National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia [ID650]

You are asked to check the ERG report from PenTAG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Wednesday 13 August 2014** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 The assumptions underlying the ERG's alternative indirect comparison are not clearly stated and evaluated

Description of problem	Description of proposed amendment	Justification for amendment
The ERG have compared the ratio of the median PFS observed for patients aged above and below age 65 in Knauf 2009 in order to support the claim that the relative efficacy of bendamustine and chlorambucil is not impacted by age. This is subsequently utilised to justify the application of the ITT PFS HR from Knauf (which featured patients eligible for fludarabine) to patients ineligible for fludarabine based therapy in the UK (who have more comorbidities and are significantly older – median age 73 in CLL11). The report does not fully reflect the assumptions underlying this application. Section 1.2.2 page 17	The assumptions underlying the ERG's alternative indirect comparison should be clearly stated and evaluated for their validity. The key assumptions not stated in the report are as follows: (1) The extent to which a patient is ineligible for fludarabine has no bearing on the patient's tolerability to, and subsequent efficacy of, bendamustine or chlorambucil (2) The comparison of the efficacy of bendamustine and chlorambucil in patients above and below age 65 is sufficient to conclude that the relative efficacy of these agents would be equivalent in patients of median age 73	The inclusion and description of the key assumptions underlying the ERG's alternative scenarios are essential if the report is to be utilised by the Committee to reach a 'fair' decision on obinutuzumab with chlorambucil. As it stands the report is factually inaccurate as it does not include this information.

Issue 2 The alternative indirect comparison approaches are not clearly stated and their impact evaluated

Description of problem	Description of proposed amendment	Justification for amendment
The executive summary doesn't report that a PFS HR between Ob Clb and R benda was derived from the MTC and that the ERG have opted not to use this in favour of use of an estimate derived from an unproven and assumed relationship between response rates and PFS (with response rates derived from a sample of 28 patients). This information, including the resulting ICER if using the MTC-derived HR, should be reflected in the executive summary (and elsewhere in the document where this is mentioned). Section 1.2.3 page 18	Text should be added to explain the assumptions underlying the ERG's analysis, and the results of the economic evaluation including use of the MTC-derived PFS HR for Ob Clb and R benda should be presented. It should be noted in the text that in the age-adjusted large network this HR is 0.37, rather than the 0.76 estimated using the ERG's approach (i.e. use of the available data on PFS results in the relative efficacy of obinutuzumab chlorambucil increasing compared to use of an unproven relationship between response rates and PFS). Please note that we do not believe benda and R benda are appropriate comparators to Ob Clb as the patients eligible for these regimens are fundamentally different.	The inclusion and description of the key assumptions underlying the ERG's alternative scenarios are essential if the report is to be utilised by the Committee to reach a 'fair' decision on obinutuzumab with chlorambucil. As it stands the report is factually inaccurate as it does not include this information.

Issue 3 The impact of using a lower dose of chlorambucil in CLL11 than in clinical practice is stated to result in the efficacy of obinutuzumab being over-estimated.

Description of problem	Description of proposed amendment	Justification for amendment
The statement that "If, as our clinical expert believes, chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab + chlorambucil versus chlorambucil is over-estimated in CLL11" is incorrect. Section 1.2.1 page 14	The word 'over-estimated' should be replaced with 'uncertain'. The report should be amended to reflect the fact that any link between the dose of chlorambucil and extended PFS would similarly impact the outcomes observed in each arm of the CLL11 study.	The dose of chlorambucil was the same in all 3 arms of the CLL11 study (ObClb, Clb, RClb; 0.5mg/kg d1 + d15 q28days). Any Clb-dose-related effect on efficacy would therefore be present in ALL arms of the study. Whilst it may be claimed that the difference in dosing of chlorambucil introduces uncertainty into the evaluation it is factually inaccurate to claim this will over-estimate the efficacy of obinutuzumab + chlorambucil as each arm will be similarly biased.

Issue 4 Miscellaneous issues – Cost of adverse events

Description of problem	Description of proposed amendment	Justification for amendment
We note the discrepancies between our AE costs and the ERG's estimates from seemingly different versions of NHS reference costs 2012/13 and on the whole given that the cost differences are small are happy to use the ERG's version. However the ERG has used costs for all types of stay in hospital (i.e. elective and non-elective). Given that when AEs occur these are unscheduled, the relevant cost for each AE should relate to "non-elective stay" only. Section 5.4.10.5 page 153-155	For the majority of AEs this has little impact but for neutropenia and febrile neutropenia we suggest the cost should be changed from £5993 to either £4519 (non-elective long stay) or £1064 (non-elective short stay).	This correction will allow for a more accurate incorporation of cost of AEs within the economic model.

Issue 5 Availability of PFS HR between R benda and R Clb

Description of problem	Description of proposed amendment	Justification for amendment
The report states that data from the MaBLe study will become publicly available in October 2014 (Section 1.5 page 28). This is factually inaccurate. Section 1.5 page 28	This statement should be updated to reflect the fact that data from MaBLe are unlikely to be publicly available before EHA in June 2015.	The MaBLe data was due to be presented at the American Society of Hematology conference in Q4 2014. Following a delay in the closing of the study database and subsequent validation of the response data observed this is no longer the case. It is expected this data will be presented at EHA in June 2015.

Issue 6 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment
The statement 'It also does not model second line treatment with fludarabine' as a criticism of the Roche model. Section 1.3.2 page 20	The statement should be removed.	The criticism is inappropriate as the HTA patient population is patients for whom fludarabine is unsuitable.

Issue 7 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment
The statement does not make sense: 'At a willingness to pay of £30,000 per QALY, obinutuzumab + chlorambucil and chlorambucil provide the best value for money, and offer very similar value. Obinutuzumab + chlorambucil is poor value. Rituximab + chlorambucil offers slightly worse value.' Section 1.5.3 page 32	The statement should be clarified.	In this statement obinutuzumab + chlorambucil is described as providing the best value and as poor value at the same time. This appears to be an error, or if not is a very confusing way of summarising the results of the economic evaluation. It would be preferable to clarify or revise this statement.

Issue 8 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment
On page 15 the following statement needs alteration 'In addition, the obinutuzumab + chlorambucil arm had a statistically significant greater event-free survival (p<0.0001 both), end of treatment response (p<0.0001 versus both chlorambucil and rituximab + chlorambucil), MRD-negative rate (26.79 [19.5 - 34.1] versus chlorambucil and 23.06 [17.0 - 29.1] versus **obinutuzumab** + chlorambucil), best overall response (p<0.0001 versus chlorambucil and p=0.0001 versus **obinutuzumab** + chlorambucil), disease free survival (p<0.0001 versus chlorambucil and p=0.0475 versus **obinutuzumab** + chlorambucil), and time to new treatment (p<0.0001 versus chlorambucil and p=0.0018 versus **obinutuzumab** + chlorambucil) compared to chlorambucil and rituximab + chlorambucil.' Section 1.2.1.1 page 15	The word obinutuzumab (bolded) should be changed to rituximab.	The correction is necessary for the accurate meaning of the sentence as the obinutuzumab + chlorambucil arm is compared to the rituximab + chlorambucil arm, not to itself.

Issue 9 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment
'The incidence of IRRs (infusion related reactions), neutropenia, thrombocytopenia, leukopenia, **anaemia, pyrexia, and nasopharyngitis** was higher (> 5% difference) in the obinutuzumab based arm than in the rituximab + chlorambucil or chlorambucil arms of the study.' Section 1.2.1.1 page 15	The words anaemia, pyrexia and nasopharyngitis (bolded), should be removed from this statement as there is not a >5% difference in the incidence of these adverse events between any of the treatment arms as per the table below (sourced from Table B30 and Table B31 of the Roche submission).	The difference in the incidence of anaemia, pyrexia and nasopharyngitis is not >5% between any of the treatment arms as per the table below (sourced from Table B30 and Table B31 of the Roche submission see pdf file below). Roche Obinutuzumab ID650 Submission - Ta This correction is necessary for the accurate reporting of data.

Issue 10 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment
'We believe the best estimate is 0.76, compared to Roche's estimate of **68**. Section 1.3.3 page 21	The number 68 should be corrected to 0.68.	The correction is necessary for the accurate reporting of data.

Issue 11 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment
On pages 102 and 146 Figure 21 and Figure 27 have a different line thickness compared with the original figures provided in the submission Section 5.2.5.1 page 102 and Section 5.4.8.2 page 146	The original figures presented in the Roche submission should be used.	This change will facilitate the reading of the figures.

Issue 12 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment
Cost of Rbenda is incorrect at £7,000. Section 1.3.5.1 page 21	The cost of Rbenda should be corrected.	The cost of RClb is reported as £10,000, as £300 for Clb and as £7,000 for benda. Therefore, the price of £12,000 for Rbenda is not accurate.

Issue 13 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment
‘We note that some discrepancy between Goede et al’s paper and the submission exists in relation to the description of the number of countries and number of centres involved in the trial. Goede et al describe the trial as “conducted in 26 countries; 189 centres enrolled patients” (Goede et al, pp 2), while in the Manufacturer’s Submission Roche state that study CLL11 was “conducted in 250 centres in 25 countries” (Source: Roche Submission, Section 6.7.2, Table B23, pp80; Section 6.10.2, pp123). There is a further inconsistency in reporting, with Goede et al reporting “this global study was conducted in 269 centres of 26 countries” in their supplementary appendix (4)’ Section 4.1.4 page 53	The following values should be used: 269 centres and 26 countries (as per Goede et al. 2014).	This discrepancy is due to differences in the number of countries and centres who enrolled patients versus those countries/centres who opened the study and differences with the number of centres enrolling into stage1a of the study versus stage 2 which continued enrolment once stage 1a was closed.