National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia

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	Janssen-Cilag Ltd	No comments	No action required.
	Chronic Lymphocytic Leukaemia Support Charity	Yes	Thank you for your comment. No action required.
	Leukaemia Care	It is appropriate that NICE appraise this treatment.	Thank you for your comment. No action required.
	AbbVie	No comments	No action required.
Wording	Janssen-Cilag Ltd	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Chronic Lymphocytic Leukaemia Support Charity	Yes	Thank you for your comment. No action required.
	Leukaemia Care	Yes, no amends.	Thank you for your comment. No action required.
	AbbVie	No comments	No action required.
Timing Issues	Janssen-Cilag Ltd	No comments	No action required.
	Chronic Lymphocytic Leukaemia Support Charity	This would be the first combination of targeted therapies and an important development in the treatment of CLL, particularly if it can be approved for all patients.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. For more information please see https://www.nice.org.uk/guidance/awaiting-development/gid-ta10746

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	Leukaemia Care	The CLL clinical community feel that it is best to use the most effective treatment upfront, maximising the response from patients. Therefore, this new combination offers the opportunity for the NHS to save time and money associated with fewer patients relapsing.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. For more information please see https://www.nice.org.uk/guidance/awaiting-development/gid-ta10746
	AbbVie	No comments	No action required.
Additional comments on the draft remit	Janssen-Cilag Ltd	No comments	No action required.
	Chronic Lymphocytic Leukaemia Support Charity	No comments	No action required.
	Leukaemia Care	No comments	No action required.
	AbbVie	No comments	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Janssen-Cilag Ltd	First paragraph: Text states “4,226 cases” however this seems to refer to all lymphoid leukaemias from the ONS website. Janssen believe it would be more appropriate to reference the number of cases for CLL specifically, as aligned with NICE appraisals TA663 and TA689 – which both stated 3,800 new cases of CLL in the UK, equating to 3,157 cases in England per year. Second paragraph: In order to provide a more clinically accurate interpretation of the data, Janssen suggest rephrasing text to “Approximately 5% to 10% of people diagnosed with CLL have a 17p deletion or TP53 mutation when they require frontline treatment, which is considered to be a marker of "high-risk" disease”. Table 1 – TA487: The second column of this table indicates that these comparators are for “untreated CLL” – however, in the third column “population” it indicates that these are patients whose disease has progressed after treatment with 2 therapies which relates to a relapsed/refractory population. Given the scope of this appraisal is for patients with untreated CLL, Janssen would remove TA487 from this table.	Thank you for your comment. The scope has been updated. Thank you for your comment. No changes made to the scope. Thank you for your comment. The scope has been updated.

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	Chronic Lymphocytic Leukaemia Support Charity	"*The presence of an immunoglobulin heavy chain gene (IgHV) mutation may also affect clinical outcomes*" – It's not precisely clear what this means. It perhaps would be better to say 'Unmutated IgHV often leads to poorer clinical outcomes'	Thank you for your comment. The scope has been updated.
	Leukaemia Care	No comments	No action required.
	AbbVie	No comments	No action required.
The technology/ intervention	Janssen-Cilag Ltd	Second paragraph: BCL-2 is a protein which allows all cells to stay alive – not just cancer cells. In order to provide a more clinically accurate description of BCL-2, Janssen recommend an amendment to the text to state "…that allows cells to stay alive"	Thank you for your comment. The scope has been updated.
	Chronic Lymphocytic Leukaemia Support Charity	Yes	Thank you for your comment. No action required.
	Leukaemia Care	No comments	No action required.
	AbbVie	No comments	No action required.
Population	Janssen-Cilag Ltd	Ibrutinib with venetoclax will likely be positioned in patients with newly diagnosed CLL patients with no genetic mutations (del17p/TP53). The subgroup of patients with del17p/TP53 genetic mutations is therefore unlikely to be included in the analysis. All other subgroups are appropriate.	Thank you for your comment. Comment noted. No changes made to the scope.

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	Chronic Lymphocytic Leukaemia Support Charity	The population is defined appropriately - all patients with untreated CLL. The following groups should be considered separately if approval for all patients is not possible: - Del17p/TP53 mutated - Unmuated IgHV gene	Thank you for your comment. These subgroups are included in the scope. No action required.
	Leukaemia Care	The population should remain as broad as possible. All potential subgroups within this population have unmet needs for their treatments and therefore all should be fully appraised.	Thank you for your comment. No action required.
	AbbVie	No comments	No action required.
Comparators	Janssen-Cilag Ltd	Based on TA663, UK clinical experts confirmed that there is limited use of BR in current NHS practice in patients who are suitable for chemotherapy. This assertion was accepted by the Committee and ERG and comparison versus BR was not provided in comparative effective or economic analyses.	Thank you for your comment. The scope is intended to be broad and inclusive so as not to exclude potentially relevant comparators. No changes made to the scope.
	Chronic Lymphocytic Leukaemia Support Charity	The comparators are appropriate, but none can be precisely described as best alternative care because this is the first novel combination. Best alternative care will depend on many clinical factors and the genetics of the CLL of the individual patient.	Thank you for your comment. No action required.

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	Leukaemia Care	Idelasib is a technology that is available but is rarely used by clincians, especially in the front-line setting. Our advisors tell us that this is due to the adverse events being significantly less favourable than the other comparators that have become available since. The proportion of patients receiving idelasib is therefore likely to be very small.	Thank you for your comment. The scope is intended to be broad and inclusive so as not to exclude potentially relevant comparators. No action required.
	AbbVie	We note that table 1 lists treatment options for untreated CLL. In people without a del (17p) or TP53 mutation Venetoclax (TA663) should not be included as this does not represent a 1L treatment option.	Thank you for your comment. TA663 recommends venetoclax plus obinutuzumab as an option for untreated CLL in adults, only if: • there is a 17p deletion or TP53 mutation, or • there is no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab

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			(BR), is unsuitable, and TA663 also recommends venetoclax plus obinutuzumab as an option for untreated CLL in adults, only if: • there is no 17p deletion or TP53 mutation, and FCR or BR is suitable. No changes made to the scope.
Outcomes	Janssen-Cilag Ltd	Yes	Thank you for your comment. No action required.
	Chronic Lymphocytic Leukaemia Support Charity	Yes but also - 1 the measurement of residual disease should be an outcome measure. Remissions are likely to be many years and measurement of residual disease can be a surrogate marker for PFS. 2 complete response rate (CR) should also be included.	Thank you for your comment. The scope has been updated to include minimal residual disease as an outcome. The response rates outcome has been updated to clarify that

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			this includes complete response.
	Leukaemia Care	We believe that minimal residual disease (MRD) status should be considered as an outcome measure for this treatment. MRD is established as a good surrogate for overall survival in the CLL population.	Thank you for your comment. The scope has been updated to include minimal residual disease as an outcome.
	AbbVie	No comments	No action required.
Economic analysis	Janssen-Cilag Ltd	NA	No action required.
	Chronic Lymphocytic Leukaemia Support Charity	No comments	No action required.
	Leukaemia Care	No comments	No action required.
	AbbVie	No comments	No action required.
Equality and Diversity	Janssen-Cilag Ltd	NA	No action required.
	Chronic Lymphocytic Leukaemia Support Charity	There is an urgent need for access to novel treatments for younger, fitter patients with CLL. Currently only FCR or V+O via the Drugs Fund is available to them. This failure of equality of opportunity needs to be addressed urgently.	Thank you for your comment. No action required.

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		Both treatments are oral and we do not see any barriers to equality of opportunity regarding this aspect.	
	Leukaemia Care	No comments	No action required.
	AbbVie	No comments	No action required.
Other considerations	Janssen-Cilag Ltd	No comments	No action required.
	Chronic Lymphocytic Leukaemia Support Charity	No comments	No action required.
	Leukaemia Care	No comments	No action required.
	AbbVie	No comments	No action required.
Innovation	Janssen-Cilag Ltd	Ibrutinib with venetoclax is innovative in that it is the first all-oral fixed duration treatment with once-daily administration for patients with untreated CLL in the NHS. An oral, fixed-treatment duration has additional value to carers of patients with CLL.	Thank you for your comment. The extent to which the technology may be innovative will be considered in the technology appraisal. No changes made to the scope.
	Chronic Lymphocytic Leukaemia Support Charity	This is an innovative treatment as it is the first combination treatment proposed for CLL.	Thank you for your comment. The extent to which the technology

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		Results from this combination in clinical trials have shown excellent results with many patients having no detectable residual disease within a few months. Although the data is immature remissions are expected to be significantly more durable than many current treatments particularly for those with high risk CLL (17p del/TP53 mut and unmutated IgHV) Information and data from the following clinical trials and references may be of assistance **Blood Cancer Journal** **Ibrutinib and venetoclax target distinct subpopulations of CLL cells: implication for residual disease eradication** https://www.nature.com/articles/s41408-021-00429-z Results of GLOW trial reported at EHA June 2021 - **GLOW: Ibrutinib plus venetoclax showed superior efficacy as first-line treatment of CLL** https://conferences.m3medical.com/eha-2021/article/%20glow-ibrutinib-plus-venetoclax-showed-superior-efficacy-as-first-line-treatment-of-cll/ **ASH Publication 2019:** **Ibrutinib (Ibr) Plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic**	may be innovative will be considered in the technology appraisal. No changes made to the scope.

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		Lymphoma (SLL): Results from the MRD Cohort of the Phase 2 CAPTIVATE Study https://www.cancertherapyadvisor.com/home/cancer-topics/chronic-lymphocytic-leukemia/chronic-leukemia-cll-sll-captivate-study-findings-risk/2/	
	Leukaemia Care	This would mark a step change in the management of the condition, as the clinical community are keen to be able to use the most effective treatment options upfront. Additionally, this treatment is innovative in it's actions compared to other comparators and also compared with each treatment alone; the combination has been shown to work synergistically in the body. The combination may also reduce the risk of resistant clones developing. The treatment is a fixed duration therapy and targets cells in two different ways, helping to reduce the risk of resistance from long term targeting via one mechanism of action only (e.g. like ibrutinib is currently delivered). We believe the fixed-duration nature of the treatment is likely to deliver several benefits not captured in the QALY, such as ability to have treatment at home for periods and shorter time frame for experiencing adverse events versus continuous treatments. The impact of these things on a patient's quality of life should be taken into account.	Thank you for your comment. The extent to which the technology may be innovative will be considered in the technology appraisal. No changes made to the scope.
	AbbVie	No comments	No action required.

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Questions for consultation	Janssen-Cilag Ltd	No barriers to adoption are anticipated for ibrutinib with venetoclax–ibrutinib has been an established treatment in clinical practice for 4 years, for the treatment of patients with untreated CLL with del17p/TP53 genetic mutations and for those with relapsed/refractory disease. This means clinicians are familiar with treatment administration and management. Venetoclax is also recommended in combination with obinutuzumab for treating untreated CLL and as a monotherapy or in combination with rituximab for treating patients with previously treated CLL and clinicians have had experience with the therapy for the last 4 years. Cost comparison would be only appropriate in instances of clinical equivalence and the data are still under evaluation. Ibrutinib with venetoclax is a fully oral, fixed-duration treatment regimen so it is possible that there will be less resource use compared to the comparators which are administered intravenously, however this/thedata is still under evaluation	Thank you for your comment. No changes made to the scope.
	Chronic Lymphocytic Leukaemia Support Charity	No comments	No action required.
	Leukaemia Care	No comments	No action required.

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	AbbVie	No comments	No action required.
Additional comments on the draft scope	Janssen-Cilag Ltd	No comments	No action required.
	Chronic Lymphocytic Leukaemia Support Charity	No comments	No action required.
	Leukaemia Care	No comments	No action required.
	AbbVie	No comments	No action required.

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

Lymphoma Action
NHS England & Improvement
Pfizer