

# Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia

Technology appraisal guidance  
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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

# Contents

1 Recommendations .....	4
2 The technology.....	5
3 The manufacturer's submission.....	6
4 Consideration of the evidence.....	14
Clinical effectiveness .....	14
Cost effectiveness .....	19
5 Implementation.....	24
6 Recommendations for further research.....	25
Appendix A: Appraisal committee members and NICE project team.....	26
Appraisal committee members .....	26
NICE project team .....	28
Appendix B: Sources of evidence considered by the committee.....	30
Update information .....	33

# 1 Recommendations

- 1.1 Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for people with relapsed or refractory chronic lymphocytic leukaemia except when the condition:
- is refractory to fludarabine (that is, it has not responded to fludarabine or has relapsed within 6 months of treatment) or
  - has previously been treated with rituximab, unless:
    - in the context of a clinical trial, at a dose lower than the dose currently licensed for chronic lymphocytic leukaemia or
    - in the context of a clinical trial, in combination with chemotherapy other than fludarabine and cyclophosphamide.
- 1.2 Rituximab in combination with fludarabine and cyclophosphamide is recommended only in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia that has previously been treated with rituximab, unless rituximab has been given as specified in section 1.1.
- 1.3 Rituximab in combination with chemotherapy other than fludarabine and cyclophosphamide is recommended only in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia.
- 1.4 People with chronic lymphocytic leukaemia that is refractory to fludarabine (as defined in section 1.1), who are currently receiving rituximab in combination with fludarabine and cyclophosphamide should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
- 1.5 People with chronic lymphocytic leukaemia that has previously been treated with rituximab other than as specified in section 1.1, who are currently receiving rituximab in combination with fludarabine and cyclophosphamide and people who are currently receiving rituximab in combination with other chemotherapy regimens that is not in the context of research, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

## 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 treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. The summary of product characteristics (SPC) states that only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus 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/m<sup>2</sup> followed by 500 mg/m<sup>2</sup> for all subsequent doses. Six cycles of rituximab equate to a total dose of 2,875 mg/m<sup>2</sup>. The SPC 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 SPC.
- 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 a 500 mg vial is £873.15 (excluding VAT; BNF edition 58). For a person with a body surface area of 1.86 m<sup>2</sup>, the cost of rituximab for the first dose is £1,222 and for subsequent doses is £1,746, including wastage of excess rituximab. The total cost of rituximab is £9,954 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 and a review of this submission by the evidence review group (ERG; [appendix B](#)).

- 3.1 The manufacturer's submission compared the combination of rituximab plus fludarabine and cyclophosphamide with the combination of fludarabine plus cyclophosphamide. This comparison was based on the REACH trial, a phase 3, multicentre, open-label, randomised controlled trial in people with previously treated chronic lymphocytic leukaemia. People were enrolled if they had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy greater than 6 months and if they had previously received treatment with chlorambucil monotherapy with or without prednisolone, fludarabine monotherapy (or other nucleoside analogue), or an alkylator-containing combination therapy (such as cyclophosphamide plus doxorubicin, vincristine and prednisolone, or cyclophosphamide plus vincristine and prednisolone). People were excluded from the trial if they had previously received treatment with interferon, rituximab or another monoclonal antibody, or fludarabine and cyclophosphamide, either concurrently or sequentially. People were also excluded if they had chronic lymphocytic leukaemia that was refractory to fludarabine (defined as not achieving at least a partial response for a minimum duration of 6 months). A total of 552 people were randomised to receive either rituximab plus fludarabine and cyclophosphamide or fludarabine and cyclophosphamide alone. The median age of people in the trial was 63 years and 67% were men. Most people (90%) had Binet stage B or C disease.
- 3.2 People in the trial were randomised to 6 cycles of treatment, with an interim assessment of response after 3 cycles. At this point, people whose disease showed a partial or complete response continued treatment to 6 cycles, people with progressive disease discontinued treatment and people with stable disease continued treatment at the investigator's discretion. Each treatment cycle of 28 days consisted of fludarabine and cyclophosphamide chemotherapy (fludarabine 25 mg/m<sup>2</sup> and cyclophosphamide 250 mg/m<sup>2</sup> on days 1, 2 and 3) with or without rituximab (375 mg/m<sup>2</sup> on day 0 of cycle 1, 500 mg/m<sup>2</sup> on day 1 of cycles 2 to 6). All 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 first year of the trial using the Functional Assessment of Cancer Therapy – General (FACT-G).
- 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 people in the trial, 59% had Binet stage B disease, 31% had Binet stage C disease, and 10% had Binet stage A disease. The trial enrolled 42 people (8%) with del(17p), a chromosome mutation associated with a poorer prognosis. The manufacturer's submission stated that most people had previously been treated with single-agent chemotherapy (82%), most commonly an alkylating agent (66%) such as chlorambucil or cyclophosphamide. Of the people in the trial 56% were alkylator sensitive, 26% were alkylator refractory, and 16% had previously received fludarabine.
- 3.5 The trial results reported in the manufacturer's submission are based on a median follow-up of 25.3 months. At this point, the median progression-free survival was 30.6 months in the rituximab plus fludarabine and cyclophosphamide group and 20.6 months in the fludarabine and cyclophosphamide group, with a hazard ratio of 0.65 (95% CI 0.51 to 0.82,  $p=0.0002$ ). The best overall response rate was 69.9% in the rituximab plus fludarabine and cyclophosphamide group and 58% in the fludarabine and cyclophosphamide group ( $p=0.0034$ ). The median overall survival was 51.9 months in the fludarabine and cyclophosphamide group and was not reached in the rituximab plus fludarabine and cyclophosphamide group (hazard ratio 0.83, 95% CI 0.59 to 1.17,  $p=0.2871$ ).
- 3.6 The manufacturer presented a number of subgroup analyses. For people with the del(17p) mutation, the hazard ratio for progression-free survival was 0.75 (95% CI 0.38 to 1.49). The hazard ratio for progression-free survival for people with Binet stage A disease was 0.75 (95% CI 0.33 to 1.72), Binet stage B disease was 0.65 (95% CI 0.47 to 0.88) and Binet stage C disease was 0.61 (95% CI 0.41 to 0.90). The REACH trial was not powered to detect differences between the treatment groups for any of these subgroups.

- 3.7 In the REACH trial, 80% of people in the rituximab plus fludarabine and cyclophosphamide group experienced a grade 3 or 4 adverse event compared with 74% in the fludarabine and cyclophosphamide group. The most common grade 3 or 4 adverse events, with at least a 2% higher incidence in the rituximab plus fludarabine and cyclophosphamide group, were neutropenia, febrile neutropenia, granulocytopenia and hepatitis B infections. In the rituximab plus fludarabine and cyclophosphamide group, there were 19 treatment-related deaths (7%) and 51% of people had their treatment modified or interrupted for safety reasons. In the fludarabine and cyclophosphamide group, there were 14 treatment-related deaths (5%) and 39% of people had their treatment modified or interrupted for safety reasons.
- 3.8 The manufacturer provided supporting data from 20 non-comparative studies. These studies examined the efficacy and tolerability of rituximab plus different chemotherapy regimens, and of rituximab-containing regimens in people with fludarabine-refractory chronic lymphocytic leukaemia, and in people previously treated with rituximab (both groups had been excluded from the REACH trial). Of these 20 studies, 19 were uncontrolled, phase 2 studies and one was a randomised phase 2 trial of fludarabine, cyclophosphamide and mitoxantrone with or without rituximab in people with previously treated chronic lymphocytic leukaemia (n=52). However, the small number of people included in each group in the randomised trial did not allow a statistical comparison to be made. Seven of the 20 trials investigated the use of rituximab outside the terms of the marketing authorisation (either rituximab monotherapy or rituximab plus non-chemotherapy regimens).
- 3.9 The largest non-comparative study was a single-arm, open-label, phase 2 study of 177 people with relapsed or refractory chronic lymphocytic leukaemia (median follow-up 28 months) treated at the MD Anderson Cancer Centre (MDACC). Of the people in the study, 82% had previously received treatment with fludarabine monotherapy or combination therapy (of whom 108 people were fludarabine sensitive and 37 were fludarabine refractory) and 18% had received prior alkylating agents only. Twenty-two of the 177 people in the study had received rituximab monotherapy or combination therapy. The overall response rate for all people in the study was 73% and the complete response rate was 25%. The overall and complete response rates were 58% and 6% respectively for the group with fludarabine-refractory chronic lymphocytic leukaemia compared with 77%



and 33% for the group with fludarabine-sensitive disease. For the group who had previously received rituximab monotherapy or combination therapy, the overall response rate was 64% and the complete response rate was 18%.

- 3.10 During consultation on the appraisal consultation document, the manufacturer provided new data from the MDACC study described above. This included longer term results for a total of 284 people who received rituximab plus fludarabine and cyclophosphamide after previous treatment for chronic lymphocytic leukaemia. One hundred of these people had previously received a rituximab-containing regimen, which may have been rituximab monotherapy or one of various rituximab combination regimens. The number of people receiving each type of treatment was not reported. The overall response rate for all people in the study was 75% and the complete response rate was 31%. For people with fludarabine-refractory chronic lymphocytic leukaemia, the overall and complete response rates were 57% and 8% respectively compared with 80% and 36% for people with fludarabine-sensitive disease. For people who had previously received rituximab, the overall and complete response rates were 73% and 32% respectively compared with 76% and 30% for people who had not previously received rituximab. There was no difference in progression-free survival between people who had previously received rituximab and those who had not (hazard ratio 1.13,  $p=0.431$ ).
- 3.11 The manufacturer submitted an economic analysis comparing rituximab plus fludarabine and cyclophosphamide with fludarabine and cyclophosphamide. The manufacturer used a three-state Markov model with a cycle length of 1 month and a 25-year time horizon (to represent a lifetime horizon). The health states in the model were 'progression-free survival', 'progressed', and '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 the REACH trial. 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, people from both groups of the trial were assumed to have equal risk of death. This assumption was based on a non-significant ( $p=0.5596$ ) difference in Kaplan–Meier curves for post-progression survival.

- 3.12 In the model, the drug costs were calculated assuming a body surface area of 1.86 m<sup>2</sup>, which reflected the average body surface area of the people in the REACH trial. The REACH 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 was the same regardless of the route of administration if the dosage was 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. In the base case, the drug doses and costs were reduced according to the proportion of people expected to progress or die each month. The average undiscounted drug cost for rituximab was £9,078 for all 6 cycles of treatment. The average undiscounted drug costs of fludarabine were £2,569 for people in the rituximab plus fludarabine and cyclophosphamide group and £2,510 for people in the fludarabine and cyclophosphamide group. The average undiscounted drug costs of cyclophosphamide were calculated as £21 and £20 for each group respectively.
- 3.13 The model included costs for supportive care. Supportive care consisted of quarterly outpatient consultations, blood transfusions and bone marrow transplants in the progression-free survival health state and monthly outpatient consultations and second-line therapies for the progressed health state. The cost for intravenous administration of rituximab was £307 per cycle of treatment and the cost for an appointment to prescribe oral fludarabine and cyclophosphamide chemotherapy was £201. 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 and one consultation with a clinical oncologist.
- 3.14 The utility values used in the manufacturer's submission were taken from a health technology assessment report that assessed the cost effectiveness of fludarabine as a first-line treatment for chronic lymphocytic leukaemia. A utility value 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 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 34 people from an

observational study of utility in people with chronic lymphocytic leukaemia. The value for the progression-free survival health state 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 because only data for 2 people were available.

- 3.15 The manufacturer provided a base-case estimate of incremental cost effectiveness of rituximab plus fludarabine and cyclophosphamide compared with fludarabine and cyclophosphamide. The incremental quality-adjusted life year (QALY) gain was 0.585 at an incremental cost of £9,128, giving an incremental cost-effectiveness ratio (ICER) of £15,593 per QALY gained. The probabilistic sensitivity analysis presented suggested that rituximab plus fludarabine and cyclophosphamide had a 75% probability of being cost effective at £20,000 and a 94% probability of being cost effective at £30,000 when compared with fludarabine and cyclophosphamide.
- 3.16 During consultation on the appraisal consultation document, the manufacturer provided an estimate of the cost effectiveness of rituximab plus fludarabine and cyclophosphamide compared with fludarabine and cyclophosphamide, for the subgroup of people who had previously received rituximab. This was calculated using the same model described in section 3.11 with an adjustment to the progression-free survival in the rituximab plus fludarabine and cyclophosphamide group using the hazard ratio (1.13) estimated from the MDACC study. This adjustment to the model resulted in a QALY gain of 0.406 at an incremental cost of £9,134, giving an ICER of £22,519 per QALY gained.
- 3.17 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:
- increasing and decreasing adverse event costs by 50%
  - 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
  - assuming upper and lower quartiles for drug administration costs (from reference costs 2007/08)

- assuming differential probabilities of death after progression between treatment arms.

One-way sensitivity analyses suggested that the results were not sensitive to a variety of parameter assumptions including adverse events costs, monthly supportive care costs, and drug administration costs. The results were also not sensitive to the function used to extrapolate progression-free survival. The results were sensitive to assumptions about utilities and assumptions about the probability of death after progression. The highest ICER reported (using both differential mortality rates between treatment arms and adjusting utilities) was £23,790 per QALY gained.

- 3.18 The manufacturer's submission also included a scenario analysis to explore the impact on the ICER of combining rituximab with chemotherapy 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 45% 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.
- 3.19 The ERG considered that all the relevant trials had been identified. The ERG noted that the manufacturer's submission was based on only one clinical trial, and this trial was unpublished. The ERG considered this trial had adequate randomisation and allocation concealment. However, it noted that the trial was open label and therefore assessments might be biased. The ERG noted that an independent assessment of response was made during a pre-planned interim analysis of the trial data (conducted when about two thirds of the total 284 events had occurred). It stated that there were differences in progression-free survival between the trial groups when assessed by the blinded independent panel and the unblinded trial investigators (independent panel data were provided as academic-in-confidence). The ERG considered that the trial population was relatively young compared with the UK population who would be eligible for rituximab and 10% of people had mild stage disease (Binet stage A), a stage at which people were not commonly treated in the UK. The ERG also noted that people with fludarabine-refractory chronic lymphocytic leukaemia were excluded from the trial although they could be eligible for rituximab. It considered that the comparator used in the cost-effectiveness analysis (that is, fludarabine and cyclophosphamide) was appropriate.

- 3.20 The ERG noted that in the manufacturer's economic model people in the progressed health state could not move back into the progression-free survival health state. They considered that this did not appropriately reflect the disease process because people with chronic lymphocytic leukaemia receive a series of treatments and therefore they may have periods of progression-free survival after relapse and further treatment. The ERG commented that not all adverse events were assigned costs in the model. In particular, hepatitis B, for which there were 6 cases in the rituximab plus fludarabine and cyclophosphamide group and no cases in the fludarabine and cyclophosphamide group.
- 3.21 The ERG completed a series of exploratory analyses. It remodelled rituximab costs so that full costs were incurred at the start of each cycle rather than spread throughout the cycle. This amendment increased the base-case analysis from £15,593 to £18,129 per QALY gained. The ICER of £18,129 was corrected to £16,607 per QALY gained during consultation on the ACD. The ERG conducted an analysis using progression-free survival curves based on the independent assessment of progression (from the interim trial analysis) rather than non-blinded, investigator-assessed progression. This increased the base-case ICER to £17,507 per QALY gained. The ERG also explored the effect on the ICER of assuming no overall survival benefit of treatment with rituximab plus fludarabine and cyclophosphamide. It used 2 methods for this; it used the mortality rate from the fludarabine and cyclophosphamide group and applied it to the rituximab plus fludarabine and cyclophosphamide group and vice versa. The resulting ICERs were £40,568 and £42,444 per QALY gained for each method respectively compared with £15,593 per QALY gained in the manufacturer's base case.
- 3.22 The ERG identified that if it is assumed there is no difference in overall survival between the rituximab plus 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 decreased by 0.1 (that is from a difference of 0.2 to 0.1), the ICER increases to between £81,135 and £84,889 per QALY gained.
- 3.23 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, having considered evidence on the nature of relapsed or refractory chronic lymphocytic leukaemia and the value placed on the benefits of rituximab by people with the condition, 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 relapsed or refractory chronic lymphocytic leukaemia. The committee heard from clinical specialists that the most frequently used first-line treatments are: fludarabine plus cyclophosphamide with or without rituximab; and chlorambucil for people unable to have fludarabine because they have a poor performance status. However, for relapsed or refractory chronic lymphocytic leukaemia there is no single standard treatment option. The choice of treatment depends on a number of factors, including the presence of genetic abnormalities such as del(17p) mutation, previous treatments the person has received, whether a response was achieved from previous treatments, and if so, the duration of response. Clinical specialists noted that for these reasons, they considered it important to have a range of treatment options available. The committee heard that, for relapsed disease, treatments used previously may be administered again either with or without the addition of another therapeutic agent, or alternatively a different agent may be used. When additional or different treatments were used, these could include fludarabine and cyclophosphamide with the addition of mitoxantrone, alemtuzumab and stem cell transplantation.
- 4.3 The committee noted that the clinical effectiveness evidence for this appraisal was based mainly on a single unpublished randomised controlled trial (the REACH trial). In this trial rituximab plus fludarabine and cyclophosphamide was compared with fludarabine and cyclophosphamide. The committee heard from clinical specialists that people in the REACH trial were younger and had a better performance status than people with chronic lymphocytic leukaemia seen in



routine practice in the NHS in England and Wales. However, the clinical specialists commented that the people in the trial were representative of the people who would be eligible for treatment with fludarabine plus cyclophosphamide. The committee discussed the inclusion in the trial of people who had Binet stage A chronic lymphocytic leukaemia. It heard from clinical specialists that the decision to treat chronic lymphocytic leukaemia would depend on symptoms and progression of disease rather than specific staging.

4.4 The committee discussed the exclusion from the REACH trial of people who were previously treated with fludarabine combination therapy, people who were previously treated with rituximab and people who had chronic lymphocytic leukaemia that was refractory to fludarabine. However, it heard from clinical specialists that, if suitable, people often had fludarabine combination regimens as a first-line treatment. It also heard that the publication of [NICE's technology appraisal guidance on rituximab for the first-line treatment of chronic lymphocytic leukaemia](#) recommending rituximab plus fludarabine and cyclophosphamide meant that in the future an increasing number of people with relapsed or refractory disease will have had rituximab and fludarabine combination therapy as a first-line treatment. The committee considered the exclusion of these groups from the clinical trial was a limitation for decision making because it meant that the trial population did not reflect all the people with relapsed or refractory disease who would be eligible for rituximab plus fludarabine and cyclophosphamide in the NHS.

4.5 The committee accepted that the REACH trial demonstrated that the addition of rituximab to fludarabine and cyclophosphamide improved progression-free survival and complete response rates. The committee noted there was potential for bias in outcome assessment because of the open-label design of the trial. The committee discussed the results of an interim analysis of the trial data. This was an independent assessment of response that was provided as academic-in-confidence. The committee noted that there was a difference between the investigator and independent assessments but was aware that the interim analysis was conducted 1 year before the investigator assessment. The committee heard from clinical specialists that assessment of progression-free survival was subjective and could change depending on familiarity with assessment tools. The committee considered that the differences in these assessments led to uncertainty in estimating the additional benefit of rituximab.

- 4.6 The committee noted that in the REACH trial median overall survival had not been reached in the rituximab group, and that survival curves for patients in the 2 treatment groups hardly diverged until 30 months. The committee heard from clinical specialists and patient experts that it is difficult for studies of chronic lymphocytic leukaemia to demonstrate an effect of treatment on overall survival because of the long natural history of the disease and because people with the disease often receive multiple treatments. It also heard that progression-free survival and response rates were often accepted as surrogates for overall survival. Furthermore, clinical specialists commented that longer term trial evidence is emerging that demonstrates an overall survival benefit of first-line treatment with rituximab plus fludarabine and cyclophosphamide. On balance, the committee was persuaded that the improvements observed in progression-free survival and response rates were likely to lead to at least some gain in overall survival, although this gain could not be quantified.
- 4.7 The committee noted that in the REACH trial there were slightly more grade 3 or 4 adverse events and treatment-related deaths in the rituximab plus fludarabine and cyclophosphamide group than in the fludarabine and cyclophosphamide group. It heard from clinical specialists that people with chronic lymphocytic leukaemia are aware of the risks of treatments and are willing to accept these risks because of the severity of the condition. The committee discussed the 6 cases of hepatitis B seen in the trial in the rituximab plus fludarabine and cyclophosphamide group. However, it heard from clinical specialists that this would be unlikely to happen in the UK because all people with chronic lymphocytic leukaemia are screened for hepatitis B before treatment, and so hepatitis B reactivation would be rare.

### **People who have previously received treatment with rituximab**

- 4.8 The committee discussed the use of rituximab plus fludarabine and cyclophosphamide in people who have previously received treatment with rituximab-containing regimens. These people were excluded from the REACH trial, and the committee heard from clinical specialists that there was uncertainty about the degree of benefit of retreatment with rituximab. However, patient experts indicated that there was anecdotal evidence that people retreated with rituximab may have a good response to treatment. The committee also noted comments received at consultation that retreatment with rituximab is common in



other lymphoproliferative conditions where there has been a good response, and that the same could be expected for chronic lymphocytic leukaemia. It was also aware that over the next few years there would be an increasing number of people who would be treated with rituximab and who would require further treatment following relapse.

- 4.9 The committee considered the evidence from uncontrolled phase II studies reporting the benefits of retreatment with rituximab and noted the methodological limitations of these studies. It discussed the MDACC data provided during consultation, reporting that there was a similar response rate and progression-free survival in people who have previously received rituximab compared with people who have not. However, it noted this study had limitations in its design, for example, it was open label and uncontrolled (and therefore not randomised). The study included 100 people who had previously been treated with a rituximab-containing regimen. However, limited data were provided about these regimens and they included rituximab monotherapy and rituximab plus chemotherapy other than fludarabine and cyclophosphamide. The committee was not persuaded that the results from this study could be considered reflective of the UK population, of whom an increasing number will have previously received rituximab plus fludarabine and cyclophosphamide.

## **People who have previously received treatment with fludarabine**

- 4.10 The committee considered the use of rituximab plus fludarabine and cyclophosphamide in people who have previously received treatment with fludarabine. It first discussed people who had previously had a response to treatment with fludarabine (that is, people with fludarabine-sensitive disease). The committee discussed evidence from the REACH trial which included people whose disease was sensitive to fludarabine monotherapy. It noted that the REACH trial did not include people who had previously received fludarabine combination therapy. However, the committee considered that the clinical effectiveness was likely to be similar for people who were sensitive to fludarabine monotherapy and for people who were sensitive to fludarabine combination therapy. Therefore the committee was persuaded that data from the REACH trial could apply to people who were sensitive to fludarabine combination therapy.

4.11 The committee then discussed the evidence for the use of rituximab plus fludarabine and cyclophosphamide in people who have chronic lymphocytic leukaemia that is refractory to fludarabine. It noted the methodological limitations of the non-comparative studies provided by the manufacturer. The committee understood that clinical specialists did not consider that people with fludarabine-refractory disease should be retreated with the same fludarabine-containing regimen. The committee considered that the results of the MDACC study indicated a lower response to treatment with rituximab plus fludarabine and cyclophosphamide in chronic lymphocytic leukaemia refractory to fludarabine than in disease that was sensitive to fludarabine. The committee concluded that although people with fludarabine-refractory disease may derive some benefit from retreatment with fludarabine-containing chemotherapy regimens such as rituximab plus fludarabine and cyclophosphamide, the benefit was likely to be less than if the disease was fludarabine sensitive.

## **Rituximab plus chemotherapy regimens other than fludarabine plus cyclophosphamide**

4.12 The committee recognised that the marketing authorisation for rituximab allowed its use with any chemotherapy regimen. It discussed the evidence on rituximab plus chemotherapy regimens other than fludarabine and cyclophosphamide. The committee discussed comments received on the appraisal consultation document that suggested that people who cannot take fludarabine and people with chronic lymphocytic leukaemia that is refractory to fludarabine may benefit from treatment with rituximab plus other chemotherapy. The committee was aware of the lack of treatment options available to these people. However, the committee noted the methodological limitations of the non-comparative evidence provided. It heard from the manufacturer that a study of rituximab plus chlorambucil for first-line treatment was under way and that preliminary data from a cross-trial analysis indicated that response rates were better for people treated with rituximab plus chlorambucil than with chlorambucil alone. Overall, the committee considered that there was significant uncertainty about the relative benefit of adding rituximab to chemotherapy regimens other than fludarabine and cyclophosphamide and therefore more research was needed.

## Cost effectiveness

- 4.13 The committee reviewed the economic model submitted by the manufacturer and the ERG's analysis of the model. It was aware that the model did not allow transition from the progressed health state to the progression-free survival health state. The committee considered that this did not appropriately reflect the disease process because people may receive later treatments with further periods of progression-free survival. The committee was aware that a similar model had been used in [NICE's technology appraisal guidance on rituximab for the first-line treatment of chronic lymphocytic leukaemia](#). On balance, the committee agreed that the model could be used as a basis for considering the cost effectiveness of rituximab.
- 4.14 The committee considered how the costs of rituximab had been incorporated into the economic model. It noted that the ERG considered the assumption that costs were spread throughout the cycle in the base-case analysis inappropriate because rituximab was provided on the first day of each cycle. Therefore, the ERG explored remodelling rituximab costs so that costs were incurred at the start of each treatment cycle. The ERG re-analysis was corrected after consultation on the appraisal consultation document, and concluded that the ICER increased from £15,600 per QALY gained in the base case to £16,600 per QALY gained, which the committee accepted.
- 4.15 The committee discussed the utilities used in the economic model and noted that the evidence base for these estimates did not reflect the NICE reference case; in particular, preference-based methods were not used. It was aware that a utility study was under way in people with chronic lymphocytic leukaemia in the UK but detailed results from this study for people who had progressed following treatment were not yet available. The committee heard from patient experts that they considered an assumption of only a small difference in utility between the progressed and progression-free survival health states was not realistic. People greatly value being progression free and asymptomatic – it is associated with a marked improvement in quality of life. The committee considered the lack of appropriate utility data contributed to uncertainty in the economic model.
- 4.16 The committee discussed whether the modelled gains in overall survival from the economic model appropriately reflected the data from the clinical trial. It noted

that the outputs from the manufacturer's economic analysis modelled a difference in overall survival between treatment groups from the start of treatment that did not reflect the trial data. The overall survival curves from the clinical trial provided by the manufacturer showed no difference in overall survival between the treatment groups before around 30 months, although, beyond this time, the extrapolated curves began to diverge. The committee considered that there was little evidence from the REACH trial to support the validity of the analysis provided by the manufacturer and that the manufacturer's base-case analysis was likely to have overestimated the benefits associated with rituximab.

- 4.17 The committee considered the estimates of cost effectiveness provided by the manufacturer and the additional exploratory analyses performed by the ERG that examined the impact on the ICER of reducing the survival advantage of treatment with rituximab. It noted that using an assumption of no overall survival advantage had the effect of increasing the cost-effectiveness estimates from £15,600 per QALY gained in the base case to £41,000 per QALY gained. Furthermore it recognised that when there was no modelled gain in overall survival the results became very sensitive to the difference between the utility values used for the progression-free survival health state and those used for the progressed health state which were uncertain. However, based on comments from the clinical specialists, the committee was persuaded that it was appropriate to assume at least some gain in overall survival in the economic model. Overall, the committee considered that the most plausible ICER was likely to be at the upper end of the range of £20,000 to £30,000 per QALY gained, which was higher than the ERG's corrected base case of £16,600 per QALY gained.
- 4.18 On balance, the committee was persuaded that even taking into account the uncertainty about utility values and the uncertainty about a gain in overall survival from treatment with rituximab, the use of rituximab plus fludarabine and cyclophosphamide was a cost-effective use of NHS resources for the population represented in the REACH trial; that is, people who have not previously received rituximab or fludarabine combination therapy and those whose disease is not refractory to fludarabine monotherapy. Additionally, the committee was persuaded that the cost effectiveness of rituximab plus fludarabine and cyclophosphamide could be generalised from people whose chronic lymphocytic leukaemia was sensitive to fludarabine monotherapy to those whose disease was sensitive to fludarabine combination therapy ([section 4.10](#)).

## People who have previously received treatment with rituximab

4.19 The committee was not persuaded of the clinical effectiveness of rituximab plus fludarabine and cyclophosphamide for people who have already been treated with rituximab. Nevertheless, the committee discussed the cost-effectiveness estimate provided by the manufacturer during consultation of £22,500 per QALY gained for people who had previously received rituximab. It noted that this did not include the correction for the timing of rituximab costs. It recognised that there was considerable uncertainty in the manufacturer's original base-case ICER because of the uncertainties in the gains in overall survival and the limitations in the health-related quality of life data available. The committee noted that even for the REACH trial population the most plausible ICER was likely to be at the upper end of the range of £20,000 to £30,000 per QALY gained. It considered that in the rituximab-pretreated population, for which there was little research, the manufacturer's estimated ICER could not provide a basis for decision making. The committee concluded that rituximab plus fludarabine and cyclophosphamide could not be recommended as an appropriate use of NHS resources for everyone who had previously been treated with rituximab. However, because of the uncertainty about the benefits of retreatment with rituximab, the committee concluded that rituximab plus fludarabine and cyclophosphamide should be recommended in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia that has previously been treated with rituximab. The committee was aware of comments from consultees that some people in clinical trials had received rituximab in combination with treatments other than fludarabine and cyclophosphamide and at doses of rituximab lower than the licensed dose. The committee considered that this technology appraisal guidance should not adversely affect recruitment to future or ongoing clinical trials. Therefore the committee concluded that rituximab plus fludarabine and cyclophosphamide could be recommended for people with relapsed or refractory chronic lymphocytic leukaemia when rituximab had previously been given in the context of a clinical trial, either at a dose lower than currently licensed for chronic lymphocytic leukaemia, or in combination with chemotherapy other than fludarabine and cyclophosphamide.

## People who have previously received treatment with fludarabine

4.20 After concluding that rituximab plus fludarabine and cyclophosphamide was cost effective for people with chronic lymphocytic leukaemia that was sensitive to fludarabine ([section 4.18](#)), the committee then considered its use in people with fludarabine-refractory disease. It noted the lower clinical response in people who were refractory to fludarabine than in people who were sensitive to it ([section 4.10](#)), and that clinical practice was not to retreat these people with the same fludarabine regimen. It also noted that the manufacturer had not provided an estimate of the cost effectiveness of rituximab plus fludarabine and cyclophosphamide in this population. The committee heard from the manufacturer that there were difficulties identifying baseline event rate data and that the relative efficacy of rituximab therapy in this group was uncertain. On this basis the committee considered that the use of rituximab plus fludarabine and cyclophosphamide for the treatment of people who had already had fludarabine could only be considered a cost-effective use of NHS resources when the chronic lymphocytic leukaemia remained fludarabine sensitive and not when it was fludarabine refractory.

## Rituximab plus chemotherapy regimens other than fludarabine and cyclophosphamide

4.21 The committee understood the potential need for other rituximab combinations for people whose disease is refractory to fludarabine or is not suitable for treatment with fludarabine. However, it concluded that there was significant uncertainty about the relative benefit of adding rituximab to chemotherapy regimens other than fludarabine and cyclophosphamide and therefore more research was needed. Furthermore, the committee noted there was no current basis for estimating the cost effectiveness of such combinations, or for considering them to be cost effective. The committee was aware that people with chronic lymphocytic leukaemia that is not suitable for treatment with fludarabine plus cyclophosphamide might be treated with rituximab plus other chemotherapy. It was also aware that this group might be older and include people with poor performance status or comorbidities. The committee considered whether equalities legislation and the requirement for fairness meant that it should make a positive recommendation for rituximab plus other

chemotherapy for this group. However, given the lack of evidence for both the clinical and cost effectiveness of this treatment, the committee concluded that rituximab plus chemotherapy other than fludarabine and cyclophosphamide should only be used for the treatment of relapsed or refractory chronic lymphocytic leukaemia in the context of research.

## 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 paragraphs above. This means that, if a patient has relapsed or refractory 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.



## 6 Recommendations for further research

6.1 The committee considered that the following research would be of value:

- Studies investigating the effectiveness of rituximab plus fludarabine and cyclophosphamide in people with relapsed and refractory chronic lymphocytic leukaemia that has previously been treated with rituximab.
- Studies investigating the effectiveness of rituximab plus chemotherapy other than fludarabine and cyclophosphamide in people with relapsed and refractory chronic lymphocytic leukaemia.
- Studies investigating the health-related quality of life of people with chronic lymphocytic leukaemia that include data collected using a generic preference-based measure.

# Appendix A: 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.

### **Dr Kathryn Abel**

Reader and Consultant Psychiatrist/Director of Centre for Women's Mental Health, University of Manchester

### **Dr David Black**

Director of Public Health, Derbyshire County Primary Care Trust

### **Dr Daniele Bryden**

Consultant in Intensive Care Medicine/Anaesthesia Sheffield Teaching Hospitals NHS Trust

### **Professor Mike Campbell**

Statistician, Institute of Primary Care and General Practice, University of Sheffield

### **David Chandler**

Lay member

**Mary Cooke**

Lecturer School of Nursing, Midwifery and Social Work, University of Manchester

**Dr Christine Davey**

Senior Researcher, North Yorkshire Alliance Research and Development Unit

**Professor Rachel A Elliott**

Lord Trent Professor of Medicines and Health, University of Nottingham

**Stephen Greep**

Chief Executive of Hull and East Yorkshire Hospitals NHS Trust

**Dr Wasim Hanif**

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

**Dr Alan Haycox**

Reader in Health Economics, University of Liverpool Management School

**Dr Catherine Jackson**

Professor of Primary Care Medicine, University of St Andrews

**Dr Peter Jackson**

Clinical Pharmacologist, University of Sheffield

**Henry Marsh**

Consultant Neurosurgeon, St George's Hospital

**Professor Gary McVeigh (Vice Chair)**

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

**Dr Eugene Milne**

Deputy Medical Director, North East Strategic Health Authority

**Dr Richard Nakielny**

Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

**Ruth Oliver-Williams**

Head of Nursing/Quality Improvement Lead Surgical Services, Royal Derby Hospital

**Dr Katherine Payne**

Health Economics Research Fellow, University of Manchester

**Dr Danielle Preedy**

Lay member

**Dr Martin J Price**

Head of Outcomes Research, Janssen-Cilag

**Miles Scott**

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

**Dr Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

**Dr Surinder Sethi**

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team

**Professor Andrew Stevens (Chair)**

Professor of Public Health, University of Birmingham

**John Stevens**

Director, Centre for Bayesian Statistics in Health Economics, University of Sheffield

**Dr Matt Stevenson**

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

**Dr Judith Wardle**

Lay member

## **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.

**Sally Gallagher**

Technical Lead

**Zoe Garrett**

Technical Adviser

**Kate Moore**

Project Manager

## Appendix B: Sources of evidence considered by the committee

The evidence review group (ERG) report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration:

- Dretzke J, et al. (2009) Rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia.

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). The manufacturer/sponsor was also invited to make written submissions. The professional/specialist and patient/carer groups and other consultees had the opportunity to give their expert views and, along with the manufacturer/sponsor, 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
  - Royal College of Nursing
  - Royal College of Pathologists
  - Royal College of Physicians, Medical Oncology Joint Special Committee
  - United Kingdom CLL Forum
  - Chronic Lymphocytic Leukaemia Support Association (CLLSA)
  - Leukaemia CARE
  - Macmillan Cancer Support

- Other consultees:
  - Department of Health
  - Knowsley PCT
  - Welsh Assembly Government
- Commentator organisations (did not provide written evidence and without the right of appeal):
  - Bayer (fludarabine)
  - Pfizer (cyclophosphamide, prednisolone, doxorubicin)
  - Institute of Cancer Research
  - Leukaemia Research Fund
  - National Institute for Health Research Health Technology Assessment Programme
  - West Midlands Health Technology Assessment Collaboration (WMHTAC)
  - National Collaborating Centre for Cancer.

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on rituximab for the 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 Chris Fegan, Consultant Haematologist, nominated by Royal College of Physicians – clinical specialist
- Professor Andrew Pettitt, Division of Haematology, nominated by Royal College of Pathologists – clinical specialist
- Jacquelyn Williams Durkin, Trustee of Chronic Lymphocytic Leukaemia Support Association, nominated by Chronic Lymphocytic Leukaemia Support Association – patient expert
- Jane Barnard, Chairman of Chronic Lymphocytic Leukaemia Support Association, nominated by Chronic Lymphocytic Leukaemia Support Association – patient expert.

Representatives from Roche Products attended committee meetings. They contributed only when asked by the committee chair to clarify specific issues and comment on factual accuracy.



# Update information

## Minor changes since publication

**February 2014:** implementation section updated to clarify that rituximab is recommended as an option for treating relapsed or refractory chronic lymphocytic leukaemia. Additional minor maintenance update also carried out.

**March 2012:** minor maintenance

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