NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 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.

1.2 People whose treatment with obinutuzumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Obinutuzumab (Gazyvaro, Roche Products) is a type 2 glyco-engineered antibody that binds to the CD20 protein present on B cells (except stem or plasma cells) and causes cell death.

Obinutuzumab plus chlorambucil has a UK marketing authorisation for 'the treatment of adult patients with previously untreated chronic lymphocytic leukaemia and with comorbidities making them unsuitable for full-dose fludarabine based therapy'. Obinutuzumab is administered as an intravenous infusion.

2.2 The summary of product characteristics lists the following common adverse reactions for obinutuzumab: urinary tract infection, nasopharyngitis, oral herpes, rhinitis, pharyngitis, squamous cell carcinoma of the skin, neutropenia, thrombocytopenia, anaemia, leukopenia, tumour lysis syndrome, hyperuricaemia, atrial fibrillation, hypertension, cough, diarrhoea, constipation, alopecia, arthralgia, back pain, musculoskeletal chest pain, pyrexia, decreased white blood cell count, decreased neutrophil count, increased weight and infusion-related reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The price of obinutuzumab is £3312 per 1000-mg vial (excluding VAT; 'British national formulary' [BNF] February 2015). The company stated that a course of treatment costs £26,496 (£9936 for cycle 1 and £3312 for cycles 2-6, excluding VAT). The recommended dosage is 1000 mg administered over days 1 and 2, 1000 mg on day 8 and 1000 mg on day 15 of treatment cycle 1, followed by 1000 mg on day 1 of treatment cycles 2-6. The company has agreed a patient access scheme with the Department of Health that makes obinutuzumab available with a discount. The size of the discount is commercial in confidence (see section 5.4). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Roche and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The company identified 1 relevant randomised controlled trial to include in its submission. The CLL11 trial was a multicentre, open-label, 3-arm trial that compared obinutuzumab plus chlorambucil, rituximab plus chlorambucil and chlorambucil alone in patients with untreated chronic lymphocytic leukaemia for whom full-dose fludarabine-based therapy was not appropriate.

3.2 Patients in CLL11 had untreated chronic lymphocytic leukaemia needing treatment (that is, those with Binet stage C or symptomatic disease). Patients who were eligible for the trial had either a total cumulative illness rating scale score greater than 6 or a creatinine clearance of less than 70 ml/minute, or both; no evidence of bone marrow dysfunction other than that caused by chronic lymphocytic leukaemia (determined by an absolute neutrophil count of 1.5×10^9/litre or greater and platelet count of 75×10^9/litre or greater); and a life expectancy greater than 6 months. The cumulative illness rating scale calculates the number and severity of chronic illnesses in patients with comorbidities.

3.3 There were 2 stages of recruitment to CLL11. In stage 1, 589 patients were randomised in a 2:2:1 ratio to have obinutuzumab plus chlorambucil, rituximab plus chlorambucil, or chlorambucil alone. In stage 2, an additional 192 patients were randomised to either the obinutuzumab plus chlorambucil group or the rituximab plus chlorambucil group. The stage 1 analysis compared obinutuzumab plus chlorambucil with chlorambucil

alone, and rituximab plus chlorambucil with chlorambucil alone. The stage 2 analysis compared obinutuzumab plus chlorambucil with rituximab plus chlorambucil.

3.4 Patients in each of the 3 treatment groups had a dose of chlorambucil on days 1 and 15 of cycles 1–6 equivalent to 0.5 mg/kg body weight (up to a maximum of the dose associated with a BMI of 35 kg/m^2). Patients in the obinutuzumab plus chlorambucil treatment group also had 1000 mg of obinutuzumab on days 1, 8 and 15 of cycle 1 and on day 1 of cycles 2-6. Patients in the rituximab plus chlorambucil group also had 375 mg/m^2 rituximab on day 1 of cycle 1 and 500 mg/m^2 rituximab on day 1 of cycles 2-6. Each treatment cycle lasted 28 days.

3.5 The primary outcome of CLL11 was progression-free survival as assessed by the investigator. This was defined as the time from randomisation to the first occurrence of progression, relapse or death from any cause. The analysis of the primary end point used an intention-to-treat population. Median progression-free survival and 95% confidence intervals were estimated using Kaplan–Meier survival methodology. Based on a data cut-off of March 2014, there were statistically significant improvements in median investigator-assessed progression-free survival:

- In stage 1 in the obinutuzumab plus chlorambucil group compared with the chlorambucil monotherapy group (29.9 months compared with 11.1 months, hazard ratio [HR] 0.19; 95% confidence interval [CI] 0.14 to 0.25, p<0.001).
- In stage 2 in the obinutuzumab plus chlorambucil group compared with the rituximab plus chlorambucil group (29.2 months compared with 15.4 months, HR 0.41; 95% CI 0.33 to 0.50).

3.6 The secondary outcomes in CLL11 were progression-free survival as assessed by an independent review committee; overall survival; event-free survival (time before disease progression or relapse, death, or start of a new anti-leukaemic therapy); disease-free survival; duration of response; time to re-treatment or new anti-leukaemic therapy; end of treatment response (response occurring more than 56 days after the end of treatment); best overall response; best overall response within 1 year of start of study treatment; molecular remission; rate of negative testing for minimal residual disease; adverse events and patient-reported outcomes. The results for the secondary outcomes at the end of stage 1 showed that obinutuzumab plus chlorambucil and rituximab plus chlorambucil were statistically significantly better than chlorambucil alone for most outcomes. At the end of stage 2, obinutuzumab plus chlorambucil was statistically significantly better than rituximab plus chlorambucil for most of the secondary outcomes. Overall survival was statistically significantly greater for obinutuzumab plus chlorambucil than for rituximab plus chlorambucil and chlorambucil alone at the end of stage 1. There was no statistically significant difference in overall survival between obinutuzumab plus chlorambucil and rituximab plus chlorambucil at the end of stage 2. However, the company stated that the overall survival data were immature. Deaths and disease-free survival rate were not statistically significantly different between the groups at the end of stage 2.

3.7 The median observation times at the March 2014 data cut-off were:

- 32.2 months in the obinutuzumab plus chlorambucil and rituximab plus chlorambucil groups (stage 1)
- 29.4 months in the chlorambucil group (stage 1)

- 27.6 months in the obinutuzumab plus chlorambucil group (stage 2)
- 26.8 months in the rituximab plus chlorambucil group (stage 2).

3.8 No direct evidence comparing obinutuzumab and bendamustine was identified by the company. To compare these 2 treatments, the company created 2 network meta-analyses of randomised controlled trials (a large network and a small network). The large network included studies regardless of whether full-dose fludarabine therapy was suitable for the enrolled patients (n=17, including CLL11). The results of the large network meta-analysis showed that the mean progression-free survival hazard ratio statistically significantly favoured obinutuzumab plus chlorambucil compared with bendamustine (HR 0.399, 95% CI 0.218 to 0.672, fixed-effects model, adjusted for age; HR 0.546, 95% CI 0.367 to 0.783, fixed-effects model, not adjusted for age). The small network only included studies of patients for whom fludarabine-based therapy was unsuitable (n=3), in line with obinutuzumab's licensed indication. The small network meta-analysis did not compare obinutuzumab with bendamustine because no studies of bendamustine monotherapy were included in the network. The network meta-analyses did not allow the calculation of the hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine plus rituximab. This was because the results of MaBLe (an ongoing trial comparing rituximab plus bendamustine with rituximab plus chlorambucil) had not been published and so were not included in the large network meta-analysis. Because the hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine plus rituximab was needed to inform the cost-effectiveness model, the company estimated a hazard ratio of 0.68 based on data from CLL11 at the

March 2014 data cut-off and the power calculation assumptions from the ongoing MaBLe trial, and used this value in its base case.

3.9 The company carried out safety analyses on data from all patients who had at least 1 dose of study medication in CLL11. The most frequent adverse events were infusion-related reactions, neutropenia and nausea. The most frequent adverse events of grade 3 or higher were infusion-related reactions, neutropenia and anaemia. The most frequent serious adverse events were infection, neoplasm and infusion-related reactions. The incidence of adverse events, serious adverse events and adverse events leading to discontinuation of study treatment was higher in the obinutuzumab plus chlorambucil arm than in either of the other groups. The differences were mainly a result of infusion-related reactions. However, the company did not report whether the differences were statistically significant. Obinutuzumab treatment was associated with increases in common chlorambucil-related adverse events (neutropenia, thrombocytopenia, anaemia). These events were mainly mild-to-moderate in severity, easily managed, and rarely led to discontinuation of all treatment.

3.10 Infusion-related reactions occurred in 166 patients (69%) in the obinutuzumab plus chlorambucil group and 88 patients (39%) in the rituximab plus chlorambucil group in stage 2 of CLL11. Most infusion-related reactions were low grade in intensity and were clinically manageable. No deaths were associated with infusion-related reactions. There were 21 deaths (6.5%) due to adverse events in the rituximab plus chlorambucil group, 15 deaths (4.5%) due to adverse events in the obinutuzumab plus chlorambucil group and 11 deaths (9%) due to adverse events in the chlorambucil alone group. The company did not report whether the

differences between the groups in the number of deaths due to adverse events were statistically significant.

Evidence Review Group's comments on the company's clinical-effectiveness evidence

3.11 The ERG stated that an open-label design may have introduced bias for the primary outcome of progression-free survival. However, it acknowledged that the outcome was reviewed by an independent review committee who was blinded to treatment and similar progression-free survival results were found between investigators and reviewers. The ERG acknowledged that the company believed that making the trial double blind would have been prohibitive and unethical because of the number of placebos needed for intravenous injections and oral medication.

3.12 The ERG believed that the dose of chlorambucil used in CLL11 was lower than that generally used in clinical practice (the typical dose was about 70 mg in the trial compared with 120 mg in clinical practice in England). The ERG stated that if chlorambucil is more effective at higher doses and the effectiveness of obinutuzumab plus chlorambucil does not depend on the dose of chlorambucil, the estimated effectiveness of obinutuzumab plus chlorambucil compared with chlorambucil alone was overestimated in CLL11. However, the ERG acknowledged that obinutuzumab plus chlorambucil may be more effective at higher doses of chlorambucil as well.

3.13 The ERG noted that the bendamustine randomised controlled trial included in the large network meta-analysis was an open-label study, which may have biased the progression-free survival outcome. The ERG also noted that the mean dose of chlorambucil used per cycle in the bendamustine randomised controlled trial

(112 mg) was lower than that used in UK clinical practice (120 mg) but higher than in CLL11 (70 mg). The ERG stated that the difference in doses may have affected the results of the network meta-analysis.

3.14 The ERG acknowledged that the estimated hazard ratio for bendamustine plus rituximab compared with rituximab plus chlorambucil depends substantially on the data used to calibrate the correlation between the hazard ratio and the proportion of patients who had a complete response. The company estimated the proportion of patients who had a complete response based on the sample size of the ongoing MaBLe trial. The ERG believed that it would have been more appropriate for the company to base its estimate on the interim proportion of patients from MaBLe who had a complete response instead. The ERG noted that this hazard ratio affected the hazard ratio for obinutuzumab plus chlorambucil and bendamustine plus rituximab.

3.15 The ERG stated that it was possible to estimate a progression-free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine in patients aged 65 years or older, based on a trial comparing bendamustine with chlorambucil (Knauf et al. 2009) and the CLL11 results. The ERG's estimate of the hazard ratio based on the Knauf et al. trial and the CLL11 results was very similar to 0.55, which the company estimated from the fixed-effects analysis of the mixed treatment comparison without adjustment for age. Therefore the ERG believed 0.55 was a more accurate estimate of the hazard ratio for the comparison of obinutuzumab plus chlorambucil and bendamustine rather than the value of 0.40 from the age-adjusted fixed-effects analysis of the company's mixed treatment comparison.

Cost effectiveness

3.16 Roche identified 1 published cost-effectiveness model of patients with chronic lymphocytic leukaemia (Walzer et al. 2013) that was relevant to this appraisal. Roche had developed this model and updated the published version to include in this appraisal.

3.17 The company's model evaluated the cost effectiveness of obinutuzumab plus chlorambucil compared with rituximab plus chlorambucil, bendamustine plus rituximab, bendamustine alone and chlorambucil alone. The model consisted of 3 health states, namely 'progression-free survival', 'progressed', and 'death', with the progression-free survival health state further divided into 'on therapy' and 'not on therapy'. The model had weekly cycles and a half-cycle correction was applied, except to the drug, administration and pharmacy costs. The model used a lifetime time horizon (maximum 20 years) and a discount rate of 3.5% per year for costs and quality-adjusted life years (QALYs).

3.18 All people in the model started in the progression-free survival health state. At the end of each weekly cycle, people in the progression-free survival health state either remained there, moved to the progressed health state, or died. People in the progressed health state either remained in the progressed health state or died. Once they moved to a different state in the model, people could not return to the previous health state. The company used data from the CLL5 trial (a randomised controlled trial comparing fludarabine with chlorambucil in untreated chronic lymphocytic leukaemia) to model overall survival distribution, because the overall survival data from CLL11 were immature. The overall survival distribution in the model was validated using the Kaplan–Meier overall survival data that were available from CLL11.

3.19 The company calculated the number of people in the progression-free survival health state using data from CLL11 for obinutuzumab plus chlorambucil, rituximab plus chlorambucil, and chlorambucil alone. For bendamustine, the company took data from the large network meta-analysis and it used its own estimated hazard ratio for rituximab plus bendamustine (see section 3.8). It modelled the transition from the progression-free survival health state using data from CLL11 and background mortality. The proportion of people in the progressed health state in each cycle was the difference between the proportion of people who were alive and the proportion of people who were progression free.

3.20 The company applied costs from the perspective of the NHS and personal social services for drug acquisition, drug administration, health state and adverse events. It made an assumption of no vial sharing for all intravenous drugs (obinutuzumab, rituximab and bendamustine); therefore all calculations of price include drug wastage. The drug costs per treatment course were £26,496 (£3312 per 1000-mg vial) for obinutuzumab, £9953.91 (£174.63 per 100-mg vial and £873.15 per 500-mg vial) for rituximab, and £5809.92 (£69.45 per 25-mg vial and £275.81 per 100-mg vial) for bendamustine. The cost per treatment course of chlorambucil was £369.45 (£40.51 per pack of 25 tablets of 2 mg each). European Society of Medical Oncology guidelines informed resource use in the progression-free and progressed health states, and this was validated with clinical experts at an advisory board. The progression-free survival health state assumed 1 outpatient appointment lasting 60 minutes every 3 months and the post-progression state assumed 1 outpatient appointment every month.

3.21 Adverse events were included in the model if they were grade 3, 4 or 5 and occurred in 2% or more people in CLL11 (obinutuzumab

plus chlorambucil, rituximab plus chlorambucil or chlorambucil alone), Knauf et al. (2009; bendamustine alone), or the MaBLe trial (rituximab plus chlorambucil and rituximab plus bendamustine). Because there was a lack of complete data for bendamustine plus rituximab from the MaBLe study, the company assumed that the frequency and cost of adverse events were the same as for rituximab plus chlorambucil in stage 2 of CLL11. The company applied the total cost of all adverse events in each treatment group as a one-off event in the first cycle of each Markov state.

3.22 Quality-of-life data were collected in CLL11 using the European Organisation for Research and Treatment of Cancer Quality of Life – Core 30 (EORTC-QLQ-C30) questionnaire. However, the company did not map these data to the EuroQol (EQ-5D) questionnaire and it did not use the quality-of-life data from CLL11 in its health economic model. To determine relevant utility values, the company did a utility elicitation study with a sample of 100 members of the UK general public. The study used health state descriptions to explore societal preferences for quality of life associated with chronic lymphocytic leukaemia. The company used utility values from the study in the model; these were: 0.71 for progression-free survival on oral treatment (chlorambucil); 0.67 for progression-free survival on intravenous treatment (rituximab and bendamustine); 0.55 for progression-free survival on initial therapy with increased hospital visits (obinutuzumab); 0.82 for progression-free survival after initial treatment was completed (all treatment arms); and 0.60 for progressed disease (all treatment arms). The company assumed health-related quality of life to be constant over time within each health state in the model.

3.23 The company's base case and incremental results (without the patient access scheme) are presented in tables 1 and 2.

Table 1 Company's base-case ICERs – pairwise comparison with obinutuzumab plus chlorambucil (without the patient access scheme)

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (per QALY gained)
Obinutuzumab plus chlorambucil	£34,888	4.03	–	–	–
Rituximab plus bendamustine	£27,215	3.65	£7673	0.38	£20,076
Rituximab plus chlorambucil	£20,002	3.33	£14,886	0.70	£21,275
Bendamustine	£15,557	3.30	£19,331	0.73	£26,463
Chlorambucil	£8020	2.92	£26,868	1.11	£24,256
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Table 2 Company's incremental cost-effectiveness analysis (without the patient access scheme)

	Costs	QALYs	Incremental costs	Incremental QALYs	ICER (per QALY gained)	Dominated
Chlorambucil	£8020	2.92	–	–	–	–
Bendamustine	£15,557	3.30	£7536	0.38	£19,983	No
Rituximab plus chlorambucil	£20,002	3.33	£4445	0.03	£144,269	Extendedly dominated*
Rituximab plus bendamustine	£27,215	3.65	£713	0.32	£22,718	Extendedly dominated*
Obinutuzumab plus chlorambucil	£34,888	4.03	£7673	0.38	£20,076	No

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

*Extendedly dominated means the treatment has an ICER that is higher than the next most effective treatment. An extendedly dominated treatment produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

3.24 The final simultaneous incremental cost-effectiveness analysis (without the patient access scheme) produced an incremental cost-

effectiveness ratio (ICER) of £19,983 per QALY gained for bendamustine compared with chlorambucil and an ICER of £26,463 per QALY gained (incremental costs £19,331 and incremental QALYs 0.73) for obinutuzumab plus chlorambucil compared with bendamustine.

3.25 The company did deterministic sensitivity analyses on a range of parameters around the base-case ICER from the simultaneous comparison with chlorambucil. These were: progression-free survival values, post-progression death rate, hazard ratios from the mixed treatment comparison, significant costs, utility values, and the discount rate for both costs and outcomes for the incremental cost-effectiveness results. The ICERs (without the patient access scheme) from the deterministic sensitivity analyses for obinutuzumab plus chlorambucil compared with chlorambucil ranged from £18,402 to £36,527 per QALY gained. The ICERs over £30,000 per QALY gained were from using:

- a lower utility value for progression-free survival off treatment
- a higher hazard ratio for progression-free survival when comparing obinutuzumab plus chlorambucil and rituximab plus bendamustine
- a higher hazard ratio for progression-free survival when comparing obinutuzumab plus chlorambucil and rituximab
- half the base-case value for the overall survival value for the transition probabilities, and
- a progression-free survival transition probability using the Gompertz tail and the Gompertz distribution.

3.26 The company did probabilistic sensitivity analyses for utility values; parameter estimates for the parametric progression-free survival and post-progression survival function; the number of adverse

events; the costs of adverse events; monthly supportive care costs for the progression-free survival and progressed health states; administration costs; and the hazard ratios of the indirect treatment comparisons. The probabilistic base-case ICER (without the patient access scheme) for obinutuzumab plus chlorambucil was £25,779 per QALY gained. The probabilistic sensitivity analyses showed that obinutuzumab plus chlorambucil had a 63.4% chance of being the most cost-effective treatment option at a threshold of £30,000 per QALY gained and bendamustine had the next highest probability at 28.5%. A probabilistic sensitivity analysis on an alternative base case (using a Weibull function only rather than using data from a Kaplan–Meier curve and parametric extrapolation) resulted in a probabilistic ICER (without the patient access scheme) of £26,206 per QALY gained and a 62.8% chance of obinutuzumab being the most cost-effective treatment option.

3.27 The company identified the key drivers of the model as the long-term projection of progression-free survival, the post-progression death rate, the results of the large network meta-analysis and the utility values used.

Evidence Review Group's comments on the company's cost-effectiveness analyses

3.28 The ERG highlighted that the company did not map the EORTC-QLQ-C30 questionnaire to the EQ-5D. The ERG identified several mapping functions that could have been used. The ERG believed that a generic questionnaire such as the EQ-5D should have been used instead of health state descriptions in the company's utility study. It also noted that the company's approach would have been more useful if utility values had been determined from patients with chronic lymphocytic leukaemia rather than the general public.

3.29 The ERG disagreed with 2 of the company's utility values. The ERG argued that the utility value while on obinutuzumab treatment after the first cycle of treatment should be the same as the utility value for progression-free survival on intravenous treatment (0.67) rather than progression-free survival off treatment (0.82). In addition, the ERG noted that the utility value used by the company for progression-free survival off treatment (0.82) was higher than the utility value for members of the UK general public with the same average age as people with chronic lymphocytic leukaemia. The ERG noted that there are no reliable data to give a more accurate figure. However, it suggested using 0.76 as an upper value, which is the mean utility value for the UK general population with the same average age as people with chronic lymphocytic leukaemia whose disease has not progressed and who are off treatment. The ERG amended these values in its exploratory analyses (see sections 3.33 and 3.34).

3.30 The ERG disagreed with the company's assumed dose intensity of 100% for both bendamustine and rituximab in the bendamustine plus rituximab arm. The ERG highlighted that the dose intensity used in the MaBLe trial is not yet available. Without these data, the ERG suggested that the dose intensity for bendamustine in the bendamustine plus rituximab arm should be equal to that for bendamustine alone (90%) and the value for rituximab should be equal to that in CLL11 (98.8%). The ERG amended these values in its exploratory analyses (see sections 3.33 and 3.34).

3.31 The ERG stated that the ICER for obinutuzumab plus chlorambucil compared with bendamustine is uncertain because the company estimated the progression-free survival hazard ratio between these treatments (0.40) using the network meta-analysis. The ERG stated that it is possible to estimate a progression-free survival value for

obinutuzumab plus chlorambucil compared with bendamustine in patients aged 65 years or older based on Knauf et al. (2009), relating to the trial that compared bendamustine with chlorambucil and the CLL11 results. Using this method, the ERG estimated a figure very similar to the company's estimate of 0.55 from the fixed-effects analysis of the mixed treatment comparison without adjustment for age. The ERG addressed this in its exploratory analyses (see sections 3.33 and 3.34).

3.32 The ERG stated that the ICER for obinutuzumab plus chlorambucil compared with bendamustine plus rituximab was highly uncertain because the progression-free survival hazard ratio for rituximab plus bendamustine compared with rituximab plus chlorambucil was not available. The ERG acknowledged that the estimated hazard ratio for bendamustine plus rituximab compared with rituximab plus chlorambucil from the network meta-analysis depends substantially on the data used to calibrate the correlation between the hazard ratio and the proportion of people who had a complete response. The company estimated the proportion of people who had a complete response based on the sample size of the ongoing MaBLe trial. The ERG believed that it would be more appropriate to base the estimate of people who had a complete response on the interim proportion from MaBLe instead. The ERG believed that the best estimate for the hazard ratio between rituximab plus bendamustine and obinutuzumab plus chlorambucil was 0.76, compared with the company's estimate of 0.68. The ERG addressed this in its exploratory analyses (see sections 3.33 and 3.34).

3.33 The ERG explored several changes to the company's assumptions in its exploratory analyses:

- Scenario 1: changing the utility value while on obinutuzumab from 0.82 to 0.67 to match progression-free survival on intravenous treatment.
- Scenario 2: changing the utility value for progression-free survival off treatment from 0.82 to 0.76 to equal the utility value for the general public of comparable age.
- Scenario 3: changing the mean doses of bendamustine and rituximab in the bendamustine plus rituximab arm of the cost-effectiveness analysis to match the mean dose of bendamustine in the bendamustine monotherapy arm of Knauf et al. (2009) and the mean dose of rituximab in the rituximab plus chlorambucil arm of CLL11 (see section 3.30).
- Scenario 4: changing the progression-free survival hazard ratio of obinutuzumab plus chlorambucil compared with bendamustine plus rituximab from 0.68 to 0.76 to reflect the interim proportion of patients who had a complete response in the MaBLe trial.
- Scenario 5: changing the progression-free survival hazard ratio for obinutuzumab plus bendamustine from 0.40 to 0.55 as estimated from Knauf et al. (2009) and CLL11.

3.34 The ERG's exploratory analysis used all the assumptions in scenarios 1-5. The results of the ERG's scenario analyses for obinutuzumab plus chlorambucil compared with the comparators (without the patient access scheme) are presented in table 3.

Table 3 ERG's exploratory analyses of obinutuzumab plus chlorambucil compared with 4 comparators (without the patient access scheme)

Scenario*	Comparators			
	Rituximab plus bendamustine (ICER per QALY gained)	Rituximab plus chlorambucil (ICER per QALY gained)	Bendamustine (ICER per QALY gained)	Chlorambucil (ICER per QALY gained)
Company's base case	£20,076	£21,275	£26,463	£24,256
Scenario 1	£23,000	£23,000	£28,000	£25,000
Scenario 2	>£23,000	>£24,000	>£30,000	>£27,000
Scenario 3	£25,000	n/c	n/c	n/c
Scenario 4	£26,000	n/c	n/c	n/c
Scenario 5	n/c	n/c	£37,000	n/c
Scenarios 1 + 2	>£25,000	>£25,000	>£31,000	>£28,000
Scenarios 1 + 2 + 3 + 4	>£43,000	>£25,000	>£31,000	>£28,000
Scenarios 1 to 5	>£43,000	>£25,000	>£44,000	>£28,000

ICER, incremental cost-effectiveness ratio; n/c, ICER has not changed from the company's base case; QALY, quality-adjusted life year

*See section 3.33 for descriptions of each scenario.

3.35 The ERG did a sensitivity analysis on the utility value while patients were off treatment in progression-free survival. The ERG had estimated an upper value of 0.76, which is the same as the mean utility value for the UK general population at the average age of people with chronic lymphocytic leukaemia whose disease has not progressed and who are off treatment. In the sensitivity analysis, the ERG applied a utility value of 0.71 because it is likely that the utility in progression-free survival off treatment will be lower for patients with chronic lymphocytic leukaemia who have comorbidities. The results of the ERG's sensitivity analysis showed that applying a utility value of 0.71 for progression-free survival off

treatment to the company's base case resulted in ICERs (without the patient access scheme) of £27,000 per QALY gained for rituximab plus bendamustine, £27,000 per QALY gained for rituximab plus chlorambucil, £34,000 per QALY gained for bendamustine monotherapy and £30,000 per QALY gained for chlorambucil monotherapy compared with obinutuzumab plus chlorambucil. Applying a utility value of 0.71 for progression-free survival off treatment to the ERG's base case results in ICERs (without the patient access scheme) of £48,000 per QALY gained for rituximab plus bendamustine, £28,000 per QALY gained for rituximab plus chlorambucil, £49,000 per QALY gained for bendamustine monotherapy and £31,000 per QALY gained for chlorambucil monotherapy compared with obinutuzumab plus chlorambucil.

Company's response to consultation

3.36 In response to consultation, the company requested that the clinical and cost effectiveness of obinutuzumab plus chlorambucil for people who cannot have fludarabine-based therapy be considered in 2 different subgroups: those who can have bendamustine-based treatment and those who cannot. The company highlighted that these groups are distinct populations because not all people covered by the scope can have bendamustine-based therapy because of comorbidities. The company submitted new cost-effectiveness estimates for the 2 subgroups, which included the following revisions to its economic model:

- Amending the costs for treating neutropenia to £867 per episode rather than £3894, to take into account that not everybody will need hospital treatment.
- Including the ERG's preferred parameters:

- A utility value of 0.67 while on obinutuzumab after the first cycle of therapy.
- A decrease in the utility value for progression-free survival off treatment, from 0.82 to 0.71.
- Changing the mean dose of bendamustine and rituximab in the bendamustine plus rituximab arm to match the mean doses used in Knauf et al. (2009) and CLL11.
- An increase in the progression-free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine plus rituximab, from 0.68 to 0.76.
- An increase in the progression-free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine, from 0.40 to 0.55.

NICE agreed that the company could submit a patient access scheme as part of its new evidence. The confidential patient access scheme was agreed with the Department of Health. The company did sensitivity analyses using an alternative utility value for progression-free survival while off treatment. This utility value of 0.76 (instead of 0.71) was derived from the COMPLEMENT-1 study used in the ongoing NICE technology appraisal of ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia. COMPLEMENT-1 was a randomised trial that evaluated ofatumumab plus chlorambucil compared with chlorambucil alone in people with untreated chronic lymphocytic leukaemia for whom fludarabine-based therapy was considered inappropriate.

3.37 The company presented revised cost-effectiveness results for the population who could not have bendamustine-based treatment. The details of the patient access scheme are confidential and therefore

the ICERs cannot be presented here because, having previously released the estimates without the patient access scheme, the estimates with the patient access scheme could reveal the confidential discount agreed between the company and the Department of Health. However, the estimates including the patient access scheme were fully taken into account during the appraisal. The revised base-case ICERs for obinutuzumab plus chlorambucil compared with both chlorambucil alone and with rituximab plus chlorambucil were between £20,000 and £30,000 per QALY gained. In its sensitivity analysis, the company applied an alternative utility value for progression-free survival while off treatment of 0.76 (instead of 0.71). This had the effect of decreasing the ICERs. In the population who could not have bendamustine-based treatment, the company stated that the probability of obinutuzumab being considered cost effective was 74.4% at £30,000 per QALY gained. If the model used an alternative progression-free survival utility value of 0.76, this probability increased to 87.9% at £30,000 per QALY gained.

3.38 The company presented revised cost-effectiveness results for the population who could have bendamustine-based treatment. In amending its model to include all the changes mentioned in section 3.36, the ICERs for obinutuzumab plus chlorambucil compared with both bendamustine alone and with rituximab plus bendamustine were all above £30,000 per QALY gained. In this population, the probability of obinutuzumab plus chlorambucil being considered cost effective was less than 10% at £30,000 per QALY gained. In its sensitivity analysis, the company applied an alternative utility value for progression-free survival while off treatment of 0.76 (instead of 0.71). Again, this had the effect of decreasing the ICERs, but they remained above £30,000 per QALY gained.

Evidence Review Group's critique of the company's response to consultation

3.39 The ERG agreed with the company that it is appropriate to consider 2 subgroups in this appraisal, that is, people who can have bendamustine-based treatment and those who cannot.

3.40 The ERG highlighted that the company's updated costs of treating neutropenia were based on those estimated from NICE's ongoing technology appraisal of erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (review of NICE technology appraisal guidance 162 and 175). The ERG commented that the evidence to support this change was inadequate and more justification was needed. However, the ERG stated that this issue was of minor importance because it had little effect on the company's cost-effectiveness estimates (see section 3.42).

3.41 The ERG commented that the alternative utility value for progression-free survival off treatment (0.76 rather than the ERG's preferred value of 0.71) was from the randomised controlled trial COMPLEMENT-1. It commented that the trial was relevant because the patients were representative of the patient populations being considered in this appraisal. The ERG highlighted that it still preferred the utility value of 0.71 for progression-free survival off treatment. This was because the data from COMPLEMENT-1 were collected during the first half of the time in progression-free survival, whereas this appraisal was interested in the mean utility value 6 months from the start of progression-free survival (end of treatment) until the end of progression-free survival. Therefore, the utility data from COMPLEMENT-1 cited by the company only partly represented the time period of interest. The ERG stated that the utility value of 0.76, estimated from Ara and Brazier (2010) using

the EQ-5D, was from a large study of the general population in England. The ERG highlighted that it was logical that the utility value appropriate for patients with multiple comorbidities with chronic lymphocytic leukaemia could be less than 0.76.

3.42 The ERG confirmed that the amendments to the company's base case had been done correctly. The ERG did scenario analyses implementing all the company's revised assumptions, but excluding the change in costs of treating neutropenia, and using a utility value for progression-free survival off treatment of either 0.71 or 0.76. The ICERs are confidential and cannot be reported here, but the effect of changing the costs of treating neutropenia was marginal. Although using the alternative source of the utility value for progression-free survival off treatment had a more moderate effect, overall, the ICERs for obinutuzumab plus chlorambucil compared with both chlorambucil alone and with rituximab plus chlorambucil remained between £20,000 and £30,000 per QALY gained. For obinutuzumab plus chlorambucil compared with both bendamustine alone and with rituximab and bendamustine, the corresponding ICERs remained above £30,000 per QALY gained.

3.43 Full details of all the evidence are in the Committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of obinutuzumab plus chlorambucil, having considered evidence on the nature of chronic lymphocytic leukaemia and the value placed on the benefits of obinutuzumab plus chlorambucil by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee discussed with the patient expert the nature of the condition. It heard that some people with chronic lymphocytic leukaemia have a variety of symptoms, some of which can be disabling, for example, fatigue and concurrent infections. The patient expert stated that because patients are on life-long treatment, patients who are in remission are concerned about imminent relapse and the need for additional treatment. The Committee agreed that chronic lymphocytic leukaemia can seriously impair health-related quality of life.

4.2 The Committee discussed the current clinical management of chronic lymphocytic leukaemia and the most likely place in the pathway of care for obinutuzumab plus chlorambucil treatment. It heard from the clinical expert that one-third of people with chronic lymphocytic leukaemia are asymptomatic and may not need immediate treatment. The Committee heard from the clinical expert that, for people with untreated chronic lymphocytic leukaemia, fludarabine combination therapy is the standard of care when they need immediate treatment. It understood that fludarabine combination therapy may not be suitable for about half the people needing immediate treatment, for example, people who are older or have comorbidities such as impaired renal function, hypertension or diabetes. The Committee heard from the clinical expert that people who cannot have fludarabine combination therapy may have bendamustine either as monotherapy or combined with rituximab. The Committee also heard from the clinical expert that bendamustine may not be appropriate for some people and these people currently have chlorambucil monotherapy or rituximab plus chlorambucil (see section 4.3). The Committee acknowledged that, for people with untreated chronic lymphocytic leukaemia, NICE technology appraisal guidance on rituximab for the first-line treatment of chronic lymphocytic leukaemia recommends rituximab

only in combination with fludarabine and cyclophosphamide. It also noted that NICE technology appraisal guidance on bendamustine for the first-line treatment of chronic lymphocytic leukaemia recommends bendamustine for people who cannot have fludarabine. The Committee heard from the clinical expert that obinutuzumab is a significant clinical advance over bendamustine and chlorambucil. Furthermore, some people may prefer to have obinutuzumab instead of bendamustine, because obinutuzumab is associated with fewer adverse events. The clinical expert and patient expert acknowledged that some people may prefer oral treatment with chlorambucil instead of having to attend a day unit for intravenous treatment with obinutuzumab or bendamustine. The Committee recognised that patients value having more treatment options.

4.3 The Committee discussed the company's response to the appraisal consultation document. In its response the company requested that 2 subgroups of people who cannot have fludarabine-based therapy should be considered: people who can have bendamustine and people who cannot have bendamustine. It heard that there are people who may not be fit enough to tolerate bendamustine, but are fit enough for active treatment with either rituximab plus chlorambucil or chlorambucil alone. The Committee noted that, of the people who cannot have fludarabine-based treatment, the proportion who would have a bendamustine-containing treatment was estimated to be around 25% in the company's original submission, whereas the CLL11 trial suggested that this could be as high as 50%. The Committee concluded that, in people who cannot have fludarabine-based treatment, it was reasonable to consider 2 distinct subgroups: those who can have bendamustine-based treatment and those who cannot.

Clinical effectiveness

4.4 The Committee considered the evidence presented by the company on the clinical effectiveness of obinutuzumab plus chlorambucil compared with chlorambucil alone or in combination with rituximab. It noted that the main source of evidence was the CLL11 open-label randomised controlled trial. The Committee noted that, in CLL11, obinutuzumab plus chlorambucil was associated with statistically significantly greater progression-free survival than chlorambucil alone (March 2014 data: hazard ratio [HR] 0.19; 95% confidence interval [CI] 0.14 to 0.25) or rituximab plus chlorambucil (March 2014 data: HR 0.41; 95% CI 0.33 to 0.50). The Committee also noted that obinutuzumab plus chlorambucil was associated with statistically significantly greater overall survival compared with chlorambucil monotherapy and that the difference in overall survival between obinutuzumab plus chlorambucil and rituximab plus chlorambucil was not statistically significant. However, the Committee acknowledged that the overall survival data were immature (see section 3.6). The Committee heard from the Evidence Review Group (ERG) that the open-label design may have biased the primary outcome of investigator-assessed progression-free survival. It also noted that, as a result of the different routes of administration of the treatments in each arm, the number of placebo treatments that would be needed to make the study double blind would be unethical. The Committee heard from the ERG and clinical expert that a lower dose of chlorambucil had been used in CLL11 than the dose routinely used in clinical practice in England (see section 3.12). The ERG and clinical expert considered that if a lower dose of chlorambucil did have a lower efficacy it was likely to be similarly lower for all the treatment groups in CLL11. The Committee considered that the lower dose of chlorambucil in CLL11 was unlikely to significantly affect the

comparative efficacy of the treatment groups (chlorambucil monotherapy, obinutuzumab plus chlorambucil, and rituximab plus chlorambucil). The Committee concluded that, for progression-free survival, obinutuzumab plus chlorambucil is a clinically effective treatment for chronic lymphocytic leukaemia compared with chlorambucil alone or with chlorambucil plus rituximab.

4.5 The Committee considered the network meta-analyses used by the company to estimate the progression-free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine monotherapy (HR 0.399; 95% CI 0.218 to 0.672) in the absence of any head-to-head trials. The Committee was aware that the small network meta-analysis did not compare obinutuzumab plus chlorambucil with bendamustine. Therefore, it was not considered further and the Committee focused on the large network meta-analysis (see section 3.8). It heard from the ERG that the large network meta-analysis included studies of patients for whom fludarabine therapy was suitable. These patients were not covered by the marketing authorisation for obinutuzumab or the scope of this appraisal. The Committee acknowledged that patients for whom fludarabine therapy is suitable are likely to be younger and have fewer comorbidities than patients in CLL11, and their disease may respond differently to treatment. The Committee agreed that the hazard ratio calculated in the large network meta-analysis for progression-free survival was not reliable when comparing obinutuzumab plus chlorambucil with bendamustine monotherapy.

4.6 The Committee considered adverse events associated with obinutuzumab treatment. It was aware that the Medicines and Healthcare Products Regulatory Agency had issued a warning about serious and fatal infusion-related reactions associated with the use of ofatumumab and other anti-CD20 monoclonal

antibodies. The Committee heard from the clinical expert that initial infusion-related reactions in people having obinutuzumab were managed in CLL11 by splitting the first dose into 2 administrations, in line with the summary of product characteristics. The clinical expert also noted that, other than infusion-related reactions, obinutuzumab seemed to be well tolerated. The Committee took into consideration the summary of product characteristics and concluded that obinutuzumab had an acceptable adverse event profile.

Cost effectiveness

4.7 The Committee considered the company's economic model (without the patient access scheme) and the critique and exploratory analyses from the ERG. The Committee noted that the company presented a comparison of obinutuzumab plus chlorambucil with chlorambucil monotherapy, chlorambucil plus rituximab, bendamustine monotherapy and bendamustine plus rituximab.

4.8 The Committee considered the utility values calculated by the company. The Committee was aware that quality-of-life data were collected during CLL11 using the European Organisation for Research and Treatment of Cancer Quality of Life – Core 30 (EORTC-QLQ-C30) questionnaire (see sections 3.22 and 3.28). However, these data were not mapped onto the EuroQol (EQ-5D) questionnaire or presented in the company's submission. The Committee heard from the company that it had considered mapping the quality-of-life data from CLL11, but decided to carry out a utility elicitation study instead. This was because the mapping tools were designed for non-chronic lymphocytic leukaemia disease areas and used different versions of the EORTC-QLQ, and the global domain scores from the EQ-5D may not be applicable to people with

chronic lymphocytic leukaemia. The Committee noted that the utility elicitation study was done with a sample of the general population and not people who had chronic lymphocytic leukaemia. It was also not stratified by age. The Committee concluded that the utility elicitation study was not the most appropriate source of utility values. The resulting utility values used in the cost-effectiveness modelling were not reliable because they were not from people with chronic lymphocytic leukaemia and were not mapped onto the EQ-5D.

4.9 The Committee acknowledged that the ERG had concerns about some of the assumptions made by the company in the base-case analysis:

- The utility value while on obinutuzumab treatment after the first cycle of treatment.
- The utility value for progression-free survival off treatment.
- The mean doses of rituximab and bendamustine in the bendamustine plus rituximab arm.
- The progression-free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine monotherapy.
- The progression-free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine plus rituximab.

The Committee considered each of these assumptions in turn, as detailed below (see sections 4.10-4.14).

4.10 The Committee discussed the utility values used after the first cycle of treatment while on obinutuzumab. The Committee noted that the company used the same utility value as for progression-free survival off treatment (0.82). The Committee heard from the ERG that the utility value while on obinutuzumab treatment should have been the same as the utility value for progression-free survival on

intravenous treatment (0.67). The Committee heard from the company that using 0.82 as a utility value was an error. The Committee concluded that the utility value of 0.67 was the more appropriate utility value for after the first cycle of treatment while on obinutuzumab treatment.

4.11 The Committee then considered the utility value for progression-free survival off treatment. The Committee was aware that the company used a utility value of 0.82 from its utility elicitation study. The Committee heard from the ERG that this utility value was higher than the utility value for members of the general public at a similar age to people with chronic lymphocytic leukaemia. The Committee agreed that it was not plausible that the utility value for progression-free survival off treatment was higher than the utility value for members of the general public without the disease. The ERG suggested an upper value for the utility value for progression-free survival off treatment of 0.76. This was based on the mean utility value for the UK general population at the same average age of people with chronic lymphocytic leukaemia whose disease has not progressed and who are off treatment. The Committee heard from the ERG that the utility value would probably be lower than 0.76 for people with chronic lymphocytic leukaemia who have comorbidities and it suggested a utility value of 0.71. This was based on progression-free survival on intravenous treatment. The Committee accepted that the utility values of 0.76 and 0.71 for progression-free survival off treatment were more plausible than those estimated by the company, but were still subject to some uncertainty.

4.12 The Committee discussed the drug acquisition costs used in the company's model (without the obinutuzumab patient access scheme) and noted that the company had used an assumed dose

intensity of 100% for bendamustine and rituximab. The Committee heard that using dose intensities from trial data would have been more appropriate. The ERG suggested that the dose intensity for bendamustine should be equal to that of bendamustine monotherapy (90%) in Knauf et al. (2009) and for rituximab should be equal to that of rituximab in the rituximab plus chlorambucil arm in CLL11 (98.8%). The Committee concluded that these dose intensities were likely to be more accurate than those suggested by the company because they were based on data rather than assumptions.

4.13 The Committee considered the progression-free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine monotherapy. It recalled that the results of the company's network meta-analysis were uncertain (see sections 3.8, 3.13 and 4.5). The Committee heard from the ERG that it was possible to do an indirect comparison of obinutuzumab plus chlorambucil with bendamustine using the CLL11 and Knauf et al. (2009) results without having to do a network meta-analysis. The Committee accepted that the hazard ratio identified by the ERG (0.55) was likely to be more accurate than the hazard ratio calculated in the company's large network meta-analysis (0.40) because the results of the network meta-analysis were uncertain. The Committee concluded that the progression-free survival hazard ratio of 0.55 for obinutuzumab plus chlorambucil compared with bendamustine monotherapy was more plausible than the hazard ratio of 0.40 calculated by the company.

4.14 The Committee considered the progression-free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine plus rituximab. The Committee was aware that the company estimated a hazard ratio for bendamustine plus rituximab

compared with rituximab plus chlorambucil using power calculation assumptions from an ongoing randomised controlled trial (the MaBLe trial). This was because the network meta-analyses did not provide a hazard ratio for this comparison. The Committee noted that the company had calibrated the correlation between the hazard ratio and the proportion of people who had a complete response for bendamustine plus rituximab and rituximab plus chlorambucil comparison using the estimated sample size of MaBLe (see section 3.8). The Committee heard from the ERG that it would have been more appropriate to calibrate the correlation using the interim proportion of patients who had a complete response in the MaBLe trial rather than using the estimated sample size. The Committee accepted the ERG's suggested calibration value and that the resulting progression-free survival hazard ratio of 0.76 was more reliable than the company's hazard ratio of 0.68, but it was still subject to some uncertainty because it was based on interim data from the MaBLe trial. The Committee concluded that the progression-free survival hazard ratio of 0.76 for obinutuzumab plus chlorambucil was more plausible than the hazard ratio of 0.68.

4.15 The Committee considered the company's response to the appraisal consultation document together with their new evidence and patient access scheme (see section 3.36). 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 4.3). The Committee noted that the company had accepted all the ERG's suggested amendments and the Committee's preferred amendments to some of the assumptions made by the company in the base-case analysis (outlined in sections 4.10-4.14). The Committee noted that the company had decreased the neutropenia costs to more accurately reflect the proportion of people needing

hospital stays for neutropenia, but it acknowledged the ERG's comments that the alternative costs made little difference to the ICERs. The Committee discussed the company's sensitivity analysis that explored an alternative utility value for progression-free survival off treatment (0.76) rather than the ERG's preferred estimate of 0.71. It was aware that the alternative utility value was from the COMPLEMENT-1 study (see section 3.36), which reflected the patient population being considered as part of this appraisal. The Committee noted that the ERG's preference for a 0.71 utility value was because COMPLEMENT-1 only partly represented the time period of interest and because of evidence from a large study that estimated a utility value of 0.76 for the general population in England (Ara and Brazier, 2010). The Committee agreed with the ERG that if the best evidence available suggests that the utility value for the general population for this age group is 0.76, then it is logical that for people with chronic lymphocytic leukaemia and multiple comorbidities the utility value for progression-free survival off treatment would be less than 0.76. The Committee recalled that people with chronic lymphocytic leukaemia who are in remission are concerned about imminent relapse that could affect their quality of life (see section 4.1). The Committee concluded that the company's revisions to its economic model, including the patient access scheme, the ERG's suggested amendments and updated neutropenia costs, were appropriate and that the company's revised base-case cost-effectiveness estimates were the most appropriate for its decision-making.

4.16 The Committee considered the cost-effectiveness estimates for people who can have bendamustine. It noted that both the company's and the ERG's ICERs (including the patient access scheme) for obinutuzumab plus chlorambucil compared with both bendamustine alone and with bendamustine plus rituximab were

above the top end of the range that would normally be considered a cost-effective use of NHS resources (£20,000–30,000 per QALY gained). The Committee also recognised that all the comparisons with bendamustine-containing treatments were based on very weak evidence (see section 4.5). The Committee concluded that it could not recommend obinutuzumab plus chlorambucil for people who can have bendamustine, especially when this group has the option of treatment with a bendamustine-based therapy.

4.17 The Committee considered the cost-effectiveness estimates for people who cannot have bendamustine. It noted that both the company's and the ERG's ICERs (including the patient access scheme) for obinutuzumab plus chlorambucil compared with both chlorambucil alone and with rituximab plus chlorambucil were all in the range considered to be a cost-effective use of NHS resources (£20,000–30,000 per QALY gained). The Committee considered that obinutuzumab plus chlorambucil is a clinically effective treatment for people who have untreated chronic lymphocytic leukaemia that is unsuitable for fludarabine-based therapy (see section 4.4). It acknowledged comments received during consultation about the lack of alternative effective treatments in people who cannot have bendamustine-based treatment. The Committee recommended obinutuzumab plus chlorambucil for untreated chronic lymphocytic leukaemia in people who cannot have fludarabine-based therapy, only if bendamustine is not suitable and the company provides obinutuzumab with the discount agreed in the patient access scheme.

4.18 The Committee considered whether obinutuzumab plus chlorambucil was innovative. It noted the company's comments that obinutuzumab plus chlorambucil results in improved progression-free survival. The Committee concluded that there were no

additional benefits with obinutuzumab plus chlorambucil that were not already captured in the QALY estimate in the modelling.

4.19 The Committee considered the potential equality issue raised by a consultee 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 decided that this was not an equality issue under the equality legislation. Therefore its recommendations did not lead to discrimination and it did not need to add to, or change, its recommendations.

4.20 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are

robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.21 The Committee considered the criterion for short life expectancy. It was aware that the overall survival data from CLL11 were immature and so it considered the overall survival estimates from CLL5, which were used to validate the extrapolation of the overall survival curves in the company's economic model. It noted that the median overall survival of patients with chronic lymphocytic leukaemia in the chlorambucil arm of CLL5 was 64 months. The Committee agreed that treatment with obinutuzumab plus chlorambucil does not fulfil the criterion for short life expectancy and did not consider it necessary to form a view on the remaining end-of-life criteria. The Committee concluded that treatment with obinutuzumab plus chlorambucil does not fulfil the criteria for special consideration in the supplementary advice from NICE.

Summary of Appraisal Committee's key conclusions

TAXXX	**Appraisal title: Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia**	**Section**
Key conclusion		
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		1.1

in the patient access scheme.	
There was uncertainty in several of the model parameters, namely: the utility value while on obinutuzumab treatment after the first cycle of treatment, the utility value for progression-free survival off treatment, the mean dose of rituximab and bendamustine in the bendamustine plus rituximab arm of the analysis, the progression-free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine monotherapy, and the progression-free survival hazard ratio for obinutuzumab plus chlorambucil compared with bendamustine plus rituximab.	4.9
In response to consultation, the company submitted a patient access scheme and revised cost-effectiveness analyses that incorporated all the ERG's suggested amendments to assumptions made by the company in the base-case analysis (see sections 4.10-4.14). The company also amended the cost of treating neutropenia. The Committee concluded that the company's revised base-case cost-effectiveness estimates were the most appropriate for its decision-making.	4.15
The Committee agreed that the population who cannot have fludarabine could be divided into people who can have bendamustine and those who cannot. For people who cannot have bendamustine, it noted that the most likely ICERs (including the patient access scheme) for treatment with obinutuzumab plus chlorambucil when compared with both chlorambucil monotherapy and with chlorambucil plus rituximab were in the range considered to be a cost-effective use of NHS resources (£20,000–30,000 per QALY gained).	4.15, 4.17
For people who can have bendamustine, the Committee noted that the most likely ICERs (including the patient access scheme) for treatment with obinutuzumab plus chlorambucil when compared with	4.16

both bendamustine alone and with rituximab plus bendamustine therapy were above the top end of the range that would normally be considered a cost-effective use of NHS resources (£20,000–30,000 per QALY gained).		
Current practice		
Clinical need of patients, including the availability of alternative treatments	Around one-third of people with chronic lymphocytic leukaemia are asymptomatic and may not need immediate treatment. Fludarabine combination therapy is the standard of care for people needing immediate treatment, but may be unsuitable for around half the people needing treatment. If fludarabine combination therapy is not appropriate, people may have bendamustine either as monotherapy or combined with rituximab. If bendamustine is not appropriate, people may have chlorambucil monotherapy or rituximab plus chlorambucil.	4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related	There were no additional benefits with obinutuzumab plus chlorambucil that were not already captured in the QALY estimate in the modelling.	4.18

benefits?		
What is the position of the treatment in the pathway of care for the condition?	For people for whom fludarabine combination therapy is unsuitable (for example people who are older or have comorbidities such as impaired renal function, hypertension or diabetes), some may prefer to have obinutuzumab instead of bendamustine because obinutuzumab is associated with fewer adverse events.	4.2
Adverse reactions	The Committee heard from the clinical expert that initial infusion-related reactions in people having obinutuzumab were managed in CLL11 by splitting the first dose into 2 administrations in line with the summary of product characteristics. Other than infusion-related reactions, obinutuzumab seemed to be well tolerated.	4.6
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The company presented evidence from 1 trial, CLL11, which was an open-label randomised controlled trial of obinutuzumab plus chlorambucil compared with chlorambucil monotherapy and chlorambucil plus rituximab. The primary outcome was progression-free survival.	4.4
	The company also presented 2 network meta-analyses to estimate the hazard ratio for obinutuzumab plus chlorambucil compared	4.5

	with bendamustine monotherapy. The Committee was aware that the small network meta-analysis did not compare obinutuzumab plus chlorambucil with bendamustine. Therefore it did not consider it further and focused on the large network meta-analysis. The Committee agreed that the hazard ratio calculated for treatment with obinutuzumab plus chlorambucil compared with bendamustine monotherapy from the large network meta-analysis was unreliable because the network included studies of patients who could have fludarabine therapy. These patients were not covered by the marketing authorisation for obinutuzumab or the scope of this appraisal. The Committee acknowledged that patients for whom fludarabine therapy is suitable are likely to be younger and have fewer comorbidities than patients in CLL11, and their disease may respond differently to treatment.	
Relevance to general clinical practice in the NHS	The ERG and clinical expert believed that a lower dose of chlorambucil was used in CLL11 than the dose routinely used in clinical practice in England. However, they acknowledged that if a lower dose of chlorambucil did have a lower efficacy, it would be similarly lower for all treatment groups in CLL11.	4.4

Uncertainties generated by the evidence	The ERG felt that the open-label design of CLL11 may have biased the primary outcome. The Committee accepted that as a result of the different routes of administration of the treatments in each arm, the number of placebo treatments needed to make the study double blind would be unethical.	4.4
	The Committee believed that the hazard ratio calculated from the large network meta-analysis was unreliable because the network included studies of patients who could have fludarabine therapy. These patients were not covered by the marketing authorisation for obinutuzumab or the scope of this appraisal. The Committee acknowledged that patients for whom fludarabine therapy is suitable are likely to be younger and have fewer comorbidities than patients in CLL11, and their disease may respond differently to treatment.	4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee heard that there are people who may not be fit enough to tolerate bendamustine, but are fit enough for active treatment with either rituximab plus chlorambucil or chlorambucil alone. It concluded that in people who cannot have fludarabine-based treatment, it was reasonable to consider 2 distinct subgroups: those who can have bendamustine-based treatment and those who cannot. No clinical	4.3

	evidence was provided for these 2 subgroups.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	In CLL11, treatment with obinutuzumab plus chlorambucil was associated with statistically significantly greater progression-free survival than chlorambucil monotherapy or treatment with rituximab plus chlorambucil. The Committee also noted that obinutuzumab plus chlorambucil therapy was associated with statistically significantly greater overall survival compared with chlorambucil monotherapy and that the difference in overall survival between treatment with obinutuzumab plus chlorambucil and rituximab plus chlorambucil was not statistically significant. The overall survival data from CLL11 were immature.	4.4
	The Committee believed that the hazard ratio calculated from the large network meta-analysis was unreliable because the network included studies of patients who could have fludarabine therapy. These patients were not covered by the marketing authorisation for obinutuzumab or the scope of this appraisal. The Committee acknowledged that patients for whom fludarabine therapy is suitable are likely to be younger and have fewer comorbidities than patients in CLL11, and their disease may respond differently to treatment.	4.5

Evidence for cost effectiveness		
Availability and nature of evidence	The company presented a comparison of obinutuzumab plus chlorambucil therapy with chlorambucil monotherapy, chlorambucil plus rituximab therapy, bendamustine monotherapy, and bendamustine plus rituximab therapy.	4.7
	European Organisation for Research and Treatment of Cancer Quality of Life (EORTC-QLQ) data were collected in CLL11, but were not mapped to the EuroQol (EQ-5D) or used in the model. Instead the company carried out a utility elicitation study to determine the utility values.	4.8
Uncertainties around and plausibility of assumptions and inputs in the economic model	Utility values were determined from a sample of the general population and not from people who had chronic lymphocytic leukaemia, and were not stratified by age. The Committee believed that the utility values used in the company's model were not reliable. Several assumptions in the company's model were queried: • The company used the incorrect utility value while on obinutuzumab treatment after the first cycle of obinutuzumab treatment. • The utility value for progression-free	4.8–4.15

	survival off treatment in the company's model was based on the utility elicitation study. • The company assumed a dose intensity of 100% for bendamustine and rituximab. • The company used its large network meta-analysis to estimate a hazard ratio of 0.40 for the comparison with bendamustine monotherapy. • The company used the estimated sample size from an ongoing trial (MaBLe) to calibrate the correlation between the number of people who had a complete response and the progression-free survival hazard ratio for treatment with bendamustine plus rituximab and treatment with rituximab plus chlorambucil. The company submitted a patient access scheme and revised cost-effectiveness analyses that incorporated all of the ERG's suggested amendments and the Committee's preferred amendments to some of the assumptions made by the company in the base-case analysis. The Committee concluded that the company's revisions to its economic model, including the patient access scheme, the ERG's suggested amendments	

	and updated neutropenia costs, were appropriate and that the company's revised base-case cost-effectiveness estimates were the most appropriate for its decision-making.	
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	EORTC-QLQ data were collected in CLL11 but were not mapped to the EQ-5D or used in the model. Utility values were determined from a sample of the general population and not from people who had chronic lymphocytic leukaemia and were not stratified by age. The Committee believed that the utility values used in the company's model were not reliable. The Committee queried: • The utility value used after the first cycle of obinutuzumab treatment in the company's model, which was based on progression-free survival off treatment. The Committee heard from the company that it had used the incorrect value. The ERG used a value based on progression-free survival on intravenous treatment. The utility value for progression-free survival off treatment in the company's model, which was based on the utility elicitation study. The ERG highlighted that this utility value was higher than the utility value for the UK general population at a similar age to people with	4.8, 4.10, 4.11

	chronic lymphocytic leukaemia whose disease has not progressed and who are off treatment.	
	No additional benefits with obinutuzumab plus chlorambucil that were not already captured in the QALY estimate in the modelling were identified.	4.18
Are there specific groups of people for whom the technology is particularly cost-effective?	The Committee agreed that the population who cannot have fludarabine could be divided into people who can have bendamustine and those who cannot. It noted that for people who cannot have bendamustine, the most likely ICERs (including the patient access scheme) for obinutuzumab plus chlorambucil compared with both chlorambucil alone and with rituximab plus chlorambucil were all in the range considered cost effective (£20,000–30,000 per QALY gained).	4.15, 4.17
What are the key drivers of cost-effectiveness?	The company identified the key drivers of the model as the long-term projection of progression-free survival, the post-progression death rate, the results of the large network meta-analysis and the utility values used.	3.27
Most likely cost-effectiveness estimate (given as an ICER)	For people who cannot have bendamustine, the Committee noted that the most likely ICERs (including the patient access scheme) for obinutuzumab plus chlorambucil compared with chlorambucil alone and with rituximab	4.17

	and chlorambucil were within the range considered cost effective (£20,000–30,000 per QALY gained).	
	For people who can have bendamustine, the Committee noted that the most likely ICERs (including the patient access scheme) for obinutuzumab plus chlorambucil compared with both bendamustine alone and with rituximab plus bendamustine were above the top end of the range that would normally be considered cost effective (£20,000–30,000 per QALY gained).	4.16
Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health that makes obinutuzumab available with a discount. The size of the discount is confidential.	2.3, 5.4
End-of-life considerations	The Committee concluded that treatment with obinutuzumab plus chlorambucil does not fulfil the criterion for short life expectancy. The Committee did not consider it necessary to form a view on the remaining criteria.	4.21
Equalities considerations and social value judgements	One consultee commented 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.	4.19

	This is because people who are ineligible for bendamustine would not have access to alternative effective treatments if obinutuzumab was not recommended. The Committee decided that this was not an equality issue under the equality legislation. Therefore its recommendations did not lead to discrimination and it did not need to add to, or change, its recommendations.	

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic lymphocytic leukaemia and the doctor responsible for their care thinks that

ofatumumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Roche have agreed that obinutuzumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

5.5 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. NICE technology appraisal guidance 216 (2011).
- Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab. NICE technology appraisal guidance 202 (2010).
- Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia. NICE technology appraisal guidance 193 (2010).
- Rituximab for the first-line treatment of chronic lymphocytic leukaemia. NICE technology appraisal guidance 174 (2009).
- Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia. NICE technology appraisal guidance 119 (2007).
- Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia. NICE technology appraisal guidance 29 (2001).

Under development

- Ofatumumab for maintaining relapsed chronic lymphocytic leukaemia. NICE technology appraisal guidance, publication expected April 2016.
- Ofatumumab for treating previously untreated chronic lymphocytic leukaemia. NICE technology appraisal guidance, publication expected May 2015.

7 Review of guidance

7.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Eugene Milne

Chair, Appraisal Committee

March 2015

8 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3 year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Director of Public Health for Newcastle upon Tyne

Professor Kathryn Abel
Director of Centre for Women's Mental Health, University of Manchester

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

David Chandler

Lay Member

Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Department of Primary Care and Population Health, University College London

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell

Consultant in Public Health, Bradford Metropolitan Borough Council

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Emily Lam

Lay Member

Dr Nigel Langford

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Allyson Lipp

Principal Lecturer, University of South Wales

Dr Claire McKenna

Research Fellow in Health Economics, University of York

Dr Patrick McKiernan

Consultant Paediatrician, Birmingham Children's Hospital

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Dr Iain Miller

Founder and Chief Executive Officer, Health Strategies Group

Dr Paul Miller

Director, Payer Evidence, Astrazeneca UK Ltd

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing and Healthcare School / Senior Clinical University Teacher, University of Glasgow

Alan Rigby

Academic Reader, University of Hull

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Dr Paul Tappenden

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

Dr Judith Wardle

Lay Member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ella Fields/Christian Griffiths

Technical Leads

Sally Doss

Technical Adviser

Nicole Fisher/Lori Farrar

Project Managers

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Peninsula Technology Assessment group (PenTAG)

- Hoyle M, Long L, Huxley N. et al. Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia: a critique of the submission from Roche, August 2014

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Roche Products

II. Professional/specialist and patient/carer groups:

- Chronic Lymphocytic Leukaemia Support Association (CLLSA)
- Leukaemia Care
- Lymphoma Association
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- The British Society of Haematology

III. Other consultees:

- Department of Health
- Welsh Government
- NHS England

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety – Northern Ireland (DHSSPSNI)
- Health Improvement Scotland

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on obinutuzumab by attending the initial Committee discussion and providing a written statement to the Committee. They were also invited to comment on the ACD.

- Dr Claire Dearden, Consultant Haematologist, nominated by the Royal College of Physicians – clinical expert
- Jacky Wilson, nominated by the Lymphoma Association – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Roche Products