NICE National Institute for Health and Care Excellence

NICE guidance

Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma

Technology appraisal guidance
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1 Recommendations

1.1 Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy.

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2 The technology

2.1 Rituximab (MabThera, Roche Products) is a chimeric (mouse and human) genetically engineered monoclonal antibody. It targets the CD20 surface antigen of mature B-cell lymphocytes. Rituximab has a marketing authorisation for the 'treatment of follicular lymphoma patients responding to induction therapy'. Other licensed indications for rituximab in non-Hodgkin's lymphoma include 'the treatment of previously untreated patients with stage 3 to 4 follicular lymphoma in combination with chemotherapy'; 'the treatment of patients with stage 3 to 4 follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy'; and 'the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy'.

2.2 Allergic and skin reactions are the most common adverse effects of rituximab infusion. Reactions during infusion can include bronchospasm and hypotension, which can be severe or life-threatening. Severe reactions occur more commonly in people with a high tumour burden, and the incidence and severity of infusion reactions decrease with successive infusions. Rituximab treatment can also be associated with blood and bone-marrow toxicity, characterised by neutropenia and leucopenia, which can lead to infections. In addition, treatment with rituximab may cause flu-like symptoms, and has been associated with progressive multifocal leukoencephalopathy. For full details of side effects and contraindications, see the summary of product characteristics.

2.3 For people with previously untreated follicular lymphoma that has responded to first-line induction treatment, the recommended dose of rituximab as maintenance treatment is 375 mg/m² body surface area, administered by intravenous infusion once every 2 months. Treatment should start 2 months after the last dose of first-line induction therapy and continue until the disease progresses, or for a maximum period of 2 years. The cost of one 100-mg vial is £174.63, and one 500-mg vial is £873.15 (excluding VAT; BNF, edition 61). The manufacturer estimates that for a person with an average body surface area of 1.8 m², the average cost of rituximab maintenance treatment for 2 years is £14,669 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

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3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of rituximab and a review of this submission by the Evidence Review Group (ERG).

3.1 The manufacturer presented information addressing the decision problem; that is, whether rituximab maintenance treatment is a clinically effective and cost-effective use of NHS resources, compared with standard management without rituximab for people with follicular lymphoma that has responded to first-line induction chemotherapy combined with rituximab. The outcomes defining effectiveness included progression-free survival, overall survival, response rates, adverse effects of treatment and health-related quality of life.

3.2 The manufacturer undertook a systematic literature review and identified only 1 trial, the Primary Rituximab and Maintenance (PRIMA) trial, that met its inclusion criteria. The manufacturer presented evidence analysed after a median follow-up of 25 months (at the close of the PRIMA trial), but also provided data from 2 post-study observational periods with median follow-up periods of 36 and 38 months. In the absence of long-term data from the PRIMA trial, the manufacturer used data from the European Organisation for Research and Treatment of Cancer (EORTC) 20981 study to model the expected longer-term outcomes that may have been experienced by participants in the PRIMA trial, had the trial gone on longer. The patient population in the EORTC 20981 study (see section 3.4), however, was different from that of the PRIMA trial.

3.3 The PRIMA trial was a phase 3, open-label, multicentre, randomised trial with 2 treatment phases. The trial included 1,193 people with previously untreated advanced follicular lymphoma with an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1 and a median age of 57 years. In the first phase (induction phase or first-line treatment), participants had 1 of 3 different regimens, all of which included rituximab: R-CVP (rituximab with cyclophosphamide, vincristine and prednisolone [n=268]), R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisolone [n=881]) or R-FCM (rituximab with fludarabine, cyclophosphamide and mitoxantrone [n=44]). People whose disease had either a partial or complete response to first-line treatment (n=1,019) entered the second phase of the trial, and were randomised

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to receive either rituximab maintenance treatment (n=506) or no treatment (that is, observation; n=513). People in the maintenance arm received 375 mg/m² rituximab intravenously: 1 dose every 8 weeks for 2 years, for a total of 12 doses or until disease progression, whichever occurred first. The trial was designed initially to estimate event-free survival as the primary outcome. However, during the course of the trial, the manufacturer amended the protocol in line with recommendations from regulatory authorities and changed the primary outcome to progression-free survival. Length of follow-up was increased from 5 to 7 years, and the study population was increased from 900 to 1,200 participants. Secondary clinical outcomes included overall survival, event-free survival, time to next anti-lymphoma treatment, overall response rate at the end of the maintenance observation phase, the proportion of people with histological transformation at first progression, quality of life and safety. Quality-of-life data were collected in the trial using the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire and the EORTC Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30). After a median follow-up of 25 months, a Data and Safety Monitoring Committee judged that the trial had met its primary objective at the pre-specified interim analysis and recommended closure of the trial. However, investigators continued to follow patients during an observational post-study period to collect longer-term data.

3.4 The EORTC 20981 study was a phase 3, open-label randomised trial that included people with relapsed or resistant follicular non-Hodgkin's lymphoma (n=465) who had not previously been treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) or R-CHOP. Instead, patients had been treated with at least 2 months of single-agent therapy (such as chlorambucil) and/or at least 2 consecutive cycles of combination chemotherapy (such as CVP [cyclophosphamide, vincristine and prednisolone]) or purine analogues. Therefore, these patients differed from those in the decision problem in that their disease had progressed after first-line therapy, and they had not been previously treated with R-CHOP, R-CVP or R-FCM as in the PRIMA trial. Participants were randomised to treatment with R-CHOP or CHOP alone after enrolment. People whose disease responded to second-line therapy (n=334) were then randomised to either second-line maintenance treatment with 375 mg/m² rituximab (1 dose every 3 months for 2 years or until relapse) or observation until relapse.

3.5 The results of the PRIMA trial showed that after 25 months' median follow-up, the

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risk of disease progression was halved in the rituximab maintenance arm compared with the observation arm (hazard ratio [HR] 0.50; 95% confidence interval [CI] 0.39 to 0.64; p<0.0001) as assessed by the study investigators. This result was based on 18.4% (93 of 505) of people in the rituximab maintenance arm and 33.9% (174 of 513) of people in the observation arm having experienced an event (disease progression, relapse or death). The estimate of the hazard ratio associated with treatment was slightly higher when assessed by an independent review committee. After a median follow-up of 36 months, progression-free survival was statistically significantly improved in people randomised to the rituximab maintenance arm (PFS 74.9%; 95% CI 70.9 to 78.9) compared with those randomised to the observation arm (PFS 57.6%; 95% CI 53.2 to 62.0). The risk of disease progression was significantly reduced for people in the rituximab maintenance arm (HR 0.55; 95% CI 0.44 to 0.68; p<0.0001). However, too few patients randomised to the rituximab maintenance arm had progressed during the study period to estimate the median time to progression. For patients randomised to observation, the median time to progression was estimated to be 48.3 months (95% CI 38.0 to not reached). After 36 and 38 months' median follow-up, a statistically significant difference in overall survival could not be established between the 2 arms because of the low number of deaths that had occurred.

3.6 During first-line induction therapy, most people in the PRIMA trial experienced an adverse event and 25% experienced a serious adverse event, consistent with the known safety profiles of these induction regimens. After the first-line maintenance phase of the trial, significantly more grade 3 or 4 adverse events occurred in people in the rituximab maintenance arm (24%) compared with people in the observation arm (17%; risk ratio 1.46; 95% CI 1.14 to 1.87; p=0.0026).

3.7 In the EORTC 20981 study, second-line maintenance treatment with rituximab significantly improved progression-free survival compared with observation (median 3.7 years versus 1.3 years). Five-year overall survival was not significantly different between the arms (74% in the rituximab maintenance arm and 64% in the observation arm). Second-line maintenance treatment with rituximab was associated with statistically significant increases in grade 3 and 4 infections compared with observation.

3.8 The manufacturer also provided a summary of other studies, as supporting

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evidence, of the efficacy and safety of rituximab maintenance in people with previously untreated or relapsed or refractory follicular lymphoma. In the ECOG 1496 study, rituximab maintenance led to longer progression-free survival compared with observation (HR 0.4; $p<0.0001$) in people who had previously received CVP as induction therapy. Interim data from another study (SAKK 35/98), which is still ongoing to compare a short course of rituximab maintenance (375 mg/m² every 2 months for a total of 4 doses) and prolonged rituximab maintenance (375 mg/m² every 2 months for a maximum of 5 years) with observation, demonstrated a longer event-free survival after prolonged rituximab maintenance compared with observation in people with either previously treated or previously untreated follicular lymphoma after induction with rituximab monotherapy. Preliminary safety results from this study also indicate that prolongation of maintenance therapy beyond 2 years does not lead to an obvious increase in toxicity.

3.9 The manufacturer produced a Markov economic model to estimate all costs and benefits over a lifetime resulting from the treatment of follicular lymphoma with rituximab compared with observation after first-line induction with different regimens of rituximab and chemotherapy (R-CHOP, R-CVP or R-FCM). Although listed as a comparator in the decision problem for this appraisal, ibritumomab tiuxetan was considered by the manufacturer to not be an appropriate comparator for inclusion in the economic model because of limited evidence available to support its benefits, and because data for local use suggested that it is seldom prescribed in the UK. The model had 4 distinct health states: progression-free survival while in the first-line maintenance phase (PF1), progression-free survival after receiving second-line induction treatment with rituximab in combination with chemotherapy (PF2), progressive disease (PD) and death. The manufacturer assumed that all people enter the economic model in the PF1 health state after successfully completing induction treatment (that is, the start of the model reflected the second phase of the PRIMA trial). The model had a cycle of 1 month and a time horizon of 25 years. A half cycle correction was applied to the model.

3.10 Data from the PRIMA trial (after 38 months' median follow-up) and the EORTC 20981 study were used by the manufacturer to estimate the transition probabilities between the health states in the economic model. To estimate median progression-free survival, which could not be estimated from the PRIMA

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trial directly, the manufacturer used the Gompertz function to extrapolate progression-free survival data beyond the end of the PRIMA trial. The manufacturer considered that this function provided a better fit than alternative functions. Based on the results from the PRIMA trial, the EORTC 20981 study and expert opinion, the manufacturer assumed that people in the PF1 health state retain a clinical benefit from rituximab maintenance treatment for 6 years; that is, 4 years beyond the end of treatment in the PRIMA trial. After this time, the risk of disease progression for people in the PF1 health state was assumed to be equal in both the rituximab maintenance and observation arms of the model (that is, both groups progress at the same rate after 6 years). Data from the EORTC 20981 study were used to derive the long-term outcomes, including death, for people according to the treatment they received after progressing from the PF1 health state.

3.11 In the PRIMA trial, participants did not routinely complete EQ-5D questionnaires. Instead, health-related quality-of-life data were collected in the PRIMA trial using the FACT-G and EORTC QLQ-C30 questionnaires developed to assess the quality of life of people with cancer. Overall, no differences in health-related quality-of-life data were observed between the rituximab maintenance and observation arms.

3.12 The manufacturer conducted a systematic literature review to identify studies addressing quality of life, but it considered that only 1 study (Pettengel et al. 2008) met the inclusion criteria. In this study, 215 adults with follicular lymphoma and an ECOG score of 0 to 2 completed EQ-5D questionnaires during outpatient appointments across 8 sites in the UK. Patients were placed in 1 of 5 categories according to the stage of their disease: 'active disease – newly diagnosed', 'active disease – relapsed', 'partial response', 'complete response to therapy (or remission)' and 'disease free (no detectable disease)'. Mean utility values from this study were 0.88 (from 'disease free' category), 0.79 (from 'complete response to therapy' category) and 0.62 (from 'active disease – relapsed' category). These utility values were assigned to the PF1, PF2 and PD health states respectively in the manufacturer's economic model. The economic model did not include values for the disutility associated with grade 3 and 4 adverse events, or with receiving chemotherapy.

3.13 The manufacturer included costs associated with drug acquisition and

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administration, supportive care, management of adverse events and monitoring for each health state in the economic model. The primary sources of these costs were the BNF (edition 56 was used by the manufacturer, and edition 59 by the ERG; however, the costs were the same in both editions), the NHS Reference Cost Schedule 2008 to 2009 and the Personal Social Services Research Unit 2009 (unit costs of health and social care). The manufacturer assumed that grade 3 and 4 adverse events incur equivalent costs, as estimated from the PRIMA and EORTC 20981 studies. Costs and benefits were discounted at 3.5% per year.

3.14 In the base-case analysis from the manufacturer's original submission, which assumed that the clinical benefit of rituximab is sustained over 6 years, the incremental cost-effectiveness ratio (ICER) of rituximab maintenance treatment compared with observation was £15,978 per quality-adjusted life year (QALY) gained (incremental costs, £18,681; incremental QALYs, 1.169). Sensitivity analyses explored the impact of varying costs of adverse events (±50%), monthly supportive care (±50%), and administering rituximab (for example, nursing time: upper, £267; lower, £176). In sensitivity analyses, the manufacturer also tested the impact of varying the time horizon (20 years and 30 years), using other types of parametric functions to extrapolate progression-free survival data from the PRIMA trial, and assuming that people who progress from the PF1 health state die (probability of death was 100%, extreme scenario) rather than experience disease progression. From the analyses, the manufacturer concluded that the model was not sensitive to assumptions around the type of parametric extrapolation fitted to the PRIMA data, around costs of supportive care and administration, or around the time horizon. The model was sensitive to assumptions regarding the duration of treatment effect; when the manufacturer assumed that the effect of treatment stopped after 47 months (instead of after 72 months as in the base case), the ICER increased to £21,151 per QALY gained. When the manufacturer assumed that all people died after progressing from the PF1 health state (extreme scenario), the ICER decreased to £13,901 per QALY gained.

3.15 The manufacturer conducted probabilistic sensitivity analyses of all major parameters in the model except age, weight and height. The mean ICER from this analysis was £15,770 per QALY gained, and the manufacturer estimated that the probability of rituximab maintenance treatment being cost effective at £20,000 per QALY gained or less was 84.2%, and at £30,000 per QALY gained or less was

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99.7%, compared with observation. The manufacturer concluded that these results demonstrated that the ICER was robust even under a wide range of variation in the model parameters.

3.16 The ERG considered that the PRIMA trial was well designed and, although it was an open-label trial, the results of progression-free survival could be considered robust because the trial used a blinded independent review committee. In the ERG's view, the rituximab chemotherapy regimens used in the induction phase of the PRIMA trial (that is, R-CHOP, R-CVP and R-FCM) were appropriate and in line with the rituximab chemotherapy regimens used in UK clinical practice. Overall, the ERG considered the results of the PRIMA trial to be generalisable to the UK setting, and that the manufacturer's decision not to include ibritumomab tiuxetan as a comparator in the economic analysis was justified.

3.17 The ERG was concerned that follow-up data were not available beyond 4 years and that the manufacturer could not estimate the median time to progression or to death by treatment group. The ERG cautioned that the data were immature (few events), which might have led the results to overestimate the clinical benefits of rituximab maintenance treatment. The ERG noted a meta-regression analysis (Bassler et al. 2010), which found large differences in the size of treatment effects between trials that were stopped early (regardless of the reason) and similar trials that ran for their originally specified time period. Using data from this study, the ERG adjusted the progression-free survival hazard ratio from the PRIMA trial to account for early reporting bias and noted that the hazard ratio increased by 30.7% from 0.55 (manufacturer's base case) to 0.719 (95% CI 0.575 to 0.889). The ERG suggested that sensitivity analyses that include the adjusted progression-free survival hazard ratio should be considered by the Committee.

3.18 The ERG noted that treatments administered after participants' disease had progressed may have affected the rate of overall survival in the PRIMA trial. The ERG stated that the post-progression treatments in the manufacturer's submission were in line with those used in UK clinical practice. However, from the data provided, the ERG was unsure whether the time at which these treatments were offered in the trial reflected the time that they would be offered in routine practice.

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3.19 Although the ERG identified a number of problems with the structure and implementation of the manufacturer's model, the ERG did not expect these problems to have a major impact on the cost-effectiveness results. The ERG noted that the manufacturer did not model the disutilities associated with grade 3 and 4 adverse events. The ERG stated that this omission would favour the rituximab maintenance arm because people treated with rituximab experience more adverse events than those not treated with rituximab (observation). The ERG was concerned that the manufacturer may have underestimated the costs of adverse events experienced in the PF2 health state because most of the people in the PRIMA trial had not progressed beyond the first-line maintenance or observation phase at the time of data analysis (up to 38 months).

3.20 The ERG noted the low proportion of patients censored (less than 3%) during the first 800 days of the PRIMA trial, and that this proportion increased greatly (70% for rituximab maintenance and 50% for observation) by 1,600 days. Consequently, the ERG believed that the Kaplan–Meier estimate of progression-free survival becomes uncertain after 800 days. The ERG had concerns about the use of long-term modelling to inform the duration of treatment benefit estimated in the economic model. The ERG noted that the manufacturer used the Gompertz parametric function in their original analyses, which generated the highest overall estimate compared with other algorithms (such as an exponential function), to model progression-free survival.

3.21 The ERG was concerned about the manufacturer's use of data from the EORTC 20981 study to inform the economic model. The ERG noted that the participants in this study received different induction treatments to those in the PRIMA study (the EORTC 20981 study included people if their disease had relapsed after 2 previous non-anthracycline-containing chemotherapy regimens) and that only half of the patients in the EORTC 20981 study received induction treatment with a rituximab-containing regimen. Therefore, the ERG questioned whether the manufacturer could reliably use the outcomes from the EORTC 20981 study to predict future outcomes for participants in the PRIMA trial.

3.22 The ERG noted that, in the base case, the manufacturer assumed rituximab maintenance treatment had a clinical benefit for 6 years (that is, the hazard ratio from the PRIMA trial was applied for 6 years). In addition, the ERG noted that a large proportion of the gain in progression-free survival in the model arises

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beyond 4 years. Therefore, the ERG cautioned that if the gain in progression-free survival progressively declines, the ICER could substantially increase depending on the time period over which one assumes a difference between the treatment arms (that is, the time until the progression-free survival curves for each arm converge). The ERG also noted that the ICERs in the manufacturer's analyses were sensitive to the age at which a patient is assumed to start treatment and suggested that the manufacturer should have adjusted this variable in its sensitivity analyses.

3.23 The ERG noted that the manufacturer's model projects future benefits associated with the increased time that a person's disease remains progression free. The manufacturer's base-case modelling estimated that the mean time before a person's disease progresses is 8.64 years for the observation arm and 10.65 years for people who receive rituximab maintenance therapy; a gain of 2.01 years. The ERG noted that the manufacturer's analysis assumed that almost all of this gain in progression-free survival occurs in the PF1 health state. This implied that the majority (89.2%) of the gains in progression-free survival achieved directly by extending the first-line induction response translated into overall survival gains. The ERG cautioned that this should represent the 'best possible' scenario and would require strong supportive evidence from clinical trials before it could be accepted. The ERG explored how different conversion rates of progression-free survival gain to overall survival gain affect the estimated ICER, and predicted that at least 50% of progression-free survival gain would need to be converted into overall survival gain to achieve an ICER below £30,000 per QALY gained. The ERG further noted that if a function other than the Gompertz parametric function were used to extrapolate and convert progression-free survival into overall survival, then the conversion rate would need to be even higher for the ICER to remain below £30,000 per QALY gained.

3.24 The ERG noted that the manufacturer's model included utility values of 0.88 and 0.79 for the PF1 and PF2 health states respectively. The ERG considered that the same utility value should be used in both health states, because people in both states are in remission or have a full response. The ERG conducted a sensitivity analysis assuming that both health states have a utility value of 0.79, and noted that the QALY gain associated with maintenance treatment with rituximab dropped by more than 10% and the ICER increased by 11%.

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3.25 In response to comments on the first and second appraisal consultation documents, the manufacturer provided revised cost-effectiveness analyses that modelled the effect on the ICER of different assumptions including progression-free survival translating into overall survival in a range from 50% to 100%; the clinical benefit from rituximab lasting for 28 months, 36 months or 48 months; and the mean age of a patient at induction being 62.5 years. Although the Committee requested analysis of potential utility gains associated with delaying the need for chemotherapy after relapse, the manufacturer was unable to incorporate these because of limitations in the structure of the model.

3.26 In response to the ERG's concern during the second Appraisal Committee meeting that the duration of clinical benefit (that is, the period during which rituximab is better than, rather than equal to, observation) may last only 28 months (based on the cumulative hazard plots from the PRIMA trial), the manufacturer provided an alternative method to model the rituximab treatment effect stopping at 28 months. This entailed using an exponential function (instead of the Gompertz function from the original submission) to extrapolate the hazard ratio observed in the rituximab arm for 28 months to the observation arm (HR 0.48; 95% CI 0.377 to 0.613). From 28 months onwards, a HR of 1.00 was then applied to both arms in the model. The manufacturer considered that this alternative modelling approach was a more accurate method for this particular sensitivity analysis, but emphasised that it represented the worst-case clinical scenario and was not in line with available clinical evidence or expert opinion and therefore should be treated with caution.

3.27 The manufacturer noted that the cost of first-line rituximab induction therapy was included incorrectly in the original economic model and that once this had been amended, and the age at the start of treatment adjusted to 62.5 years, the revised base-case ICER (which assumed that rituximab maintenance treatment had a clinical benefit for 72 months) decreased to £15,404 per QALY gained (incremental costs, £16,918; incremental QALYs, 1.10). The manufacturer considered that the assumptions in its revised base-case analysis allowed for an undiscounted conversion rate of 89.2% from progression-free survival to overall survival. The manufacturer explained that the conversion rate is not a specific input in the model, and therefore, to analyse the effect of assuming different conversion rates, other parameters in the model had to be altered. When a conversion rate of 70%, 80% or 90% was assumed in the manufacturer's

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sensitivity analysis, the ICERs ranged from £17,349 to £18,615 per QALY gained when the duration of clinical benefit from rituximab maintenance was 28 months (using an exponential function); £25,038 to £27,397 per QALY gained when the duration of clinical benefit was 36 months and £21,507 to £23,355 per QALY gained when the duration of clinical benefit was 48 months (both using the Gompertz function). The manufacturer questioned the plausibility of these revised analyses because they were based on assumptions that the manufacturer considered worse than those observed in clinical practice and in the clinical trials.

3.28 The ERG provided an additional critique of the sensitivity analyses conducted by the manufacturer in response to the 2 appraisal consultation documents (sections 3.25 to 3.27). It noted that the manufacturer had not corrected the model for certain errors that the ERG had previously identified. After revising these errors, the ERG noted that the new base-case ICER increased slightly to £17,136 per QALY gained. The ERG considered that the structure of the manufacturer's model did not allow sufficient flexibility to enable the sensitivity analyses, which the Committee had requested from the manufacturer, to be robustly undertaken.

3.29 The ERG conducted its own exploratory sensitivity analyses of the clinical scenarios requested by the Committee; that is, assuming rituximab maintenance has a clinical benefit of 28 months, 36 months or 48 months and a conversion rate of progression-free survival to overall survival of 70%, 80% and 90%. The ERG considered that it was not possible to adjust the parameters in the manufacturer's model to assess the impact of different assumptions on the proportion of progression-free survival gain which may be expected to result in overall survival gain. Instead, the ERG adjusted the outcomes and costs generated by the model to reflect long-term outcome scenarios, and calculate the post-progression survival rate per patient. This estimate was subsequently discounted using a simple linear regression equation and used to revise the estimated overall discounted cost per patient in the model.

3.30 After adjusting the mean age of the population in the model at the start of treatment to 62.5 years, and using a hazard ratio for progression-free survival of 0.55 (in line with the manufacturer's base case), the ICERs in the ERG's analyses ranged from £24,595 to £27,558 per QALY gained, if the duration of clinical benefit was 48 months; £31,067 to £35,327 per QALY gained, if the duration of clinical benefit was 36 months; and £38,234 to £43,934 per QALY gained, if the

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duration of clinical benefit was assumed to be only 28 months. The ERG also presented sensitivity analyses using its revised hazard ratio of 0.719 (adjusted for early reporting bias) and noted that the ICERs ranged from £39,319 to £66,870 per QALY gained. The ERG also explored the effect on the ICER of adjusting the hazard ratios for progression-free survival for specific patient ages to reflect a reduction in clinical effect with the increase of age, however this did not change the ICER substantively.

3.31 Full details of all the evidence are in the manufacturer's submission and the ERG report.

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4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of rituximab maintenance treatment for people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy, having considered evidence on the nature of follicular non-Hodgkin's lymphoma 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 and comments received during consultation on both appraisal consultation documents.

4.2 The Committee noted that the decision problem for this topic defines the population as 'adults with advanced follicular lymphoma that has responded to first-line chemotherapy', and that the population considered by the manufacturer was 'adults with advanced follicular lymphoma that has responded to first-line treatment with rituximab plus chemotherapy'. The manufacturer indicated that the population in its analysis was restricted to those who had high tumour burden (indicative of advanced disease) and who had received first-line treatment with rituximab plus chemotherapy because this reflected standard first-line treatment used in UK clinical practice. The Committee noted that the manufacturer assumed that rituximab maintenance would be given for a maximum period of 2 years or until disease progression, in line with the marketing authorisation. The Committee also noted that the manufacturer had not identified any clinical evidence to support the use of ibritumomab tiuxetan as a maintenance treatment for people who have received first-line treatment with rituximab in combination with chemotherapy, and that ibritumomab tiuxetan is infrequently used in the UK. For these reasons the manufacturer excluded ibritumomab tiuxetan from the list of the comparators originally specified in the decision problem. The Committee accepted the manufacturer's justifications for the changes to the decision problem.

4.3 The Committee was aware that rituximab in combination with chemotherapy is currently the standard of care in the UK for first-line induction therapy of people with follicular non-Hodgkin's lymphoma. The Committee noted that NICE's previous technology appraisal guidance on rituximab for follicular lymphoma (now

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replaced by NICE's technology appraisal guidance on rituximab for follicular lymphoma) recommends R-CVP for the first-line induction treatment of advanced follicular non-Hodgkin's lymphoma, but that other rituximab-containing chemotherapeutic regimens (such as R-CHOP and R-FCM) are routinely used, but have not yet been appraised by NICE. The Committee noted that 'watchful waiting' (observation) is the current standard treatment for people with advanced follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy. The Committee heard from the clinical specialists that current management aims to prolong remission, delay progression (and therefore delay the use of chemotherapy) and improve quality of life. The clinical specialists expressed the view that rituximab maintenance treatment after first-line induction therapy constituted optimal management for non-Hodgkin's lymphoma because it can offer people longer periods of remission and better quality of life. The Committee was also aware that rituximab is used in combination with chemotherapy for people whose disease has relapsed or did not respond to treatment, or as monotherapy for maintenance treatment after successful second-line treatment of recurrent or refractory disease (in line with NICE's technology appraisal guidance on rituximab for the treatment of relapsed or refractory stage 3 or 4 follicular non-Hodgkin's lymphoma).

4.4 The Committee heard from patient experts that using rituximab maintenance treatment instead of watchful waiting may delay the need for eventual chemotherapy on relapse of the disease. The patient experts also expressed the view that chemotherapy is associated with more adverse events than rituximab, that it may cause symptoms worse than those caused by follicular non-Hodgkin's lymphoma itself, and that chemotherapy therefore has a substantial negative impact on an individual's quality of life. The patient experts stated that while on chemotherapy they experienced symptoms of weakness and fatigue and were not able to do simple routine tasks without the support of family and carers. However, they were aware that people who received rituximab maintenance treatment did not have adverse effects associated with chemotherapy and were able to continue with their normal daily routine.

Clinical effectiveness

4.5 The Committee considered the data presented by the manufacturer on the

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clinical effectiveness of rituximab maintenance treatment after first-line induction with rituximab plus chemotherapy. The Committee noted that the manufacturer derived data on efficacy primarily from the PRIMA trial that compared rituximab maintenance with observation in people whose disease had responded to first-line induction therapy. The Committee noted that the most recent data from this trial were available from the post-study observational follow-up period, which had a median follow-up of 38 months, and indicated that progression-free survival was statistically significantly improved in people who had been randomised to rituximab maintenance treatment compared with people who had been randomised to observation. The Committee was aware that the manufacturer could not estimate time to progression for patients randomised to rituximab, because too few people had progressed during the trial, and the manufacturer therefore had to extrapolate this value using a statistical distribution. The Committee noted the concerns of the ERG that because progression-free survival had been estimated from the period after the end of the trial, patients may have received other therapies, which in turn could have affected the chance of disease progression. The Committee also noted that despite following patients beyond the end of the trial, the manufacturer could not estimate the overall survival associated with rituximab maintenance treatment because of the small number of deaths during this period. The Committee was aware that the trial stopped earlier than originally planned on advice from a Data and Safety Monitoring Committee (section 3.3), and heard from the ERG that there is evidence suggesting that studies that have stopped earlier than planned often overestimate the clinical benefit. However, the Committee was satisfied, after advice from the clinical specialists, that progression-free survival for people treated with rituximab maintenance therapy in the PRIMA trial reflected the clinicians' observations from clinical practice. The Committee concluded that the available evidence shows that first-line maintenance treatment with rituximab significantly improves progression-free survival compared with observation (36 months' median PFS: 74.9% versus 57.6% respectively; HR 0.55; $p<0.0001$), but that the size of the overall survival benefit could not be determined.

4.6 The Committee was aware that the PRIMA trial was the only trial that directly addressed the decision problem, and included the relevant population, intervention, comparison and outcomes. The Committee heard from the clinical specialists that the results from the PRIMA trial inform clinical practice in the UK. The Committee learned from the manufacturer that another trial (ECOG 1496)

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demonstrated that rituximab maintenance led to longer progression-free survival compared with observation, but that this trial had been conducted in people who had not previously had first-line induction treatment with rituximab-containing chemotherapy. The Committee understood that another trial (SAKK 35/98) had observed a longer event-free survival for people randomised to rituximab maintenance compared with those who had been randomised to no treatment (observation), but that the participants of this trial had either not been treated before rituximab maintenance or had only received an induction regimen with rituximab monotherapy, not rituximab combined with chemotherapy.

4.7 The Committee considered the adverse-event profile of rituximab. It noted that the incidence of grade 3 or 4 adverse events was significantly higher in the rituximab maintenance arm than in the observation arm of the PRIMA trial (section 3.6). However, the Committee heard from the clinical specialists and patient experts that rituximab maintenance treatment is generally well tolerated and that adverse events are easily managed. The patient experts also considered the adverse effects associated with rituximab maintenance therapy to be less severe than those experienced with chemotherapy on relapse of disease. The Committee concluded that, overall, most adverse events associated with rituximab treatment are not severe, and that using rituximab to extend remission may delay the need for chemotherapy and, in turn, delay the associated adverse events.

Cost effectiveness

4.8 The Committee reviewed the original and revised economic analyses provided by the manufacturer and the exploratory sensitivity analyses performed by the ERG. It heard from the ERG that inconsistencies and errors were identified in the manufacturer's revised model, but that correcting them had only a small effect on the manufacturer's base-case results. The Committee noted that in the PRIMA trial the median age at randomisation was 57 years. However, it heard from the clinical specialists that the mean age at the start of first-line treatment in the UK is usually between 60 and 65 years. The Committee acknowledged that people in clinical trials tend to be younger and fitter than those in clinical practice, but it noted from sensitivity analyses conducted by the ERG that the ICER varied depending on the age assumed at the start of treatment. Therefore, the

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Committee considered that the average age of people with advanced non-Hodgkin's lymphoma seen in UK clinical practice should be used in the analysis to provide a more accurate estimate. The Committee considered the revised base-case ICER from the manufacturer of £15,400 per QALY gained, which assumed that the mean age at induction was 62.5 years. The Committee heard from the ERG that the method that the manufacturer had used to adjust for age in its economic model did not reflect the prognostic importance of incident age. The Committee considered exploratory sensitivity analyses from the ERG in which the hazard ratios for progression-free survival were adjusted for specific patient ages to reflect a reduction in clinical effect with the increase of age. The Committee noted that age was not the only variable that had an impact on prognosis and, therefore considered that the ERG's adjustment of the hazard ratios for different age groups was not needed. The Committee was satisfied that the manufacturer's base-case analysis had appropriately adjusted for age and reflected the average patient population seen in UK clinical practice.

4.9 The Committee noted that the manufacturer had assumed in the base case that the clinical benefit of rituximab maintenance would last for 6 years (2 years of treatment and 4 years of sustained benefit once treatment was stopped). The Committee heard from the ERG that the manufacturer's extrapolation of the clinical benefit of rituximab beyond the period observed in the PRIMA trial assumed a proportional increase in survival with time, which may not reflect the true effect. The Committee also noted the ERG's concerns that patient-level data from the PRIMA trial indicated that the duration of effect from rituximab maintenance treatment appears to be 28 months, after which time patients treated with rituximab maintenance therapy experience a rate of progression no better or worse than that of patients not treated with rituximab maintenance therapy. The Committee heard from the clinical specialists that data from the PRIMA trial demonstrated that rituximab maintenance treatment is clinically effective to 36 months at least and without evidence that the effect diminishes over time; therefore, assuming a duration of benefit of only 28 months, as suggested by the ERG, may underestimate the actual effect of treatment. The Committee also heard from the clinical specialists that the period over which rituximab is likely to have an additional benefit over observation is probably 3 to 4 years (that is, 1 to 2 years beyond treatment). However, it further heard from the clinical specialists that it was not possible to predict a definite time period, and a duration of effect of up to 6 years, as seen in the EORTC 20981 study for

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second-line rituximab maintenance treatment, could be plausible. The Committee considered sensitivity analyses conducted by the manufacturer that assumed a duration of treatment effect of 28 months, 36 months and 48 months and noted that the ICERs ranged from £17,300 to £27,400 per QALY gained. The Committee noted that these estimates were lower than those calculated by the ERG for the same scenarios (range: £24,600 to £43,900 per QALY gained) but acknowledged that the manufacturer and the ERG had used different modelling approaches to calculate their results (section 3.29). The Committee considered that the duration of clinical benefit of rituximab maintenance was a key driver of cost effectiveness, but was satisfied that the manufacturer's sensitivity analyses presented the most plausible range of estimates for the treatment effect in line with clinical opinion and the available data.

4.10 The Committee noted that the manufacturer's revised base-case analysis assumed that most (89.2%) of the progression-free survival benefit translated to an overall survival gain in its model. The Committee heard from the clinical specialists that it was not possible to verify the specific conversion rate from progression-free survival to overall survival from the literature or clinical experience, but that they would expect a conversion rate of at least 70%. The Committee also heard from the clinical specialists that patients with non-Hodgkin's follicular lymphoma live longer than in the past, and it is reasonable to assume that this is at least partly due to the introduction of treatment with rituximab. The Committee considered that the manufacturer should have sought data from patient registries or observational data to validate the conversion rate assumed for the base-case estimate, and to confirm the degree to which rituximab maintenance treatment might prolong life. However, it was satisfied that the manufacturer's sensitivity analyses, which assumed conversion rates of 70%, 80% and 90%, provided a plausible range of conversion rate estimates. The Committee heard from the manufacturer that the conversion rate was not an actual input in the model and could only be adjusted by artificially modifying other parameters. As such, the manufacturer was concerned that its revised analyses, which were requested by the Committee, were driven by implausible assumptions. The Committee noted the manufacturer's concerns but was satisfied that the sensitivity analyses addressed the uncertainty that the Committee initially had about the translation from progression-free survival to overall survival gain in the original analysis.

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4.11 The Committee considered the concerns of the ERG that the early closure of the PRIMA trial may have overestimated the benefit from rituximab, and therefore the hazard ratio for progression-free survival (0.55) derived from the PRIMA trial should be increased to adjust for this bias. The Committee noted the revised sensitivity analyses from the ERG, which took account of the adjusted hazard ratio, but considered that adjusting for early reporting bias is not routinely included in technology appraisals and is not a current requirement in the NICE methods guide. The Committee therefore concluded that the manufacturer had used an appropriate hazard ratio and that the ERG's revised analyses using the higher hazard ratio would not be considered.

4.12 The Committee discussed the utility values used in the manufacturer's model. The Committee appreciated that no differences in health-related quality of life were observed between the arms of the PRIMA trial. The Committee considered sensitivity analyses from the ERG that showed that changes to the gains in utility in different health states in the model had a marginal effect on the base-case ICER, and the Committee was therefore persuaded that the ICERs presented by the manufacturer were largely driven by gains in overall survival.

4.13 The Committee noted that the ICERs for rituximab maintenance compared with observation in the manufacturer's submission and sensitivity analyses were less than £30,000 per QALY gained for most scenarios. The Committee also noted that the ERG's exploratory sensitivity analyses, which assumed a duration of clinical benefit from rituximab maintenance treatment of 36 to 48 months (in line with clinical opinion), resulted in ICERs ranging from £24,600 to £35,000 per QALY gained, depending on the conversion rate of progression-free survival to overall survival gain assumed. The Committee was aware that the model did not include the utility associated with delaying chemotherapy, and that if it were included, it would decrease the ICER (that is, improve the cost effectiveness) to an estimate which would be considered as a cost-effective use of NHS resources. Therefore, the Committee considered that rituximab maintenance therapy should be recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction treatment with rituximab in combination with chemotherapy.

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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 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

5.3 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.

5.4 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 follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy and the healthcare professional responsible for their care thinks that rituximab maintenance therapy is the right treatment, it should be available for use, in line with NICE's recommendations.

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6 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 Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital, Cambridge

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

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Dr Michael Boscoe
Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation

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Trust

Professor John Cairns
Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty
External Relations Director, Pharmaceuticals and Personal Health, Oral Care Europe

Professor Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Mrs Eleanor Grey
Lay member

Dr Neil Iosson
General Practitioner

Dr Rosa Legood
Lecturer, London School of Hygiene and Tropical Medicine

Mr Terence Lewis
Lay member

Professor Ruairidh Milne
Director of Strategy and Development, and Director for Public Health Research, NIHR Evaluation, Trials and Studies Coordinating Centre, University of Southampton

Dr Rubin Minhas
General Practitioner and Clinical Director, BMJ Evidence Centre

Dr Peter Norrie
Principal Lecturer in Nursing, DeMontfort University

Professor Stephen Palmer
Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel

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Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr Casey Quinn
Lecturer in Health Economics, Division of Primary Care, University of Nottingham

Dr John Rodriguez
Assistant Director of Public Health, NHS Eastern and Coastal Kent

Mr Alun Roebuck
Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Dr Florian Alexander Ruths
Consultant Psychiatrist and Cognitive Therapist, Maudsley Hospital, London

Mr Navin Sewak
Primary Care Pharmacist, NHS Hammersmith and Fulham

Mr Roderick Smith
Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling
Lay member

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

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

Dr Colin Watts
Consultant Neurosurgeon, Addenbrooke's Hospital

Mr Tom Wilson

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Director of Contracting and Performance, NHS Tameside and Glossop

NICE project team

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

Panagiota Vrouchou and Alfred Sackeyfio
Technical Leads

Fiona Rinaldi
Technical Adviser

Jeremy Powell
Project Manager

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7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by the Liverpool Reviews and Implementation Group:

- Bagust A, Boland A, Blundell M, et al. Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma, October 2010

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 documents (ACD1 and ACD2). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Roche Products

Professional or specialist and patient or carer groups:

- British Society for Haematology
- Cancer Networks Pharmacists Forum
- Cancer Research UK
- Leukaemia CARE
- Lymphoma Association
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee

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- United Kingdom Oncology Nursing Society

Other consultees:

- Department of Health
- NHS Camden
- Welsh Assembly Government

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

- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Leukaemia and Lymphoma Research
- Medicines and Healthcare products Regulatory Agency
- NHS Quality Improvement Scotland

The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on rituximab by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD1 and ACD2.

- Professor Peter Johnson, Professor of Medical Oncology, nominated by National Cancer Research Institute, Royal College of Physicians, Royal College of Radiologists, Association of Cancer Physicians, Joint Collegiate Council for Oncology – clinical specialist
- Dr Helen McCarthy, Consultant Haematologist, nominated by the Royal College of Pathologists – clinical specialist
- Dr Robert Marcus, Consultant Haematologist, nominated by National Cancer Research Institute, Royal College of Physicians, Royal College of Radiologists, Association of Cancer Physicians, Joint Collegiate Council for Oncology – clinical specialist

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- Mandy Childs, nominated by Lymphoma CARE – patient expert
- Elizabeth Nelson, nominated by the Lymphoma Association – patient expert

Representatives from the following manufacturer or sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Roche Products

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