National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pirtobrutinib for treating chronic lymphocytic leukaemia or small lymphocytic lymphoma after 1 or more BTK inhibitors [ID6269]

Response to consultee and commentator 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

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Eli Lilly and Company (company)	Yes, this topic is appropriate to refer to NICE for review via the single technology appraisal route.	Comment noted. No action required
	CLL support	Yes, appropriate topic for evaluation and STA route	Comment noted. No action required
Wording	Eli Lilly and Company (company)	The wording of the remit should be updated to reflect the anticipated regulatory label. Please revise the remit to 'Adults with relapsed or refractory CLL who have been previously treated with a BTK inhibitor'.	Comment noted. The remit is kept broad as the anticipated marketing authorisation wording is currently confidential and may be subject to change. The remit has been updated to 'adults with chronic

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			lymphocytic leukaemia or small lymphocytic lymphoma whose cancer has been previously treated with a BTK inhibitor'
	CLL support	Yes	Comment noted. No action required
Timing Issues	Eli Lilly and Company (company)	Yes, the timings of this appraisal are appropriate	Comment noted. The appraisal will follow scheduled timelines. No action required
	CLL support	Fairly urgent – within 6 months	Comment noted. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.

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Additional comments on the draft remit	Eli Lilly and Company (company)	No further comments	Comment noted. No action required

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Eli Lilly and Company (company)	No comments.	Comment noted. No action required
	CLL support	Fine	Comment noted. No action required
Population	Eli Lilly and Company (company)	The wording of the population should be updated to reflect the anticipated regulatory label. Please revise the remit to 'Adults with relapsed or refractory CLL who have been previously treated with a BTK inhibitor'.	Comment noted. The population is kept broad as the anticipated marketing authorisation wording is currently confidential and may be subject to change. The population has been updated to 'Adults with CLL or SLL whose cancer has been previously treated with a BTK inhibitor'

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	CLL support	Yes	Comment noted. No action required
Subgroups	Eli Lilly and Company (company)	Please amend the wording from 'Adults with CLL or SLL who have previously had both a BTK inhibitor and venetoclax' to 'Adults with CLL who have received at least two prior lines of therapy including a BTK inhibitor and BCL2 inhibitor'.	Comment noted. The subgroup wording has been updated.
	CLL support	Yes. The so called 'double refractory' subgroup of patients who have relpased after both non covalent BTK inhibitors and BCL2 inhibitors – venetoclax. They have an urgent need for this treatment and managed access could be considered here.	Comment noted. If evidence allows the company can present subgroups in their submission for the committee to consider. The committee will consider the relevance of these subgroups in line with NICE's methods outlined in the CHTE 2022 manual.
Comparators	Eli Lilly and Company (company)	Since pirtobrutinib is indicated for patients who have been previously treated with a BTK inhibitor, zanubrutinib, acalabrutinib, and ibrutinib are not considered appropriate comparators. These therapies are typically used only in the relapsed/refractory (R/R) setting when patients become intolerant to another BTKi. Patients who are refractory to one BTKi would typically switch to a BCL2 inhibitor.	Comment noted. The list of comparators is intended to be kept inclusive at this stage. The appraisal committee will discuss the most appropriate comparator(s) during

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			the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical and cost-effectiveness evidence and current clinical practice.
	Astra Zeneca	The comparators appear broadly appropriate; however, it is important to highlight BTKi rechallenge is only available on the NHS for relapsed/refractory CLL as outlined in the Cancer Drugs Fund list, where: - The patient is treatment naïve to a Bruton's kinase inhibitor or the patient has been previously commenced on ibrutinib or acalabrutinib monotherapy for previously treated CLL/SLL and the ibrutinib or acalabrutinib has had to be discontinued solely due to dose-limiting toxicity and in the clear absence of disease progression. - Or the patient has previously been treated with the 1st line combination of ibrutinib plus venetoclax and was still in response on completion of treatment but has since relapsed and this application will be the first use of a BTK inhibitor since the 1st line combination of ibrutinib plus venetoclax.	Comment noted. The list of comparators is intended to be kept inclusive at this stage. 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 evidence and current clinical practice. No action required.

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		(https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1.352-03mar.pdf)	
	CLL support	Yes	Comment noted. No action required
Outcomes	Eli Lilly and Company (company)	Please include 'time to next treatment' as a relevant outcome measure. This outcome is important in CLL as it reflects the effectiveness of a treatment in delaying disease progression or relapse. In managing a chronic condition like CLL, extending the time between treatments can significantly improve patient outcomes and quality of life.	Comment noted. Time to next treatment has been added as an outcome measure.
	CLL support	Yes	Comment noted. No action required
Equality and Diversity	Eli Lilly and Company (company)	No equality issues have been identified.	Comment noted. No action required
Other considerations	Eli Lilly and Company (company)	No additional comments	Comment noted. No action required
Questions for consultation	Eli Lilly and Company (company)	**1. Where do you consider pirtobrutinib will fit into the existing care pathway for CLL/SLL?** The treatment pathway for Chronic Lymphocytic Leukemia (CLL) in England and Wales is guided by clinical guidelines from the British Society for Haematology (BSH) and previous NICE appraisals. Treatment for frontline CLL is determined by the patient's fitness for chemoimmunotherapy and the	Comments noted. The positioning of the technology in the treatment pathway will be considered by the

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		presence of genetic abnormalities, specifically 17p deletion and/or TP53 mutation. For patients fit for chemoimmunotherapy, the typical treatments include venetoclax-based regimens (in combination with obinutuzumab or ibrutinib) or chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR). However, the use of FCR has become increasingly rare since the introduction of venetoclax in the frontline setting. For the majority of frontline CLL patients (>90%) who are unfit for chemoimmunotherapy, the common treatments are either a BTK inhibitor as monotherapy (acalabrutinib or zanubrutinib) or a venetoclax-based regimen (in combination with obinutuzumab or ibrutinib). Patients with 17p deletion and/or TP53 mutation have treatment options including BTK inhibitors (ibrutinib, acalabrutinib, or zanubrutinib), venetoclax-based regimens, or idelalisib plus rituximab, although the latter is rarely used due to perceived inferior efficacy and safety profiles. In the relapsed/refractory (R/R) setting, similar treatment options are available, including BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib), venetoclax-based regimens (as monotherapy or in combination with rituximab), or idelalisib plus rituximab. The choice of treatment in R/R CLL depends on factors such as prior treatments received, reasons for discontinuation, toxicity profiles, and patient preference. If approved by NICE, pirtobrutinib is expected to be used across the R/R setting as a second or later line of therapy after prior treatment with one or more BTK inhibitors. Due to its mechanism of action as the first in class non-covalent BTK inhibitor, pirtobrutinib allows for the continuation of treatment via the BTK pathway in the post-BTKi setting, irrespective of the reason for	committee during the appraisal.

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		discontinuation of the prior BTK inhibitor. This represents a significant change in the management of CLL. **2. Would pirtobrutinib be a candidate for managed access?** The comparative efficacy data to be presented in this submission are expected to be suitably robust to allow pirtobrutinib to be considered for routine commissioning. However, should NICE deem that a managed access agreement may be more appropriate for pirtobrutinib in this indication, future additional data is expected to become available, although the time of data availability is currently uncertain. **3. Do you consider that the use of pirtobrutinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** No comments 4. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** No comments	
Additional comments on the draft scope		n/a	

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

AbbVie
BieGene

Lymphoma Action