**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

# Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable (Managed access partial review of TA663) [ID6291]

## 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 | AbbVie UK (Company) | Following over 4 years of access via the CDF, Venetoclax with Obinutuzumab (VenO) is now an established treatment option for fit patients with untreated CLL. To ensure continued patient access to VenO, the appraisal of this technology to achieve routine reimbursement is pertinent. | Comments noted. No action required. |
| | Johnson & Johnson Innovative Medicine | Yes, the proposed evaluation route is appropriate. | Comment noted. No action required. |
| | CLL Support Charity | Yes, appropriate | Comment noted. No action required. |
| Wording | AbbVie UK (Company) | The NICE manual states that "*for technologies that were recommended with managed access, NICE will update the original scope. This is to make sure that the guidance update considers the care pathway and use of the technology in England at the time the guidance update starts. NICE can review any element in the scope, including changes that happened during the* | Comments noted. To distinguish the population being reviewed in ID6291 with the population |

| Section | Stakeholder | Comments [sic] | Action |
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| | | *managed access period to the: eligible patient population, treatment pathway or relevant health outcomes measures.*"<br><br>Additionally, per "NICE's strategic ambition to produce high quality guidance that is relevant, timely, useable and impactful (NICE, 2024)" AbbVie believe that the wording in the remit and population should be updated.<br><br>The treatment landscape has changed considerably since the initial appraisal with targeted treatments such as Ibrutinib with Venetoclax (I+Ven) and VenO via CDF being the preferred treatments in this population, with FCR and BR having been superseded by these targeted agents. Therefore, we propose that the wording of the remit is changed to<br>Venetoclax with obinutuzumab for fit patients with untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation.<br><br>Please note, we are only suggesting a change to the population wording to reflect the change in the treatment landscape, whereby, FCR/BR are no longer used. The patient cohort remains the same, this was the cohort previously considered for FCR/BR.<br><br>**Reference**<br>NICE, 2024. Consultation themed responses: Including NICE technology appraisal guidance in guidelines. [Online]<br>Available at: https://www.nice.org.uk/guidance/pmg47/documents/html-to-pdf#:~:text=The%20approach%20set%20out%20has,appraisal%20guidance%20into%20NICE%20guidelines. | recommended through routine commissioning in TA663 "Venetoclax plus obinutuzumab is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if there is no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is unsuitable", the information on the suitability of FCR or BR has been retained. No action required. |
| | Johnson & Johnson | Yes, the wording of the remit does reflect the issues. | Comment noted. No action required. |

| Section | Stakeholder | Comments [sic] | Action |
|---|---|---|---|
| | Innovative Medicine | | |
| | CLL Support Charity | Yes | Comment noted. No action required. |
| Timing issues | AbbVie UK (Company) | No Comment. | Comment noted. No action required. |
| | Johnson & Johnson Innovative Medicine | N/A | Comment noted. No action required. |
| | CLL Support Charity | This is a valuable treatment for CLL patients and it is urgent and important that it remains available. | Comment 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-ta11495. No action required. |
| Additional comments on the draft remit | AbbVie UK (Company) | None | Comment noted. No action required. |
| | Johnson & Johnson Innovative Medicine | None | Comment noted. No action required. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | AbbVie UK (Company) | As explained above, the NICE manual states that "*for technologies that were recommended with managed access, NICE will update the original scope. This is to make sure that the guidance update considers the care pathway and use of the technology in England at the time the guidance update starts"* (NICE, 2023).<br><br>Therefore, AbbVie would like the background information to reflect the current treatment landscape of the population relevant to this appraisal.<br>We recommend the following changes:<br>"Treatment of CLL is complex and depends on several factors such as stage of disease, previous treatment, person's age, symptoms, and general state of health. Many people with CLL will not have symptoms when they are first diagnosed and will have a period of active surveillance. The disease is monitored for progression and treatment is initiated upon progression. Chemoimmunotherapy **was previously used in fit patients without 17p deletion or TP53 mutation, however targeted therapies such as ibrutinib in combination with venetoclax and venetoclax in combination with obinutuzumab (CDF commissioned)** can achieve complete remission **and improve survival compared to chemo-immunotherapy and is recommended as a preferred treatment option for previously untreated, fit patients without TP53 mutations/17p deletions. Despite effective front line treatment options** ~~but~~ the disease may eventually relapse. **BTKi (ibrutinib, acalabrutinib or zanubrutinib) and venetoclax alone or in combination with anti-CD20 antibody, is the standard treatment options for relapsed CLL regardless of presence or absence of TP53 disruption** (Walewska, et al., 2022) (ESMO Guideline Committee, 2024) (NICE, 2023)**.** ~~Immunotherapies, such as rituximab, have been shown to improve survival and remission rates., particularly when combined with chemotherapy. Targeted therapies, such as acalabrutinib, ibrutinib, idelalisib and venetoclax are particularly useful in people with a poor prognosis, such as those with relapsed or refractory disease, and those with 17pdeletion or TP53 mutation.~~" | Comments noted. This section of the scope aims to provide a brief overview of the background for the evaluation; additional details may be considered by the committee, if appropriate, at the time of the evaluation. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | **References**<br>ESMO Guideline Committee, 2024. ESMO Clinical Practice Guideline interim update on new targeted therapies in the first-line and at relapse of chronic lymphocytic leukaemia. Annals of Oncology.<br>NICE, 2023. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia. [Online]<br>Available at: https://www.nice.org.uk/guidance/ta891<br>[Accessed 14 04 2025].<br>NICE, 2023. NICE health technology evaluations: the manual. [Online]<br>Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741<br>[Accessed 14 04 2025].<br>Walewska, R. et al., 2022. Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology, pp. 544-557. | |
| | Johnson & Johnson Innovative Medicine | Background statement amended for completeness:<br><br>The risk of developing CLL increases with age, is more common in men, those of white ethnicity, and have a family history of CLL.<br><br>***Reference:*** *What is chronic lymphocytic leukaemia (CLL)? (2024). Cancer Research UK. Accessed: March 2025.* | Comments noted. The background section provides a brief overview. The mentioned risk factors are aligned with that provided in the source reference. No action required. |
| | CLL Support Charity | Ok | Comment noted. No action required. |
| Population | AbbVie UK (Company) | Per the wording box above, we propose a change to the population definition. For ease of reference, we have copied this below:<br><br>The treatment landscape has changed considerably since the initial appraisal with targeted treatments such as I+Ven (and VenO via CDF) being the | Comments noted. To distinguish the population being reviewed in ID6291 with the population |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | preferred treatments in this population, with FCR and BR not considered as an appropriate option when making treatment decisions, having been superseded by these targeted agents r Therefore, we propose that the wording of the remit is changed to:<br>• Venetoclax with obinutuzumab for fit patients with untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation.<br><br>Please note, we are only suggesting a change to the wording to reflect the change in the treatment landscape, whereby, FCR/BR are no longer considered relevant treatment options. The patient cohort remains the same. | recommended through routine commissioning in TA663 "Venetoclax plus obinutuzumab is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if there is no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is unsuitable", the information on the suitability of FCR or BR has been retained. No action required. |
| | Johnson & Johnson Innovative Medicine | Yes, the population is defined appropriately. | Comment noted. No action required. |
| | CLL Support Charity | Yes | Comment noted. No action required. |
| Subgroups | AbbVie UK (Company) | N/A | Comment noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | Johnson & Johnson Innovative Medicine | N/A | Comment noted. No action required. |
| | CLL Support Charity | All groups should be considered for this technology but if resources are limited then the 17pdel and TP53 disrupted patients must be given priority. | Comment noted. No action required. |
| Comparators | AbbVie UK (Company) | As explained above AbbVie consider that I+Ven is the only relevant comparator given changes in the treatment landscape based on clinical expert feedback, guidelines and prior NICE technology appraisals.<br><br>**Bendamustine plus rituximab (BR):** Per the 2022 BSH Guidelines (Walewska, et al., 2022) which no longer recommend the use of BR in CLL patients, BR should not be a comparator. This aligns with the I+Ven appraisal (TA891) whereby it was noted that BR is 'rarely used in clinical practice and is no longer recommended in the 2022 BSH guidelines' (NICE, 2023). This feedback aligns with AbbVie clinical consultations.<br><br>**Fludarabine with cyclophosphamide and rituximab (FCR):** FCR should no longer be considered a relevant comparator, given advice from several clinical engagements and an advisory board with clinicians across England who agreed that FCR is not used anymore. Additionally, in TA891 the clinical experts and NHS England representatives noted that FCR and BR "are hardly used" (NICE, 2023). FCR usage has been superseded by targeted agents such as VenO and I+Ven. Furthermore, the ESMO guidelines (which are the most up-to-date guidelines in lieu of awaited updated BSH guidelines), no longer recommend FCR as a treatment option where targeted therapies are reimbursed (ESMO Guideline Committee, 2024). Per TA891 in 2022 the CLL Forum and the British Society for Haematology state that VenO has displaced chemoimmunotherapy as the preferred front-line treatment (NICE, 2023). Patient safety demands that when there are newer, more effective, and safer treatments, that these are favoured over scarcely used, outdated, unsafe | Comments noted. This section has been kept broad. The company will have the opportunity during the full evaluation to outline which comparators it considers to be most relevant. No action required. |

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| | | treatments. SCIT not only faces concerns regarding toxicity and the risk of secondary malignancies, for example in TA891 it was noted that FCR can have an 'extremely negative impact on patients' (NICE, 2023), but its use has been superseded by targeted agents.<br><br>**Acalabrutinib with venetoclax with or without obinutuzumab:** The NICE Methods manual (section 2.2.12) states that the scope should identify 'all potentially relevant comparators that are established practice in the NHS' (NICE, 2023). Given that acalabrutinib with venetoclax with or without obinutuzumab is not reimbursed in the UK, it cannot be established practice in the NHS and therefore should not be a comparator in this appraisal.<br><br>**References**<br>ESMO Guideline Committee, 2024. ESMO Clinical Practice Guideline interim update on new targeted therapies in the first-line and at relapse of chronic lymphocytic leukaemia. Annals of Oncology.<br>NICE, 2023. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia. [Online]<br>Available at: https://www.nice.org.uk/guidance/ta891<br>[Accessed 14 04 2025].<br>Walewska, R. et al., 2022. Guideline for the treatment of chronic lymphocytic leukaemia. British Journal of Haematology, pp. 544-557. | |
| | Johnson & Johnson Innovative Medicine | Yes, these seem to represent standard treatments currently used in the NHS. | Comment noted. No action required. |
| | CLL Support Charity | Yes<br>Please note patients appear to be opting for this time limited treatment in preference to an ongoing BTKi. | Comment noted. No action required. |
| Outcomes | AbbVie UK (Company) | No comment | Comment noted. No action required. |

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| | Johnson & Johnson Innovative Medicine | Yes, these outcome measures capture the most important health related benefits and harms of the technology. | Comment noted. No action required. |
| | CLL Support Charity | Yes.<br>Recent publications have shown that this is a treatment which gives excellent results on all the outcome measures when compared to the comparators. | Comment noted. No action required. |
| Equality | AbbVie UK (Company) | No comment | Comment noted. No action required. |
| | Johnson & Johnson Innovative Medicine | N/A | Comment noted. No action required. |
| | CLL Support Charity | No comment | Comment noted. No action required. |
| Other considerations | AbbVie UK (Company) | For completeness and stakeholder awareness, per TA663 VenO is already routinely funded where patients:<br>- have a 17p deletion or TP53 mutation regardless of their fitness status, or<br>- there is no 17p deletion or TP53 mutation, and FCR or BR is unsuitable<br><br>Please note, in TA663 FCR/BR unsuitability was used given the historical usage, and therefore, does not align with the update/changes in the treatment pathway highlighted earlier. | Comments noted. TA663 recommendations for routine commissioning are stated in Table 1. No action required. |
| | Johnson & Johnson Innovative Medicine | N/A | Comment noted. No action required. |
| | CLL Support Charity | None | Comment noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Questions for consultation | AbbVie UK (Company) | *Where do you consider venetoclax with obinutuzumab will fit into the existing care pathway for untreated chronic lymphocytic leukaemia when there is no 17p deletion or TP53 mutation and FCR (fludarabine, cyclophosphamide, rituximab) or BR (bendamustine, rituximab) are suitable?*<br><br>Given that this appraisal is for a cancer drugs fund (CDF) exit, AbbVie believe there will be no change to the care pathway vs. the established pathway which already exists. This appraisal aims to ensure continued access for 1L fit CLL patients to VenO to avoid an unmet need arising.<br><br>Per above, it would be appropriate to remove FCR and BR from the remit/population wording. | Comment noted. To distinguish the population being reviewed in ID6291 with the population recommended through routine commissioning in TA663 "Venetoclax plus obinutuzumab is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if there is no 17p deletion or TP53 mutation, and fludarabine plus cyclophosphamide and rituximab (FCR), or bendamustine plus rituximab (BR), is unsuitable", the information on the suitability of FCR or BR has been retained. No action required. |
| | | *Please select from the following, will venetoclax with obinutuzumab be:*<br>*A. Prescribed in primary care with routine follow-up in primary care*<br>*B. Prescribed in secondary care with routine follow-up in primary care* | Comments noted. No action required. |

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| | | *C. Prescribed in secondary care with routine follow-up in secondary care*<br>*D. Other (please give details):*<br>*For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.*<br><br>AbbVie believe VenO will continue to be prescribed in secondary care with routine follow-up in secondary care, and the comparators and subsequent treatments would be the same.<br><br>*Do you consider that the use of venetoclax with obinutuzumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?*<br><br>No comment<br><br>*Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.*<br><br>No comment<br><br>*Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics.*<br><br>No comment | |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | *NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:*<br>*•could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which venetoclax with obinutuzumab is licensed;*<br>*•could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*<br>*•could have any adverse impact on people with a particular disability or disabilities.*<br>*Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.*<br><br>No comment | |
| | Johnson & Johnson Innovative Medicine | N/A | Comment noted. No action required. |
| Additional comments on the draft scope | AbbVie UK (Company) | No comment | Comment noted. No action required. |
| | Johnson & Johnson Innovative Medicine | Add the below information for completeness:<br><br>**Related NICE guidelines:**<br>Suspected cancer: recognition and referral (June 2015, updated October 2023) NICE guideline NG12<br><br>**Related National Policy:** | Comments noted. The most relevant NICE guidelines have been referenced. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | | The NHS Long Term Plan, 2019. NHS Long Term Plan<br>NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 105 | |
| | CLL Support Charity | None | Comment noted. No action required. |

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

Lymphoma Action