

Rituximab for the first-line treatment of chronic lymphocytic leukaemia

Technology appraisal guidance

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1 Recommendations

- 1.1 Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia in people for whom fludarabine in combination with cyclophosphamide is considered appropriate.
- 1.2 Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of chronic lymphocytic leukaemia.

2 The technology

- 2.1 Rituximab (MabThera, Roche) is a chimeric monoclonal antibody that binds selectively to the CD20 antigen expressed on the surface of mature B lymphocytes and tumour cells that express CD20. Rituximab is licensed for the first-line treatment of people with chronic lymphocytic leukaemia in combination with chemotherapy. Rituximab is administered intravenously, once every 4 weeks for a total of 6 cycles; a complete course of treatment with rituximab lasts 24 weeks. Dosing is calculated according to body surface area, with an initial dose of 375 mg/m² followed by 500 mg/m² for all subsequent doses. Six cycles of rituximab equate to a total dose of 2,875 mg/m². The summary of product characteristics states that rituximab should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available.
- 2.2 The most frequently observed adverse events in people receiving rituximab are infusion-related reactions, including cytokine release syndrome. The majority of these reactions occur during the first infusion. Serious but rare adverse events associated with rituximab include neutropenia and leucopenia (including febrile neutropenia), infections (predominantly bacterial and viral) and cardiovascular events (hypotension, hypertension, arrhythmias and angina). Very rare serious adverse events include hepatitis B reactivation and progressive multifocal leucoencephalopathy. For full details of side effects and contraindications, see the summary of product characteristics.
- 2.3 Rituximab is available in 100 mg (10 ml) and 500 mg (50 ml) vials. The cost of a 100 mg vial is £174.63, and of a 500 mg vial is £873.15 (excluding VAT; BNF edition 57). For a person with a body surface area of 1.93 m², the cost of rituximab for the first dose is £1,397 and for subsequent doses £1,746 including wastage of excess rituximab. The total cost of rituximab is £10,128 per course. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The appraisal committee ([appendix A](#)) considered evidence submitted by the manufacturer of rituximab for the first-line treatment of chronic lymphocytic leukaemia and a review of this submission by the evidence review group (ERG; [appendix B](#)).

- 3.1 The manufacturer's submission compared rituximab in combination with fludarabine and cyclophosphamide with fludarabine and cyclophosphamide combination therapy. This comparison was based on the CLL-8 trial, a phase 3 randomised controlled trial. The CLL-8 trial was a multicentre, open-label, parallel-group study in people with previously untreated chronic lymphocytic leukaemia. In the CLL-8 trial a total of 817 people were randomised to receive either fludarabine and cyclophosphamide or rituximab in combination with fludarabine and cyclophosphamide; data were reported on 810 people. The median age of trial participants was 61 years and 74% of participants were men. Participants had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and 95% of participants had Binet stage B or C disease. People with Binet stage A disease (n=40) were enrolled into the trial until a protocol amendment stopped further enrolment.
- 3.2 Trial participants were randomised to 6 cycles of treatment, with an interim staging after 3 cycles. People with progressive or stable disease at interim staging were offered alternative treatments by their clinicians outside the trial. People in the control group whose disease did not respond to treatment did not cross over to the treatment group, but could be offered rituximab-containing regimens. People whose disease showed a partial or complete response at the interim staging received all 6 cycles of treatment. Each cycle of 28 days consisted of fludarabine and cyclophosphamide chemotherapy (fludarabine [25 mg/m²] and cyclophosphamide [250 mg/m²] on days 1, 2 and 3) with or without rituximab (375 mg/m² on day 0 of cycle 1, 500 mg/m² on day 1 of cycles 2 to 6). All trial treatments were administered intravenously.
- 3.3 The primary outcome of the trial was progression-free survival, defined as the time between randomisation and the date of the first documented disease progression, relapse or death by any cause. Secondary outcomes were event-free survival, overall survival, disease-free survival, duration of response, time to

new chronic lymphocytic leukaemia treatment and response rates. Quality-of-life data were collected in the trial using the Spitzer Quality of Life Index and the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30 (EORTC-QLQC30).

- 3.4 Demographic characteristics and disease characteristics, including Binet stage B symptoms and prognostic markers such as cytogenetic abnormalities, were well balanced between the trial groups. Of all trial participants, 64% had Binet stage B disease, 31% had Binet stage C disease, and 5% had Binet stage A disease. The trial also enrolled 46 people (8%) with p53 deletion, a chromosome abnormality associated with a poorer prognosis.
- 3.5 A pre-planned interim analysis of the trial data after a median follow-up of 20.7 months showed a statistically significant difference in progression-free survival between the treatment groups. At this point the trial was halted and the interim analysis became the main analysis. The reported median progression-free survival was 39.8 months in the rituximab in combination with fludarabine and cyclophosphamide group and 32.2 months in the fludarabine and cyclophosphamide group, with a hazard ratio of 0.56 (95% confidence interval [CI] 0.43 to 0.72, $p < 0.0001$). The trial also reported an overall response rate of 86.1% in the rituximab in combination with fludarabine and cyclophosphamide group and 72.7% in the fludarabine and cyclophosphamide group. At this point median overall survival had not been reached and the trial reported a hazard ratio of 0.64 (95% CI 0.41 to 1.00, $p = 0.05$).
- 3.6 The manufacturer also submitted analyses of data from the CLL-8 trial collected from 3 follow-up points of a longer duration. After a median duration of follow-up of 25.4 months, the reported median progression-free survival was 42.8 months in the rituximab in combination with fludarabine and cyclophosphamide group and 32.5 months in the fludarabine and cyclophosphamide group, with a hazard ratio of 0.60 (95% CI 0.48 to 0.76, $p < 0.001$). At the end of this follow-up period the statistically significant difference in overall survival was not maintained (hazard ratio 0.72, 95% CI 0.48 to 1.09, $p = 0.13$). However, the data remained highly censored, because the majority of people were still alive. A further analysis after a median follow-up of 25.5 months reported a rate of progression-free survival of 76.6% in the rituximab in combination with fludarabine and cyclophosphamide group and 62.3% in the fludarabine and cyclophosphamide

group ($p < 0.001$). At this follow-up point, the CLL-8 trial reported an overall response rate of 95% in the rituximab in combination with fludarabine and cyclophosphamide group and 88% in the fludarabine and cyclophosphamide group ($p = 0.001$). The overall survival rate was 91% in the rituximab in combination with fludarabine and cyclophosphamide group and 88% in the fludarabine and cyclophosphamide group ($p = 0.18$). In a further analysis after a median follow-up of 26.4 months the reported mean progression-free survival was 37.1 months in the rituximab in combination with fludarabine and cyclophosphamide group and 30.8 months in the fludarabine and cyclophosphamide group ($p < 0.001$). The hazard ratio for progression-free survival was 0.6 (95% CI 0.47 to 0.75, $p < 0.0001$). Mean overall survival was 47.7 months in the rituximab in combination with fludarabine and cyclophosphamide group and 48.2 months in the fludarabine and cyclophosphamide group ($p = 0.18$).

- 3.7 The manufacturer presented a number of subgroup analyses. For the people with the p53 mutation the hazard ratio for progression-free survival was 0.6 (95% CI 0.31 to 1.19). The hazard ratio for progression-free survival for people with Binet stage A disease was 0.13 (95% CI 0.03 to 0.61, $p = 0.01$), Binet stage B disease was 0.46 (95% CI 0.32 to 0.63, $p < 0.0001$) and Binet stage C disease was 0.88 (95% CI 0.58 to 1.33, $p = 0.54$). The CLL-8 trial was not powered to detect differences in treatment effect for any of these subgroups.
- 3.8 In the CLL-8 trial, 77% of people in the rituximab in combination with fludarabine and cyclophosphamide group experienced a grade 3 or 4 adverse event compared with 62% in the fludarabine and cyclophosphamide group. In the rituximab in combination with fludarabine and cyclophosphamide group 46% of people experienced a serious adverse event; this figure was 41% of people in the fludarabine and cyclophosphamide group. The main adverse events were haematological toxicities, with neutropenia, leucopenia, febrile neutropenia and pancytopenia having a higher incidence (at least 2% difference) in the rituximab in combination with fludarabine and cyclophosphamide group, and thrombocytopenia, anaemia and pyrexia having a higher incidence (at least 2% difference) in the fludarabine and cyclophosphamide group. There were no differences in the rate of other adverse events between the trial groups.
- 3.9 The manufacturer provided data from 4 uncontrolled phase 2 trials on the efficacy and tolerability of combining rituximab with different chemotherapy

regimens. The combination chemotherapies included fludarabine, pentostatin, cyclophosphamide and mitoxantrone for the first-line treatment of chronic lymphocytic leukaemia. One of the studies (n=300) compared a group of people treated with rituximab in combination with fludarabine and cyclophosphamide with a group of people who had been treated with fludarabine-based regimens in the past and provided data with a median follow-up of 6 years. For the group receiving rituximab the rate of overall survival after 6 years was 77% with a 95% overall response rate. Median time to progression was 80 months. In comparison with the historical control group, rituximab in combination with fludarabine and cyclophosphamide was associated with statistically significant overall survival and was the strongest independent predictor of survival (hazard ratio 0.48, $p < 0.001$).

- 3.10 In their submission, the manufacturer also compared rituximab in combination with fludarabine and cyclophosphamide with chlorambucil using a mixed treatment comparison. A mixed treatment comparison was conducted because there were no head-to-head studies comparing rituximab with comparators other than fludarabine and cyclophosphamide. As well as chlorambucil, this analysis also included alemtuzumab, fludarabine alone and bendamustine. In addition to CLL-8, a further 7 trials were identified and used to create a network of evidence to make indirect comparisons of rituximab in combination with fludarabine and cyclophosphamide with the other comparators. The studies were combined using a fixed effect model because there was no apparent gain in goodness of fit when a random effects model was used. The mixed treatment comparison showed that chlorambucil had the shortest progression-free survival and therefore this was used as the reference treatment. The mean hazard ratios for other treatments compared with chlorambucil were 0.24 for rituximab in combination with fludarabine and cyclophosphamide, 0.43 for fludarabine and cyclophosphamide, 0.59 for alemtuzumab and 0.86 for fludarabine alone. The mean hazard ratio for progression-free survival was 0.56 for rituximab in combination with fludarabine and cyclophosphamide compared with fludarabine and cyclophosphamide, 0.24 for rituximab in combination with fludarabine and cyclophosphamide compared with chlorambucil, 0.42 for rituximab in combination with fludarabine and cyclophosphamide compared with alemtuzumab and 0.28 for rituximab in combination with fludarabine and cyclophosphamide compared with fludarabine alone.

- 3.11 The manufacturer's submission presented an economic analysis comparing rituximab in combination with fludarabine and cyclophosphamide with fludarabine and cyclophosphamide, and rituximab in combination with fludarabine and cyclophosphamide with chlorambucil. The manufacturer developed a 3-state Markov model with a cycle length of 1 month and a 15-year time horizon (to represent a lifetime horizon). The health states in the model were 'progression-free survival', 'progressed', or 'death'. People entered the model in the progression-free survival health state. The probability of transition from the progression-free survival to the progressed health state was taken from the groups in CLL-8. For the transition from the progression-free survival to the death health state, trial data were used and supplemented with Office of National Statistics data to inform the background mortality rate. Transition from the progressed to the progression-free survival health state was not possible. For the transition from the progressed to the death health state, data for people from both groups of the trial were aggregated and a single probability from the trial applied as there was a non-significant difference in survival following progression between the groups in the trial.
- 3.12 In the model, the drug costs were calculated assuming a body surface area of 1.93 m^2 , which reflects the average body surface area of the people in the CLL-8 trial. The CLL-8 trial used fludarabine and cyclophosphamide administered intravenously, but it is more common to use oral chemotherapy in the UK. In the model it was assumed that the efficacy of fludarabine and cyclophosphamide is the same regardless of the route of administration if the dosage is adjusted to ensure equivalent bioavailability. The costs of fludarabine and cyclophosphamide treatment in the model were adjusted to allow for the difference in the route of administration. The drug costs for rituximab were £1,397 for the first cycle of treatment and £1,746 for subsequent cycles. For 6 cycles of treatment the total drug cost of rituximab was £10,128. The total drug costs of fludarabine, cyclophosphamide and chlorambucil were calculated as £2,790, £22 and £286, respectively. In the base case, all people received 6 cycles of therapy unless disease progression occurred before the end of the 6 cycles.
- 3.13 The model included costs for supportive care that varied between the health states. This included costs for blood transfusions and bone marrow transplant in the progression-free survival health state taken from the CLL-8 trial and costs for second-line therapies for the progressed health state. In the model rituximab had

a cost for intravenous administration of £430 per cycle of treatment and the cost for an appointment to prescribe oral fludarabine and cyclophosphamide chemotherapy was £280. It was assumed that oral chemotherapy could be prescribed in the same appointment as rituximab so no additional cost of prescribing oral chemotherapy was included for the rituximab treatment group. Costs were also added for the pharmacist's time to prepare the infusion.

- 3.14 The utility values used in the manufacturer's submission were taken from a health technology assessment report (Hancock et al. 2002) that assessed the cost effectiveness of fludarabine as a first-line treatment for chronic lymphocytic leukaemia. A utility of 0.8 was attached to the progression-free survival health state and 0.6 to the progressed health state. The estimates of utility were not preference based, and were estimated by the authors of the health technology assessment report from condition-specific health-related quality-of-life data. No disutility for adverse events was included in the model. The manufacturer provided an interim analysis of 11 people from an observational study of utility in people with chronic lymphocytic leukaemia. The value for progression-free survival was consistent with that used in the manufacturer's submission. No conclusions could be drawn about the utility value appropriate for the progressed health state, as data for only 2 people were available.
- 3.15 The manufacturer provided a base-case estimate of incremental cost effectiveness of rituximab in combination with fludarabine and cyclophosphamide in comparison with fludarabine and cyclophosphamide. The incremental quality-adjusted life year (QALY) gain was 0.88 at an incremental cost of £11,617, giving an incremental cost-effectiveness ratio (ICER) of £13,189 per QALY gained. The probabilistic sensitivity analysis presented suggested that rituximab in combination with fludarabine and cyclophosphamide had a 91.9% probability of being cost effective at £20,000 and 98.6% probability of being cost effective at £30,000 when compared with fludarabine and cyclophosphamide. The manufacturer also provided an estimate of the incremental cost effectiveness of rituximab in combination with fludarabine and cyclophosphamide in comparison with chlorambucil. The incremental QALY gain was 1.91 at an incremental cost of £12,250, giving an ICER of £6,422 per QALY gained. Probabilistic sensitivity analysis suggested that the probability of rituximab in combination with fludarabine and cyclophosphamide being cost effective in comparison with chlorambucil was 100% at both £20,000 and £30,000 per QALY gained.

- 3.16 A sensitivity analysis was presented in the manufacturer's submission using different parametric models for the progression-free survival extrapolation. Additional sensitivity analyses were completed as follows:
- including costs for adverse events
 - including costs for febrile neutropenia episodes (as in CLL-8)
 - increasing and decreasing supportive care costs for the health states by 50%
 - assuming utility values for the health states such that the difference in the values between the health states was 0.4 and 0.1.

The assumption of a similar rate of adverse events for chlorambucil and fludarabine and cyclophosphamide was tested by assuming no bone-marrow transplants, fewer transfusions and less febrile neutropenia for the chlorambucil arm. One-way sensitivity analyses suggested that the results were not sensitive to a variety of parameter assumptions including utility values, monthly supportive care costs and drug administration costs. The results were sensitive to the function used to extrapolate progression-free survival (exponential, Gompertz), and the highest ICER reported (using a Gompertz function) was £22,661 per QALY gained.

- 3.17 The manufacturer's submission also included a scenario analysis to explore the impact on the ICER of using intravenous administration of fludarabine and cyclophosphamide chemotherapy instead of oral administration. This analysis demonstrated that the ICER was not sensitive to assumptions about the mechanism of administration. A further scenario analysis modelled the cost effectiveness of rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide. The results of this analysis suggested that the QALY gain from combining rituximab with chemotherapy would need to decrease to about 40% of that in the base case, all else remaining the same, for the ICER for rituximab to increase to over £30,000 per QALY gained.
- 3.18 At the request of the ERG, the manufacturer performed a further 1-way sensitivity analysis to explore the impact on the ICER of using alternative assumptions about different mortality rates between the progression-free survival and progressed health states. The manufacturer increased the mortality rate in the rituximab in combination with fludarabine and cyclophosphamide group by 315% so that the

life years gained in both treatment groups were the same (0.24 QALYs). In this scenario, the incremental QALY gain was 0.24 at an incremental cost of £7,226, giving an ICER of £30,336 per QALY gained.

- 3.19 The ERG considered that all the relevant studies had been identified. The ERG noted that the manufacturer's submission was based on only 1 completed clinical trial, and that this was unpublished. However, it considered this study to be of good quality. In addition, it noted that this study used intravenous administration of fludarabine and cyclophosphamide rather than oral administration which is normally used in UK clinical practice. The ERG considered the study population was appropriate. It noted that the subgroup of people with chronic lymphocytic leukaemia and the p53 deletion was only considered in relation to progression-free survival and not assessed in the cost-utility model. The ERG considered that the main comparators used in the cost-effectiveness analysis (fludarabine and cyclophosphamide, and chlorambucil) were appropriate. It noted that the mixed treatment comparison provided estimates of clinical effectiveness comparing rituximab in combination with fludarabine and cyclophosphamide with additional comparators, including alemtuzumab, fludarabine monotherapy and bendamustine. The ERG considered that the mixed treatment comparison completed by the manufacturer was appropriate.
- 3.20 The ERG considered the fact that in the manufacturer's economic model people in the progressed health state could not move back into the progression-free survival health state was unrealistic due to the natural history of chronic lymphocytic leukaemia. People with chronic lymphocytic leukaemia may receive further treatment at progression, which may then result in further periods of progression-free survival. The relapsing nature of chronic lymphocytic leukaemia means that subsequent relapses are less likely to respond to further treatment. This implies that subsequent relapses are likely to be associated with higher disease-related mortality. Therefore, the ERG considered that the manufacturer's assumption of a constant hazard of death after progression may not be appropriate. The ERG highlighted that the overall effect of the aggregated progressed health state and constant hazard of death from this health state was to imply a correlation between progression-free survival and overall survival which it did not consider had been empirically demonstrated in the manufacturer's submission. The ERG further considered that the sensitivity analyses presented by the manufacturer did not fully investigate the uncertainty

associated with the extent to which gains in progression-free survival led to gains in overall survival.

- 3.21 The ERG performed an exploratory analysis of the comparison of rituximab in combination with fludarabine and cyclophosphamide with fludarabine and cyclophosphamide. First, it conducted a component analysis to examine the relative contributions to utility gain from the gain in progression-free survival and the gain in overall survival. This analysis showed that progression-free survival contributed to 0.24 QALYs and overall survival to 0.64 QALYs (of a total gain of 0.88 QALYs). The ERG concluded that this demonstrated that in the model the majority of the benefit is derived from overall survival, making it sensitive to changes in assumptions about overall survival benefits from rituximab. The ERG noted that within the model, because a single transition probability is attached to all people in the progressed health state, the benefit in overall survival is derived almost entirely from the different rate of transfer from the progression-free health state to the progressed health state.
- 3.22 The ERG repeated the analysis completed by the manufacturer (see section 3.18) that removed the differences in overall survival between the 2 groups in the model. This was done by decreasing the probability of death in the progressed health state for the fludarabine and cyclophosphamide group. A decrease in the probability of death in the fludarabine and cyclophosphamide group to 57% of the base-case level removed the difference in overall survival between the groups and resulted in a QALY gain of 0.24 at an incremental cost of £7,228 and an ICER of £30,304 per QALY gained. When assuming no difference in overall survival between the 2 treatment groups in the analysis, the results suggested that the probability of rituximab in combination with fludarabine and cyclophosphamide being cost effective compared with fludarabine and cyclophosphamide at £20,000 per QALY gained was 29% and at £30,000 per QALY gained was 49%. The ERG identified that if it is assumed that there is no difference in overall survival between the rituximab in combination with fludarabine and cyclophosphamide and fludarabine and cyclophosphamide groups, the model outputs become sensitive to the assumed utility differences between the progression-free and the progressed health states. If the difference in utility between the health states is reduced by 0.1 (that is from 0.2 to 0.1), the ICER increases to £60,302 per QALY gained.

- 3.23 The ERG completed another exploratory analysis that assumed that the actual overall survival benefit from treatment with rituximab was somewhere between the manufacturer's base case and the assumption of no overall survival benefit. The ERG incorporated this assumption into the probabilistic sensitivity analysis by adding an additional variable, in which the decrease in probability of death in the fludarabine and cyclophosphamide group was sampled as a uniform distribution between 1 and 0.574. The results suggested that rituximab in combination with fludarabine and cyclophosphamide had a 72% probability of being cost effective compared with fludarabine and cyclophosphamide at £20,000 per QALY gained and 88% probability of being cost effective at £30,000 per QALY gained.
- 3.24 In response to consultation on the appraisal consultation document, the manufacturer submitted additional evidence in support of the combination of rituximab with chlorambucil compared with chlorambucil alone. The manufacturer presented data from 4 randomised controlled trials in follicular lymphoma, another low-grade B-cell cancer with a relapsing and remitting course. In these studies the addition of rituximab to a range of chemotherapy regimens showed a benefit in progression-free survival and response rates. A further phase 2 trial of rituximab in combination with chlorambucil in 29 people with a range of low-grade lymphoproliferative disorders showed an overall response rate of 89%, with a complete response rate of 63%.
- 3.25 The manufacturer also provided additional economic analysis comparing rituximab in combination with chlorambucil with chlorambucil alone. This used the same model as the original submission, with a number of amendments. The age of the cohort was increased to 70 years to reflect the fact that people treated with chlorambucil in routine clinical practice are generally older than those treated with fludarabine and cyclophosphamide. The baseline risk for the chlorambucil group was taken from the mixed treatment comparison included in the original submission. It was assumed that the hazard ratio for the addition of rituximab to fludarabine and cyclophosphamide observed in the CLL-8 trial (0.595) could be applied to this baseline risk to estimate the effect of adding rituximab to chlorambucil. Drug and administrative costs for rituximab and chlorambucil were included and all other model inputs and assumptions remained the same. Assuming the same hazard ratio meant the relative effect of adding rituximab to chlorambucil was the same as adding rituximab to fludarabine and cyclophosphamide. However, the absolute treatment effect would be smaller

because single agent chlorambucil is less effective than fludarabine and cyclophosphamide. The analysis suggested the incremental QALY gain was 0.51 at an incremental cost of £11,570, giving an ICER of £22,490 per QALY gained. A probabilistic sensitivity analysis using the 95% CIs around the assumed hazard ratios showed an 18.6% probability of the ICER being below £20,000 per QALY gained and a 99.7% probability of the ICER being below £30,000 per QALY gained.

- 3.26 The manufacturer also noted that a single arm phase 2 trial is underway of rituximab in combination with chlorambucil in people with untreated chronic lymphocytic leukaemia who are not fit for fludarabine-based treatment. The primary objective of the study is a safety analysis of the combination of rituximab and chlorambucil. Secondary objectives include: response rate, progression-free survival, overall survival, disease-free survival and duration of response. An interim analysis of the data is to be presented in December 2009 and a full analysis is expected towards the end of 2010.
- 3.27 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

4 Consideration of the evidence

- 4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia, having considered evidence on the nature of the condition and the value placed on the benefits of rituximab by people with chronic lymphocytic leukaemia, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

- 4.2 The appraisal committee discussed current standard clinical management of people with chronic lymphocytic leukaemia. The committee heard from clinical specialists that approximately 90% of people with chronic lymphocytic leukaemia are asymptomatic and that diagnosis may be made as a chance finding on routine blood testing. People who are asymptomatic may not need immediate treatment, although some will need treatment later in life. The committee heard that fludarabine in combination with cyclophosphamide is frequently used for people who need immediate treatment. However, chlorambucil alone is normally used for people with poor performance status or comorbidities, especially impaired renal function. The committee heard from patient experts that people with chronic lymphocytic leukaemia who need treatment will often have a series of treatments following first-line treatment, with further lines of treatment used after each relapse. The committee specifically considered the clinical management of people whose chronic lymphocytic leukaemia has the p53 mutation. The committee heard from clinical specialists that these people have a poorer prognosis and are usually treated with alternative treatments (for example, alemtuzumab) rather than chemotherapy.
- 4.3 The committee noted that the evidence of clinical effectiveness was based mainly on a single unpublished randomised controlled trial (the CLL-8 trial), which compared rituximab in combination with fludarabine and cyclophosphamide with fludarabine and cyclophosphamide. The committee accepted that the CLL-8 trial demonstrated a benefit in progression-free survival, and increased overall and

complete response rates for rituximab. The committee heard from clinical specialists that the CLL-8 trial population was younger and fitter than the population of people with chronic lymphocytic leukaemia seen in routine practice within the NHS in England and Wales. However, for the study population fludarabine in combination with cyclophosphamide was the appropriate comparator, and these people reflected the group who would receive fludarabine in combination with cyclophosphamide in clinical practice. The committee noted that an interim analysis of the clinical trial results had demonstrated a statistically significant gain in overall survival but this gain had not been maintained during longer follow-up. The committee accepted that crossover and subsequent lines of treatment in the trial made the overall survival benefit difficult to prove. The committee heard expert opinion that the degree of response to treatment and the duration of progression-free survival were generally accepted as surrogates for overall survival. In addition, the committee heard that cohort studies using historical controls had also shown survival benefits for people treated with rituximab-containing regimens, although results may have been influenced by changing clinical management, such as earlier identification of people with chronic lymphocytic leukaemia. On balance, the committee was persuaded that the benefits observed in progression-free survival and response rate were likely to lead to a gain in overall survival, although currently this would be difficult to quantify.

- 4.4 The committee recognised that the manufacturer had also provided evidence from uncontrolled phase 2 trials that reported the benefits of adding rituximab to other chemotherapy regimens for the first-line treatment of people with chronic lymphocytic leukaemia. The committee discussed the methodological limitations of obtaining an estimate of clinical effectiveness from uncontrolled and historical comparison studies. In addition, the committee discussed the further evidence from comparative studies of follicular lymphoma provided by the manufacturer in response to consultation on the appraisal consultation document. The committee was specifically mindful of comments from consultees about the addition of rituximab to chlorambucil for the treatment of people who are unable to tolerate fludarabine therapies. It accepted that it was reasonable to expect that rituximab would be of benefit when added to any chemotherapy regimen. However, the committee considered that the additional comparative studies provided by the manufacturer involved the use of more toxic regimens than chlorambucil and were likely to have enrolled people who were on average younger and had a

better performance status than people treated with chlorambucil in clinical practice. The committee were not persuaded that the estimates of treatment effects from different studies were transferable. The committee heard from clinical specialists that they considered that there was no evidence to support adding rituximab to chlorambucil, but that there was an ongoing trial investigating this. The committee concluded that there was considerable uncertainty about the relative clinical benefit associated with adding rituximab to chemotherapy regimens other than fludarabine and cyclophosphamide in the treatment of chronic lymphocytic leukaemia.

- 4.5 The committee was aware that fludarabine and cyclophosphamide were administered intravenously in the CLL-8 trial. It heard from clinical specialists that these chemotherapy agents were routinely administered orally in the NHS. The committee accepted that the efficacy of both methods of administration was equivalent as long as doses were adjusted to ensure equivalent bioavailability.
- 4.6 The committee heard from patient experts that progression-free survival was associated with a marked improvement in quality of life compared with the symptomatic progressed state. Patient experts commented that the first treatment-induced remission was likely to be the longest and associated with the most substantial improvements in quality of life. For this reason, people with chronic lymphocytic leukaemia valued having a choice of first-line treatments.

Cost effectiveness

- 4.7 The committee discussed the economic model submitted by the manufacturer. It noted that the manufacturer had only presented estimates of cost effectiveness for rituximab in combination with fludarabine and cyclophosphamide, and that this was compared with fludarabine in combination with cyclophosphamide and chlorambucil monotherapy. The committee heard from clinical specialists that for those people for whom chlorambucil was the most appropriate treatment (that is, people with poor performance status or comorbidities), rituximab in combination with fludarabine and cyclophosphamide would not be considered an appropriate treatment option. Therefore, the committee was not persuaded that the comparison of rituximab in combination with fludarabine and cyclophosphamide with chlorambucil was valid as the chemotherapy regimens were used in different

populations and such a choice between the 2 treatments was not expected to be clinically meaningful.

- 4.8 The committee reviewed the manufacturer's economic model and the critique of it by the ERG. The committee noted that the model was based on all people entering the model in the progression-free survival health state and moving to the progressed health state, and did not allow people to move from the progressed health state to the progression-free survival health state. The committee was mindful that the economic model allowed for costs of subsequent lines of therapy to be included but noted that this did not allow any benefit from further therapy to be taken into account. More importantly a single transition probability from the progressed health state to death was applied to people from both trial groups in the progressed health state. The committee recognised that although the manufacturer had not assumed any relative advantage in survival following progression, the use of a single transition probability from the progressed health state to death had the effect of associating improved progression-free survival with improved overall survival. The committee considered that the assumed association between progression-free survival and overall survival in the model could overestimate the benefits of the clinical effectiveness of rituximab as taken from the CLL-8 trial, because this had not demonstrated a statistically significant difference in overall survival between treatment groups.
- 4.9 The committee discussed the analysis by the ERG that suggested that two-thirds of the QALY gain (0.64 out of 0.88) in the model was because of the modelled improvement in overall survival, which is driven by gain in progression-free survival being reflected in gain in overall survival. The committee noted that when the overall survival benefit was removed from the model the ICER increased from £13,000 to £30,000 per QALY gained. The committee recognised therefore that the assumption about the amount of gain in overall survival from treatment with rituximab was an important assumption in the economic model and the use of different assumptions could have a large impact on the estimates of cost effectiveness.
- 4.10 The committee noted that condition-specific quality-of-life data collected in the rituximab trial had not been fully reported in the manufacturer's submission and that the utility values used in the model were not consistent with the NICE

reference case because they were not preference-based. The committee considered that the manufacturer may have been able to map the health-related quality-of-life data from the rituximab trial to a preference-based measure to derive utilities and that this may have provided an alternative to the utility data used. The committee noted that, if there was no difference in overall survival between the treatment groups in the model, the results became very sensitive to the difference between the utility values used for the progression-free survival health state and the progressed health state. The committee considered the lack of appropriate utility data contributed to substantial uncertainty in the economic modelling.

- 4.11 The committee discussed the additional exploratory analysis done by the ERG using an assumption that the actual survival benefit from treatment with rituximab was somewhere between that presented in the base case and an assumption that there was no gain in survival (see [section 3.23](#)). The committee noted that the probability, using the base-case utilities (that is, 0.80 for the progression-free survival health state and 0.60 for the progressed health state), of rituximab in combination with fludarabine and cyclophosphamide being cost effective at £20,000 per QALY gained was 71% and at £30,000 per QALY gained was 87%. On balance, the committee was persuaded that even taking into account the additional uncertainty about the utility values, the economic analysis had demonstrated that rituximab in combination with fludarabine and cyclophosphamide for the first-line treatment of chronic lymphocytic leukaemia was a cost-effective use of NHS resources.
- 4.12 The committee considered the economic analysis provided by the manufacturer after consultation on the appraisal consultation document. It examined the assumptions used in the economic modelling for the comparison of rituximab and chlorambucil with chlorambucil alone. The committee noted that the economic analysis assumed that the hazard ratio observed in the CLL-8 trial was exactly transferable to other chemotherapy regimens. However, the committee noted that subgroup analyses of the CLL-8 trial demonstrated that there were differences in effect between different subgroups of patients based on age and staging. The committee recognised that the marketing authorisation for rituximab allowed its use with any chemotherapy regimen. However, the committee was not persuaded that the relative effects of the treatment or hazard ratio were transferable between various chemotherapies

combined with rituximab and between different subgroups of people.

- 4.13 The committee was also mindful that the base-case ICER for rituximab in combination with chlorambucil from the manufacturer's additional analysis was £22,000 per QALY gained (section 3.25). The committee considered that this estimate would be higher if benefits in progression-free survival did not lead to benefits in overall survival (section 4.9). The committee noted that these uncertainties had increased the base-case ICER estimate for rituximab in combination with fludarabine and cyclophosphamide compared with fludarabine and cyclophosphamide in the main analysis from £13,000 to £30,000 per QALY gained. This estimate was also associated with uncertainty because no preference-based utility values were available (section 4.10). The committee was also aware that the analysis did not allow for the possibility of increased costs and disutilities because of adverse events that a population with poorer performance status or comorbidities may experience. The committee considered that these uncertainties could make the ICER for rituximab in combination with chlorambucil considerably less favourable.
- 4.14 The committee agreed that the uncertainty regarding the relative clinical effectiveness and the assumptions that had to be included in the additional economic analysis did not support the clinical and cost effectiveness of the use of rituximab in combination with chlorambucil. The committee was therefore not persuaded that it could recommend rituximab in combination with chlorambucil as a cost-effective use of NHS resources. The committee noted that the group of patients who are not suitable for a regimen of fludarabine in combination with cyclophosphamide, and who might therefore be treated with rituximab in combination with chlorambucil, would include a high proportion of people with poor performance status or comorbidities. The committee considered whether the equalities legislation and the requirement for fairness meant that it should make a positive recommendation for rituximab in combination with chlorambucil for this group. However, the committee noted that a negative recommendation for rituximab in combination with chlorambucil did not appear to have an impact on any group protected by the equalities legislation. It is not obvious that there is a clear correlation between the comorbidity factors which rendered this patient group unsuitable for certain chemotherapies and 'disability' as defined in the Disability Discrimination Act 1995. The committee could not be satisfied that a negative recommendation of rituximab in combination with chlorambucil

represented less favourable treatment or loss of benefit, given the lack of clear evidence as to the relative clinical effectiveness of rituximab in combination with chlorambucil in this particular patient group. Given the lack of evidence for both the clinical and cost effectiveness of this combination, the committee could not justify a positive recommendation of rituximab in combination with chlorambucil.

- 4.15 The committee was aware that new data on the combination of rituximab with chlorambucil in chronic lymphocytic leukaemia would soon be available. It considered that even though this was not a comparative trial, the data could potentially provide more certain estimates of cost effectiveness of rituximab in combination with chlorambucil. The committee therefore agreed that the current guidance should be reviewed when all data from the ongoing trial become available.

5 Implementation

- 5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 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 rituximab is the right treatment, it should be available for use, in line with NICE's recommendations.

Appendix A: Appraisal committee members and NICE project team

Appraisal committee members

The appraisal committee is one of NICE's standing advisory committees. Its members are appointed for a 3-year term. The appraisal committee meets three times a month except in December, when there are no meetings. The committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

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.

The following is a list of the committee members who took part in the discussions for this appraisal.

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Darren Ashcroft

Reader in Medicines Usage and Safety, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor John Cairns

Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty

External Relations Director – Pharmaceuticals & Personal Health, Oral Care Europe

Professor Jack Dowie

Health Economist, London School of Hygiene and Tropical Medicine

Dr Martin Duerden

Medical Director, Conwy Local Health Board

Dr Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch

Independent Nursing and Healthcare Consultant

Mrs Eleanor Grey

Lay Member

Mr Terence Lewis

Lay Member, Mental Health Consultant, National Institute for Mental Health in England

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queen's University, Belfast

Dr Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Neil Milner

General Practitioner, Tramways Medical Centre, Sheffield

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Rosalind Ramsay

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital

Dr Ann Richardson

Lay Member

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling

Lay Member

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Ms Nathalie Verin

Health Economics Manager, Boston Scientific UK and Ireland

Dr Colin Watts

Consultant Neurosurgeon, Addenbrookes Hospital

NICE project team

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

Kim Jeong, Elangovan Gajraj

Technical Leads

Zoe Garrett

Technical Adviser

Jeremy Powell

Project Manager

Appendix B: Sources of evidence considered by the committee

The evidence review group (ERG) report for this appraisal was prepared by the Peninsula Technology Assessment Group, University of Exeter:

- Main C, Moxham T, Pitt M and Stein K (2009) The clinical and cost-effectiveness of rituximab for the 1st line treatment of chronic lymphocytic leukaemia: an evidence review of the submission from Roche.

The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). The manufacturer/sponsor was also invited to make written submissions. Professional/specialist and patient/carer groups and other consultees had the opportunity to give their expert views. The manufacturer/sponsor, professional/specialist and patient/carer groups and other consultees also have the opportunity to appeal against the final appraisal determination.

- Manufacturer/sponsor:
 - Roche Products
- Professional/specialist and patient/carer groups:
 - British Society for Haematology
 - Cancer Research UK
 - Chronic Lymphocytic Leukaemia Support Association
 - Leukaemia CARE
 - Royal College of Nursing
 - Royal College of Pathologists
 - Royal College of Physicians, Medical Oncology Joint Special Committee
 - Royal College of Radiologists

- United Kingdom CLL Forum
- Other consultees:
 - Department of Health
 - Hampshire Primary Care Trust
 - Welsh Assembly Government
- Commentator organisations (did not provide written evidence and without the right of appeal):
 - Bayer
 - Department of Health, Social Services and Public Safety for Northern Ireland
 - NHS Quality Improvement Scotland
 - Pharmacia.

The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on rituximab for the first-line treatment of chronic lymphocytic leukaemia by attending the initial committee discussion and providing written evidence to the committee. They were also invited to comment on the ACD.

- Dr Donald Milligan, Consultant Haematologist, NCRI, nominated by the Royal College of Physicians – clinical specialist
- Professor Andrew Pettitt, Professor of Haematology, University of Liverpool, nominated by the Royal College of Pathologists – clinical specialist
- Mrs Jane Barnard, nominated by the Chronic Lymphocytic Leukaemia Support Association – patient expert
- Mrs Jacquelyn Williams Durkin, nominated by the Chronic Lymphocytic Leukaemia Support Association – patient expert.

Update information

February 2014: The implementation section was updated to clarify that rituximab is recommended as an option for treating chronic lymphocytic leukaemia. Additional minor maintenance was also carried out.

March 2012: Minor maintenance.

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Accreditation

