NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia
Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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.

Comments received from consultees

Consultee	Comment	Response
CLL Support Association	CLL Support Association can confirm our disappointment at the committee's decision [ACD1] not to recommend Obinutuzumab in combination with chlorambucil for treatment of chronic lymphocytic leukaemia patients who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them. CLL displays extreme heterogeneity underpinned by considerable biological diversity, and yet patients who are unfit for FCR have little choice of treatment and rely on old technology drugs. The old technology drugs are not targeted to the individual patient, and are characterised by lower overall response, early relapse, reduced quality of life, and additional toxicity. Repeat treatment is therefore required at further cost to both the NHS and at personal cost to patients and their families There is concern in the CLL patient community that there is no UK approved alternative monoclonal antibody to Rituximab, a longstanding agent of limited effectiveness in CLL. In addition, it is difficult to accept that Obinatuzumab has been granted breakthrough status in the US, it is now fully approved by the FDA, it is licensed in Europe but it has been rejected by NICE in the draft guidance when all these appraisals were conducted using the same trial data from CLL11. This technology would offer the majority CLL group a combination therapy that provides an opportunity for a more durable remission and improved quality of life. Equitable access to treatments that better extend life without disease and improve the quality of that life should also be considered important. Without these new technologies and improved outcomes the CLL patient group made up by a large portion of people with protected characteristics of age and disability will continue to receive second best treatment and limited choice.	Comments noted. The Committee considered the responses to the appraisal consultation document (ACD1) that failure to consider the population who cannot have fludarabine as 2 separate groups (those who can have bendamustine and those who cannot) may be interpreted as discriminatory. This is because people who cannot have bendamustine would not have access to alternative effective treatments if obinutuzumab was not recommended. The Committee also considered new evidence and a patient access scheme submitted by the company (see section 3.36 of the FAD). It agreed that the population who cannot have fludarabine could be divided into 2 subgroups of people; those who can have treatment with bendamustine and those who cannot (see section 4.4 of the FAD). The Committee recommended obinutuzumab, in combination with chlorambucil, as an option for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if: • bendamustine-based therapy is not suitable **and** • the company provides obinutuzumab with the discount agreed in the patient access scheme. Therefore its recommendations did not lead to

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	If more effective treatment alternatives are not made available in this era of patient choice then such inconsistency must be clearly explained to the patient community.	discrimination and it did not need to add to, or change, its recommendations.
Leukaemia Care	Thank-you for giving us the opportunity to comment on the appraisal consultation document for 'Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia [ID650]'. We would like to comment that Leukaemia CARE is happy with the appraisal committee's preliminary recommendations that: "Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if: • bendamustine-based therapy is not suitable **and** • the company provides obinutuzumab with the discount agreed in the patient access scheme."	Comments noted. No action required.
Lymphoma Association	We are pleased that a patient access scheme has been agreed and we are happy to support the content of the ACD.	Comment noted. No action required.
NHS England	**Has all of the relevant evidence been taken into account?** Yes **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes NHS England believes this is a robust review of the clinical and cost effectiveness data. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Yes – NHS England supports the recommendations within the draft guidance **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**	Comments noted. The Committee considered the responses to the appraisal consultation document (ACD1) together with new evidence and patient access scheme submitted by the company (see section 3.36 of the FAD). It agreed that the population who cannot have fludarabine could be divided into 2 subgroups of people; those who can have treatment with bendamustine and those who cannot (see section 4.4 of the FAD). The Committee recommended obinutuzumab, in combination with chlorambucil, as an option for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for

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	None have been identified The National CDF panel have also considered obinutuzumab – please see the summary of the panels considerations below: The application was for the use of obinutuzumab as part of 1st line chemotherapy with chlorambucil for patients with chronic lymphocytic leukaemia with significant comorbidities contraindicating full dose fludarabine-based combination therapy. A trial has been published in the New England Journal of Medicine (NEJM) in 2014 which was in two parts. The first phase compared the 3 options of chlorambucil (Cb) plus obinutuzumab vs Cb plus rituximab vs Cb alone. The second part just randomised patients to obinutuzumab plus Cb vs rituximab plus Cb. All patients had a clinically meaningful burden of comorbidities: either a score of >6 on the Cumulative Illness Rating Scale (CIRS, range of potential scores 0-56) or an estimated creatinine clearance of 30-69 mls/min. Cross over was allowed for the Cb patients if they progressed whilst on Cb or within 6 mo of completing Cb. Chlorambucil was taken on 2 days of a 28 day cycle. A maximum of 6 cycles of treatment was given. The median durations of follow-up were not stated in the publication. In terms of the the comparison between obinutuzumab plus Cb vs Cb alone, the response rate was significantly superior (77 vs 31%). Median progression free survival (PFS) was significantly superior with obinutuzumab plus Cb arm (26.7 vs 11.1 months). Overall survival was significantly superior in the obinutuzumab plus Cb arm but the median survivals were not reached. Quality of life using the EORTC QLQ C30 tool was assessed and did not deteriorate but there are no details or statistics in the appendix to the NEJM paper. Toxicity was increased with obinutuzumab plus Cb with any WHO grade ≥3 toxicity being 70 vs 50% and grade ≥3 neutropenia being 33 vs 16% but there was no difference in infections. The panel noted that the schedule of administration of Cb in the trial was not one that is standard in the UK. The current British Committee for Standards in Haematology (BCSH) guideline in CLL states that the highest response rate and longest PFS have been reported in the UK Leukaemia Research Fund CLL4 trial in which chlorambucil was administered at a dose of 10 mg/m² for 7 days every 4 weeks initially for 6 months but extending to 12 months in those patients still responding after 6 months of treatment. This schedule of Cb is the only one	them, only if: • bendamustine-based therapy is not suitable **and** • the company provides obinutuzumab with the discount agreed in the patient access scheme.

Consultee	Comment	Response
	specifically mentioned in the guideline. The CDF panel heard from experts that this BCSH documented dose and schedule is by far the most commonly used way of administering Cb in England. The CDF panel noted that the publication did not state the median duration of follow-up. The panel also observed that in the OS analysis there were relatively few patients at risk after 27 mo. In a disease such as CLL where there are likely to be a number of treatment options and in which the median survival is measured in years, the survival difference is of great interest but needs further follow-up. The CDF panel scored the application as follows: 9 for PFS (using the revised CDF scoring system for PFS differences beyond 12 mo), 0 for OS (this recognised the significant difference in OS in the comparison between obinutuzumab plus Cb vs Cb alone but also that the median duration of follow-up was not stated and there were relatively few patients at risk beyond 27 mo), 0 for QOL (no details or statistics), -1 for toxicity and 0 for unmet need. The overall score was 8 B. The CDF panel was mainly concerned about 2 aspects of the design of the trial, both impinging on the control arm of Cb in this study. The trial employed a schedule of Cb which is not one that is recommended as standard by the BCSH and hence one that is not in general use in England. The CDF panel noted that in the appendix of the obinutuzumab NEJM publication, the dose of Cb per cycle for a patient of 70 kg and 170 cm body height in the obinutuzumab trial was calculated to be 70 mg as opposed to 129 mg in the CLL4 study (an 84% increase in Cb dose). In addition, the maximum duration of treatment with Cb in the obinutuzumab trial was 6 mo, in contrast to a potential treatment duration of up to 12 mo as stated in the BCSH guideline. The CDF panel recognised the clear superiority of obinutuzumab plus Cb over a schedule of Cb alone. It considered that this twice monthly schedule may be inferior to the standard schedule of administration of Cb used in England which delivers a much higher dose in a very different way but is one that is recommended by the BCSH. A similar issue was also considered to apply to the shorter duration of Cb treatment employed in the trial vs standard practice as indicated in the BCSH guideline. The CDF panel therefore declined to approve the inclusion of obinutuzumab in combination with Cb in the 1st line treatment of CLL as it could not separate the positive contribution of obinutuzumab from the potential effect of the reduced dose intensity of Cb.	

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	The manufacturer also submitted an application for obinutuzumab plus Cb to be the preferred option to the combination of rituximab and Cb. In this part of the randomisation in the above clinical trial, the response rate was significantly superior with obinutuzumab plus Cb (78 vs 65%), as was PFS (26.7 mo vs 15.2months). There was no significant difference in overall survival. Quality of life as measured by the EORTC QLQ C30 instrument was stated to not deteriorate with obinutuzumab plus Cb but the only details were in the appendix of the NEJM publication and no statistics were given. WHO grade ≥3 toxicity was greater in the obinutuzumab plus Cb arm (70 vs 55%). The manufacturer proposed the option of obinutuzumab plus Cb for those patients with CLL who could not tolerate full dose fludarabine-based therapy. The CDF panel noted these results and again had the same concern about the scheduling of chlorambucil in this trial being one that was not standard in England and potentially inferior to the one recommended by the BCSH in its 2012 guideline. In addition, the panel heard from experts at the CDF meeting that there was a group of patients who, whilst not being fit enough to tolerate full dose fludarabine-based therapy, were nevertheless able to cope with more robust treatment than Cb alone: these patients received the combination of bendamustine and rituximab and not the combination of Cb plus rituximab nor single agent Cb. The CDF panel was also aware that the combination of Cb plus rituximab is not routinely commissioned in England (whereas bendamustine plus rituximab is). The CDF panel therefore did not regard the comparison of Cb plus obinutuzumab with Cb plus rituximab as being a relevant decision problem to England. The CDF panel thus declined to approve the inclusion of obinutuzumab as part of 1st line chemotherapy in the treatment of CLL. The panel observed that there was now an evidence base for the comparison of Cb plus rituximab vs Cb alone from this trial which demonstrated the superiority of Cb plus rituximab. However, this conclusion also suffered the same criticism as regards the dose and scheduling of Cb employed in this trial.	
Roche Products	We are pleased that the Committee has chosen to issue positive guidance for the sub group of patients that are unsuitable for bendamustine. If converted to final guidance this will allow people with chronic lymphocytic leukaemia to benefit from the significant survival advantage that obinutuzumab offers over existing treatment. I would also like to extend my thanks for identifying an earlier Committee meeting for development of the FAD, which could provide patients access to this important drug	Comments noted. No action required.

Consultee	Comment	Response
	by the end of May. We would be happy to provide any additional information that is needed by the Committee to conclude this appraisal.	
Royal College of Physicians	We believe that the proposal to split the patient population into those for whom a bendamustine based regimen is a potentially suitable alternative therapy to chlorambucil/obinutuzumab combination therapy and those for whom bendamustine is not appropriate, appears very sensible. This is in keeping with real life physicians thought processes when trying to decide the most appropriate therapy for any individual patient. We note that NICE have accepted the revised costs for neutropenic fever management. We note that the company have provided NICE with details of a Patient Access Scheme which they will make available to increase patient access to chlorambucil/obinutuzumab combination therapy. Our experts do not feel qualified to comment on the various points of disagreement, in terms of the most appropriate utility value to apply to the various scenarios examined with regards to PFS. We note in the ACD that the Committee are recommending the use of chlorambucil/obinutuzumab for patients unsuitable for a bendamustine based regimen but not for those patients suitable for a bendamustine based regimen providing that the PAS is supplied by the company. We believe that this is an appropriate recommendation as it gives patients with few other therapeutic options the opportunity of receiving chrlorambucil/obinutuzumab, which will prolong their survival. Our experts feel that this recommendation, if accepted, will also enable clinicians the full range of appropriate therapeutic options to their very heterogeneous CLL patients. In conclusion, we support the recommendations regarding the provision of chlorambucil/obinutuzumab combination therapy to CLL patients as outlined in the Appraisal Consultation Document	Comments noted. No action required.

Comments received from commentators

Commentator	Comment	Response
Napp Pharmaceuticals	We would like to suggest, in order to avoid any confusion and in line with the licensed indication, that unless being compared directly as monotherapy to other single agent anti CD20 immunotherapies such as rituximab or ofatumumab, NICE and the ERG should refer to obinutuzumab throughout the text as obinutuzumab-chlorambucil. The standard practice in haemtaology is for a CD20 monoclonal antibody to be combined with a chemotherapy "backbone". The standard therapies used as the chemo backbone in the treatment of CLL are chlorambucil, bendamustine and fludarabine with or without cyclophosphamide. The comparator anti CD20 antibodies used in conjunction with the above chemotherapy agents are rituximab and ofatumumab. Therefore it would be illogical and highly unlikely that the monoclonal antibody obinutuzumab as a single agent would ever be compared to bendamustine, or any other cytotoxic chemotherapy directly. Indeed, rituximab monotherapy as a front line treatment is rarely, if ever used.	Comments noted. This technology appraisal considered obinutuzumab within its marketing authorisation, that is, in combination with chlorambucil for 'the treatment of adult patients with previously untreated chronic lymphocytic leukaemia and with comorbidities making them unsuitable for full-dose fludarabine based therapy'. The Committee recommended obinutuzumab, in combination with chlorambucil, as an option for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if: • bendamustine-based therapy is not suitable and • the company provides obinutuzumab with the discount agreed in the patient access scheme

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	N/A	I would like to support the proposal for use of obinutuzumab in this indication. A very significant achievement with the study was the achievement of negative minimal residual disease in over 30% of patients who received obinutuzumab. This is not seen with many others therapies for CLL - and was not detectable at all with the rituximab arm. Experience in many trials of drugs in CLL has shown that the 'depth' of the response to treatment is highly predictive of subsequent overall time to next treatment and to overall survival. It is therefore highly likely that the positive results for this new antibody on negative MRD will translate directly into an improvement in overall survival.	Comments noted. The Committee considered the responses to the appraisal consultation document (ACD1) together with new evidence and patient access scheme submitted by the company (see section 3.36 of the FAD). It agreed that the population who cannot have fludarabine could be divided into 2 subgroups of people; those who can have treatment with bendamustine and those who cannot (see section 4.4 of the FAD). The Committee recommended obinutuzumab, in combination with chlorambucil, as an option for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if: • bendamustine-based therapy is not suitable and • the company provides obinutuzumab with the discount agreed in the patient access scheme

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.