Obinutuzumab in combination with Chlorambucil for untreated chronic lymphocytic leukaemia

Appendix to ACD Response –
Use of utility values from ID642 and
the correction of a factually inaccurate costing of Neutropenia

New evidence has recently been made public in the NICE appraisal of ofatumumab in combination with chlorambucil, for the treatment of previously untreated chronic lymphocytic leukemia [ID642]. These new values are likely to alter the Committee's preferred value for the PFS off-treatment utility and subsequently have a material impact upon their decision.

The Committee concluded in the ACD, that the PFS off treatment utility value should be no higher than 0.76 (the general population average for patients of this age) and stated 0.71 as their preferred value.

The EQ-5D data presented by the manufacturer of ofatumumab from the COMPLEMENT-1 study was collected from patients directly relevant to the scope of this appraisal and produced observed values of 0.78, 0.79 and 0.76 for patients with complete response, partial response and stable disease[i] as best response to treatment respectively. The general population of this age are likely to have multiple morbidities (by virtue of their age) and so it may be the case that (as suggested by the ofatumumab EQ-5D data) the quality of life of comorbid patients with CLL may be comparable, or potentially slightly higher, than that of the general population.

This new data is important as it resolves one of the key issues raised by the committee in the ACD and allows the assumption of a 0.71 utility value to be replaced with one based upon gold standard EQ-5D data (with values of 0.78, 0.79 and 0.76 observed for patients with complete, partial response and stable disease as best response to treatment respectively).

In addition a minor error has been identified and corrected in the economic model. Previously every incidence of Neutropenia in the model was associated with the cost of Febrile Neutropenia in the model (a significantly more costly adverse event - £3894). The results provided within this ACD include the use of the cost of Neutropenia estimated by LRiG in NICE ID620, valued at £867 per episode.

Impact of these corrections on cost-effectiveness

Following the introduction of a patient access scheme the ICERs associated with use of obinutuzumab in patients unsuitable for treatment are now within the range typically considered acceptable in technology appraisals. As a result the two pieces of information highlighted above may have a material impact upon the Committee's decision and should be considered in the next Committee meeting.

In light of the information presented above the cost of Neutropenia has been amended and a sensitivity analysis has been carried out using the PFS off treatment utility value based upon those from ID642 (0.76). We consider that this remains a conservative estimate given the values of 0.78 and 0.79 for complete and partial response reported for ofatumumab from the COMPLEMENT-1 trial[i].

The impact of changing the PFS utility value upon the base-case ICERs submitted is shown in Figure 1 below. The impact of correcting the cost of Neutropenia is shown in Figure 2.

Figure 1. Submitted base-case ICERs with utility variation

Utility Values	R-Benda	R-Clb	Benda	Clb
0.82	£19,898	£21,275	£26,463	£24,256
0.76	£23,167	£24,191	£29,965	£27,168
0.71	£26,843	£27,311	£33,680	£30,188

Figure 2. Submitted base-case ICERs with Neutropenia cost correction

Cost of Neutropenia	R-Benda	R-Clb	Benda	Clb
Incorrect	£19,898	£21,275	£26,463	£24,256
Correct	£18,652	£20,588	£25,169	£23,289

The Updated Roche Base Case

The updated Roche base case incorporates the following revisions:

1. The economic model has been updated with the parameter assumptions preferred by the Committee in the ACD:

a. Utility whilst on obinutuzumab after first cycle of therapy

b. Utility PFS off treatment decreased from 0.82 to 0.71

c. Mean dose of bendamustine and rituximab in bendamustine + rituximab arm

d. PFS hazard ratio between obinutuzumab + chlorambucil and bendamustine + rituximab increased from 0.68 to 0.76

e. PFS hazard ratio obinutuzumab + chlorambucil vs. bendamustine from 0.40 to 0.55

2. A minor error has been identified and corrected in the economic model. Previously every incidence of Neutropenia in the model was associated with the cost of Febrile Neutropenia in the model (a significantly more costly adverse event - £3894). The results provided within this ACD include the use of the cost of Neutropenia estimated by LRiG in NICE ID620, valued at £867 per episode.

Note that the PFS off-treatment utility value has been maintained at 0.71 in the base-case with 0.76 tested as a sensitivity analyses.

Cost-effectiveness results

Within our ACD response we have requested that the Committee consider the clinical and cost-effectiveness of obinutuzumab plus chlorambucil in two different fludarabine-unsuitable patient populations:

1) Those unsuitable for treatment with a bendamustine-based regimen
2) Those suitable for treatment with a bendamustine based regimen

These two groups are clinically distinct populations as not all patients within scope are suitable for bendamustine based therapy – due to this we believe they should also be regarded as separate populations under public sector equality duty. This point is further elaborated within our ACD response but is highlighted here so that the context underlying the scheme proposed is clear.

The below figures demonstrate revised base case ICERs for these two populations including the PAS submitted to the Department of Health (□% discount on the current list price of obinutuzumab).

People unsuitable for treatment with a bendamustine-based regimen

Population	Comparator	(1) ICER with Committee preferred ACD assumptions + Neutropenia cost	2) As per (1) with utility value based upon EQ-5D rather than ACD assumed value of 0.71
Patients unsuitable for bendamustine based therapy	Chlorambucil	[redacted]	[redacted]
	Rituximab + Chlorambucil	[redacted]	[redacted]

In this population probability of obinutuzumab being considered a cost-effective use of NHS resources is 74.4% at £30,000/QALY gained. If an alternative PFS utility value of 0.76 is used in the model rather than use of 0.71 (a reasonable modification considering the EQ-5D values from ID642) this probability increases to 87.9% at £30,000/QALY gained.

Due to the fact that the ICERs, and associated PSA results, are within the range commonly considered acceptable we believe it is important the Committee consider the information presented above in their decision making.

People suitable for treatment with a bendamustine-based regimen

Population	Comparator	(1) ICER with Committee preferred ACD assumptions + Neutropenia cost	2) As per (1) with utility value based upon EQ-5D rather than ACD assumed value of 0.71
Patients suitable for bendamustine based therapy	Chlorambucil	[redacted]	[redacted]
	Rituximab + Chlorambucil	[redacted]	[redacted]
	Bendamustine	[redacted]	[redacted]
	Rituximab + Bendamustine	[redacted]	[redacted]

In this population probability of obinutuzumab being considered a cost-effective use of NHS resources is less than 10% at £30,000/QALY gained

[i] Cost Effectiveness Presentation – slides for projector and public observers. Lead Team presentation: Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia. Slide 7 – Costs and Utility values per health state.