-cell transplantation. **Rationale:** Allogeneic stem-cell transplantation is not recommended for first-line therapy of MCL. Autologous stem-cell transplant offers potentially long-term survival, but long-term follow-up studies have displayed a pattern of relapse for transplants in first-line.	Thank you. The background section of the scope has been updated to reflect this.
Population	Gilead Sciences Ltd	**Current text:** People with relapsed or refractory mantle cell lymphoma who have had at least 2 previous lines of therapy including a Bruton's tyrosine kinase (BTK) inhibitor **Proposed text:**	Thank you for your comments. The wording has been updated to more accurately reflect the marketing authorisation.

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		Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor. **Rationale:** To accurately describe the marketing authorisation.	
Subgroups	Gilead Sciences Ltd	TA677 did not identify relevant subgroups within the population.	Thank you for your comment.
Comparators	Gilead Sciences Ltd	Zanubrutinib is not an appropriate comparator. Zanubrutinib is a BTK inhibitor; it has not been studied in patients who have previously received another BTK inhibitor. Hence, there is no relevance to the population studied in this appraisal: adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor. At the time of writing Zanubrutinib is not recommended by NICE for MCL and the NICE website has no date by which guidance is expected. We are not aware of any intention to study zanubrutinib in the population of MCL patients that have already received BTKi. In the main study supporting use of Zanubrutinib, MCL patients were BTKi naïve. It is very unlikely that Zanubrutinib will become standard of care within the timeframe of this appraisal. Allogeneic haemopoietic stem cell transplant (AlloSCT) is not an appropriate comparator. Due to the high non-relapse mortality alloSCT is generally reserved for a very small number of young, fit patients to consolidate a response to ibrutinib (BTKi). In contrast brexucabtagene autoleucel is given to patients in the third-line plus setting who have failed on BTKi i.e. a different/later setting (BSH Guideline 2018). Data for AlloSCT post BTKi are extremely limited and there are no published studies considering AlloSCT	Thank you for your comments. The NICE scope includes all potentially relevant comparators that are (or may be) part of established clinical care at the time of the evaluation, even if only offered to a small number of patients. Zanubrutinib has been included as “subject to NICE evaluation”, but will not be considered as a relevant comparator if it has not been recommended by NICE by the time of this

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		post CAR-T treatment at present. The evidence is insufficient to evaluate the potential effectiveness and cost-effectiveness of AlloSCT in current practice.	appraisal. No change to scope required. The scope has been kept broad to include allogeneic haemopoietic stem cell transplantation as a potential comparator. The company can provide justification for its choice of comparators in its submission and the committee will seek clinical expert input to determine which comparators are relevant for the appraisal. No change to scope required.
	BeiGene UK	Zanubrutinib should not be included as a comparator for brexucabtagene autolucel (brexu-cel) in this appraisal for the following reasons: Brexu-cel marketing authorisation is for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor. This positions brexu-cel beyond BTK inhibitor zanubrutinib (or ibrutinib) in the	Thank you for your comments. Please see response above. No change to scope required.

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		treatment pathway, as a subsequent treatment option to zanubrutinib rather than as an alternative treatment option. This is reflected in the BSH Guidelines which recommend that *"MCL patients who are relapsed or refractory (including stable disease) after anti-CD20 antibody-containing immunochemotherapy and BTKi should be offered Brexu-cel*". With no overlap in the target patient populations for brexu-cel and zanubrutinib, the products cannot be considered comparators in HTA appraisal. Moreover, at present, zanubrutinib is neither licensed for use in MCL in the UK, nor has it been through a NICE HTA process to determine reimbursement. Zanubrutinib is therefore not currently used in UK clinical practice and consequently, in line with NICE's own methods guidance, should not be considered a comparator in this HTA appraisal.	
Questions for consultation	Gilead Sciences Ltd	**Please select from the following, will brexucabtagene autoleucel be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details):** C. Prescribed in secondary care with routine follow-up in secondary care. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention** Not applicable	Thank you for your comments.

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		Is the treatment pathway for mantle cell lymphoma outlined in the background section of this scope accurate? The treatment pathway in the scope is not an accurate description of current UK practice: • Allogenic SCT is not recommended for first line therapy of MCL. Fit patients obtaining an objective response to induction therapy should be offered consolidation Autologous SCT. • According to current UK clinical consensus, the standard of care after two lines of systemic therapy including a BTKi is brexucabtagene autoleucel. • TA677: Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma has been omitted. **Have all relevant comparators for brexucabtagene autoleucel been included?** Please see comments above **Do you consider that the use of brexucabtagene autoleucel can result in any potential substantial health-related benefits that are unlikely to be**	The background section has been updated to reflect this. Brexucabtagene autoleucel has been available through the Cancer Drugs Fund rather than through standard commissioning. It is therefore not yet possible for it to be considered as part of standard care. No change to scope required.

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		included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Patients and carers may experience a short-term reduction in their quality in life relating to the administration of brexucabtagene autoleucel and potential side effects, which are most likely to occur within the first 4 weeks of treatment, and the stress inherent to hospitalisation for intensive treatment of a life-threatening illness. The longer-term impact should be positive, considering the potential of sustainable remission and long-term survival with brexucabtagene autoleucel. Not only can this physically improve patients' quality of life, it also provides hope to patients and their carers, which should not be undervalued. There are administration benefits of a single treatment infusion versus the recurrent cyclic nature of conventional immunochemotherapy. Unlike immunochemotherapy that requires several cycles of toxic treatment, typically administered over a 4–6 month period, brexucabtagene autoleucel is a single-infusion treatment. Although there are some pre-infusion treatments and post-infusion monitoring, the total treatment period for brexucabtagene autoleucel is closer to 4–6 weeks than months. For patients living with severely reduced life expectancy these additional months of 'disease-free' living – time without progression or major toxicity – are an important benefit.	
Additional comments on the draft scope	Gilead Sciences Ltd	Early experience of brexucabtagene autoleucel through the CDF included unexpected rates of failure in the period between CDF application, T-cell harvest and infusion. It was hypothesised that this resulted from delays initiating therapy. In August 2022 UK clinical practice changed to introduce	Thank you for your comments. No change to scope required.

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		early monitoring of patients likely to progress on second line therapy, to minimise delays initiating brexucabtagene autoleucel. Subsequent to this guideline change, therapy success rates improved. In order to describe the real-world effects of brexucabtagene autoleucel, evidence from SACT should include enough patients treated after August 2022 and with sufficient follow--up to appropriately reflect the benefits of treatment as currently used in the NHS. The NICE process specifies that consultation will take place around the draft scope. The draft scope contained inaccurate statements about the size of the patient population, the current standard of care, the current place of brexucabtagene autoleucel in therapy, relevant comparators and related NICE guidance. The company believes that the information provided in the draft scope may not be sufficient to allow consultees – especially those not already expert in relapsed and refractory mantle cell lymphoma - to provide informed comment on the appraisal and that consultees might therefore have the opportunity to challenge this appraisal on grounds of failure to follow process. The company believes that additional consultation with a revised scope would be beneficial and allow consultees to provide appropriately informed comment.	

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

- **Lymphoma Action**