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Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma

Review of technology appraisal guidance 37

**This guidance was developed using the
single technology appraisal process**

NICE technology appraisal guidance 137

Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (review of technology appraisal guidance 37)

Ordering information

You can download the following documents from www.nice.org.uk/TA137

- The full guidance (this document).
- A quick reference guide for healthcare professionals.
- Information for people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma and their carers ('Understanding NICE guidance').
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N1475 (quick reference guide)
- N1476 ('Understanding NICE guidance').

This guidance is written in the following context

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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NOTE: This guidance replaces NICE technology appraisal guidance 37 issued in March 2002.

The Institute reviews each piece of guidance it issues. The review and re-appraisal of the use of rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma has resulted in a change in the guidance. In people with relapsed stage III or IV follicular non-Hodgkin's lymphoma, rituximab is now an option in combination with chemotherapy to induce remission or alone as maintenance therapy during remission. Rituximab monotherapy is also an option for people with relapsed or refractory disease when all alternative treatment options have been exhausted.

1 Guidance

- 1.1 Rituximab, within its marketing authorisation, in combination with chemotherapy, is recommended as an option for the induction of remission in people with relapsed stage III or IV follicular non-Hodgkin's lymphoma.
- 1.2 Rituximab monotherapy as maintenance therapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed stage III or IV follicular non-Hodgkin's lymphoma in remission induced with chemotherapy with or without rituximab.
- 1.3 Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).

2 The technology

- 2.1 Rituximab (MabThera, Roche) is a chimeric (mouse/human) genetically engineered monoclonal antibody. It targets the CD20 surface antigen of mature B-cell lymphocytes.
- 2.2 Rituximab has a marketing authorisation in relapsed non-Hodgkin's follicular lymphoma as follows.
- Rituximab is indicated for the treatment of patients with stage III-IV follicular non-Hodgkin's lymphoma who are chemoresistant or who are in their second or subsequent relapse after chemotherapy.
 - Rituximab maintenance therapy is indicated for patients with relapsed/refractory follicular non-Hodgkin's lymphoma responding to induction therapy with chemotherapy with or without rituximab.
- 2.3 Allergic and skin reactions are the most common side effects of rituximab infusion. Infusion reactions can be complicated by bronchospasm and hypotension and can occasionally be severe or life threatening. Severe reactions are more common in patients with a high tumour burden, and the incidence and severity of infusion reactions decreases with successive infusions. Rituximab treatment is associated with blood and bone marrow toxicity manifested by neutropenia, leucopenia and infections. In addition, rituximab treatment is associated with flu-like symptoms and neurological problems. For full details of side effects and contraindications, see the summary of product characteristics.
- 2.4 A single dose of rituximab is 375 mg/m² body surface area. When used as monotherapy, this dose is given every week for 4 weeks. When used in combination with chemotherapy for induction of

remission, this dose is given with each cycle of chemotherapy. For maintenance therapy, the same dose is given every 3 months until relapse or for a maximum of 2 years (a total of eight doses). The cost of one 100-mg vial is £174.63 and one 500-mg vial is £873.15 (excluding VAT; 'British national formulary' [BNF] edition 53). For an average patient (body surface area 1.6–1.87 m²) the cost per dose is £1222. 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 identified best supportive care as the comparator for rituximab monotherapy at second and subsequent relapse (the indication appraised in TA 37). No new evidence was provided for this indication. For the use of rituximab with chemotherapy for induction of remission in relapsed follicular non-Hodgkin's lymphoma, the main comparator identified was cyclophosphamide, hydroxydaunomycin, vincristine and prednisolone (CHOP) chemotherapy, and fludarabine-containing regimens were also considered appropriate. For the use of rituximab as maintenance therapy, the appropriate comparator was considered to be observation only. For the latter two indications the manufacturer identified two trials.
- 3.2 The European Organisation for Research and Treatment of Cancer (EORTC) trial was an open-label study conducted in patients with follicular non-Hodgkin's lymphoma, in first and subsequent relapse, who had not previously received rituximab. Patients (N = 465) were randomised to induction with six cycles of CHOP chemotherapy

plus rituximab (N = 234) or CHOP without rituximab (N = 231). Those patients in remission after six cycles (N = 334) were subject to a second randomisation: to observation only (N = 167) or eight doses of maintenance therapy with rituximab, given over 2 years (N = 167). For induction of remission, there was a statistically significant higher overall response rate following combination therapy with CHOP plus rituximab compared with CHOP alone (85% versus 72%, respectively; $p < 0.0001$). The median progression-free survival was also statistically significantly longer for patients who received combination therapy (33 months versus 20 months; $p = 0.0003$).

- 3.3 For patients on rituximab maintenance, the median progression-free survival was 52 months compared with 15 months for patients being observed only, and this was statistically significant ($p < 0.0001$). When CHOP plus rituximab was used for induction, the median progression-free survival for patients who received rituximab maintenance therapy was 52 months compared with 23 months for patients being observed only ($p = 0.0043$), a risk reduction of 46%. When CHOP only was used for induction, the corresponding figures were 42 months and 12 months, respectively ($p < 0.0001$), and the risk reduction was 70%. Median overall survival could not be calculated because fewer than half the patients in each group had died at last reported follow-up. For patients who received CHOP plus rituximab for induction, the adverse effects reported with a $\geq 5\%$ higher incidence than in the control group (CHOP only) were skin problems, infections, allergies and neutropenia. During the maintenance phase, patients on rituximab experienced a $\geq 5\%$ higher incidence of flu-like symptoms, neurological problems, infections, blood and bone marrow problems, pulmonary problems and allergies, than those who were observed only.

- 3.4 The German Low-Grade Lymphoma Study Group-Fludarabine, Cyclophosphamide, Mitoxantrone (GLSG-FCM) trial was an open-label study conducted in patients with indolent lymphomas. Patients (total N = 137; follicular non-Hodgkin's lymphoma N = 65) were randomised to induction with four cycles of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab. This randomisation was stopped early when patients in the FCM plus rituximab group had a statistically significant better outcome. In the maintenance period, patients (total N = 176; follicular non-Hodgkin's lymphoma N = 105) were randomised to rituximab therapy of two 4-weekly treatment blocks of rituximab at 3 and 6 months or observation only.
- 3.5 For induction of remission in patients with follicular non-Hodgkin's lymphomas, the combined complete and partial response rates were statistically significantly higher following combination therapy with rituximab (94% versus 70%; $p = 0.011$) compared with FCM alone. For patients with follicular non-Hodgkin's lymphoma treated with FCM plus rituximab at induction, the median progression-free survival was not reached, whereas median progression-free survival was 21 months in those who received induction with FCM only; this difference was statistically significant ($p = 0.0139$). Fewer than half the patients in each group had died at last follow up, and there was no statistically significant difference in the proportions surviving to 2 years. For patients with follicular non-Hodgkin's lymphoma who received FCM plus rituximab induction, the median time to progression was 26 months in patients under observation only, but fewer than half of those receiving maintenance rituximab therapy had progressed; this was a statistically significant difference ($p = 0.035$). Adverse effects with a $\geq 5\%$ higher incidence in the rituximab maintenance therapy group compared with the observation only group were blood and bone marrow

problems, infection, fever, diarrhoea, pulmonary toxicity and liver enzyme elevation.

3.6 The cost-effectiveness models submitted by the manufacturer were based on the EORTC trial. A four-arm model allowed for use of rituximab at induction compared with chemotherapy alone, with the responders in each of these arms being further randomised to rituximab maintenance or observation only. This allowed for comparison of four treatment strategies: rituximab and chemotherapy induction followed by rituximab maintenance; rituximab and chemotherapy induction followed by observation; chemotherapy induction followed by rituximab maintenance; and chemotherapy induction followed by observation. The four treatment strategies allowed for the comparison of six pairs of between-strategy comparisons. The model consisted of five states: progression-free in induction setting; progression-free in maintenance setting; progression-free not in induction/maintenance setting; progressive disease; and death. The model assumed maintenance treatment continued for 2 years or until disease progression. The time horizon for the model was 30 years and each cycle was 1 month. A two-arm model with similar structure and assumptions, comparing rituximab maintenance therapy with observation, was also submitted.

3.7 The hazard rates were taken from the trial up to 24 months and extrapolated to 30 years using a Weibull function. In order to fit the parametric model to the survival data, data from the clinical trial were limited to 1500 days because this was the point at which the survival curves flattened. The hazard for death and progression for rituximab (that is, the duration of benefit) was assumed to be equivalent to baseline risk after 5 years. Quality of life scores for the health states were derived from a study commissioned by the manufacturer. A utility of 0.805 was attached to the progression-

free states and of 0.618 to the progressive disease state. Each patient was assumed to relapse every 2 years and undergo further treatment. The cost of post-protocol treatments was based on the average costs observed in the trial. Patients received an average of 5.93 cycles of maintenance rituximab. Administration costs were calculated as being equal to an outpatient visit (£86). Follow-up costs were equal to an outpatient visit every 3 months for the progression-free state and an outpatient visit every month in the progressive disease state. The model was subjected to univariate sensitivity analysis, and a probabilistic sensitivity analysis was also conducted.

3.8 From the four-arm model, the most effective treatment intervention, using rituximab for induction and maintenance, compared with the next most effective, using rituximab for maintenance alone, gave an incremental cost-effectiveness ratio (ICER) of £16,749 per quality-adjusted life year (QALY) gained. Comparing the use of rituximab for maintenance alone with no use of rituximab gave an ICER of £9076 per QALY gained. Decreasing the duration of treatment benefit to 2 years increased the ICER for using rituximab in induction and maintenance compared with rituximab as maintenance alone to £36,497 per QALY gained. Decreasing the time horizon to 4 years increased the ICER for the comparison of the same treatment strategies to £48,116 per QALY gained. The model was not sensitive to the utility values of the health states.

3.9 The ERG considered that the manufacturer had not adequately described the methods for the systematic review of rituximab as monotherapy for induction at second or subsequent relapse (the indication appraised in TA 37) or explicitly reported on its results. However the ERG was confident that no relevant studies for this or any other indications had been missed. The ERG also confirmed that CHOP and fludarabine-containing regimens were the

appropriate comparators for rituximab when used with chemotherapy for induction in relapsed follicular non-Hodgkin's lymphoma. The main clinical trial was conducted in patients who were rituximab-naive. In view of previous NICE guidance (TA 110), patients in routine practice in the NHS can be expected to have received rituximab with first-line chemotherapy. The ERG considered that the effectiveness of rituximab in patients who had previously received the drug was not certain.

- 3.10 The ERG considered the four-arm model appropriate. The model assumed further treatment at relapse with attached costs, but it did not assume any health benefits from these treatments despite incurring the costs. The ERG noted that the best way to overcome this deficiency was to limit the gains to the observed period only. The ERG did not consider the two-arm model suitable because it did not differentiate between patients on the basis of treatment at induction.
- 3.11 The ERG noted that the administration of rituximab was assumed to occur in the outpatient setting and was costed accordingly. Given the duration of infusion it was considered more appropriate for this to occur in the day-case setting and the ERG calculated a cost of £504. The ERG also recalculated post-progression treatment costs by aggregating treatments into a small number of meaningful categories. This avoided the wide variation in treatment costs, some of which are very expensive, skewing the average post-progression treatment costs of individual strategies. The new categories were 'chemotherapy', 'rituximab' and 'other'. It was assumed that 25% of patients in each treatment strategy would receive other treatments, and 75% would be split between chemotherapy and rituximab treatments depending upon previous use of rituximab. The ERG also added an estimated cost of £5000 towards terminal-care costs.

- 3.12 The ERG considered that the choice of the Weibull model for the analysis had not been sufficiently justified. In addition, the manufacturer had assumed that the pairs of patient groups to be compared shared common parameters, estimating only three parameters rather than the four required to fit the functions independently. This approach made a proportional hazard assumption, which was not substantiated by reference to trial data. The ERG also noted the lack of an initial period of non-zero hazards for those groups that went on to be randomised at maintenance as these groups would have a protocol-driven event-free period. The ERG repeated the analyses overcoming the problems with model projections by limiting the extrapolation to use of the Kaplan-Meier estimates derived from the data to 1500 days.
- 3.13 The ERG exploratory analyses with changes to costs and with outcomes limited to 1500 days using the Kaplan-Meier estimates gave the following results. The single use of rituximab, as either induction or maintenance when compared with no use gave ICERs of approximately £16,000 and £13,000 per QALY gained, respectively. Dual use of rituximab at induction and maintenance compared with no use was associated with an ICER of approximately £26,000 per QALY gained. The dual-use strategy compared with single-use strategies was associated with ICERs of about £43,000 per QALY gained for the use of rituximab at maintenance only and about £42,000 per QALY gained for the use at induction only. The ERG suggested that a comprehensive probabilistic sensitivity analysis in the form of a combined cost-effectiveness acceptability probability plot would indicate which strategy would have the highest probability of being preferred across a range of willingness to pay thresholds.
- 3.14 The manufacturer provided additional analyses relating to the cost effectiveness of using rituximab for induction and maintenance

compared with the use of rituximab for maintenance only, as requested by the Committee. All the following ICERs relate to the comparison of these two treatment strategies only. Changing the cost for administration and aggregating post-progression treatment costs as suggested by the ERG (see 3.11) and using the original four-arm model (see 3.6 and 3.7) increased the ICER to £24,161 per QALY gained. Excluding the event-free period when fitting the Weibull model (see 3.12) decreased the ICER to £21,379 per QALY gained. However, with the event-free period excluded, the exponential model gave the best fit and resulted in an ICER of £16,183 per QALY gained. When the proportional hazards assumption was relaxed and the Weibull functions were fitted independently with the event-free period excluded (see 3.12), the ICER decreased to £15,775 per QALY gained. One-way sensitivity analysis showed that these ICERs were sensitive to the assumed time horizon and duration of benefit. A time horizon of 4 years increased the ICERs to above £56,000 per QALY gained, and reducing the duration of treatment benefit to 3 years increased the ICERs to £24,000–£34,200 per QALY gained, depending on the survival model used. A probabilistic sensitivity analysis was conducted with the scenario that resulted in a deterministic ICER of £21,379, and this suggested that, at a threshold above £18,700, the use of rituximab for induction and maintenance had the greatest probability of being the most cost-effective option.

- 3.15 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TA137

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of rituximab for the treatment of

relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, having considered evidence on the nature of the condition and the value placed on the benefits of rituximab by people with follicular non-Hodgkin's lymphoma, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.2 The Committee discussed the manufacturer's interpretation of the marketing authorisation, and was satisfied with this following clarification from the European Medicines Agency. It understood that rituximab can be used as follows:

- as monotherapy for the treatment of patients with stage III-IV follicular non-Hodgkin's lymphoma who are chemoresistant or who are in their second or subsequent relapse after chemotherapy
- as monotherapy maintenance therapy for patients with relapsed or refractory follicular non-Hodgkin's lymphoma responding to induction therapy with chemotherapy with or without rituximab
- in combination with chemotherapy as induction therapy for patients with relapsed follicular non-Hodgkin's lymphoma.

Clinical effectiveness

4.3 The Committee considered the use of rituximab as recommended (only in the context of a prospective case series) in the original appraisal (TA 37): as monotherapy for the treatment of patients with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, when there is resistance to or intolerance of chemotherapy). Resistance was defined as the absence of a response to the last course of chemotherapy following several courses of treatment. The guidance also applied to people who have or are likely to become intolerant of chemotherapy because of

adverse effects that severely limit the safety of further treatment. The Committee was concerned that no new evidence for this use of rituximab was made available, particularly because it had been a condition of use that patients only received rituximab if their data were collected as part of a case series. It agreed with the ERG that there was a lack of clarity in the manufacturer's search for relevant new data. The clinical specialists pointed to the diminishing use of rituximab at last line because it has been licensed and recommended for earlier use as first-line therapy (TA 110), and they felt that no new evidence would now be collected at later stages of the treatment pathway. They stated that rituximab was still needed as a last-line option for frail patients in whom the use of toxic chemotherapy may not be possible. The Committee agreed that the previous recommendation should stand, but recognised the limitations of treatment recommendations based on the need for future data collection. The Committee concluded that rituximab monotherapy should continue to be recommended as an option for the treatment of patients with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted.

- 4.4 The Committee considered the evidence for the clinical effectiveness of rituximab monotherapy as maintenance therapy and the use of rituximab as induction therapy in relapsed follicular non-Hodgkin's lymphoma. Both of these indications were evaluated in the EORTC trial, and in both indications rituximab-treated patients had higher response rates and longer remissions than control patients. The Committee heard from clinical specialists that rituximab was a valuable treatment and that the possibility of maintaining remission was particularly encouraging. The Committee also heard from the patient representatives of the

importance attached by patients to the remission state and the value of maintenance treatment in prolonging it.

- 4.5 The Committee accepted that the EORTC trial demonstrated the effectiveness of rituximab for maintenance therapy and for the induction of remission in patients at first and second relapse. The Committee was mindful that the results from the EORTC trial were based on rituximab-naïve patients. The number of rituximab-naïve patients is decreasing due to increased prescribing of rituximab as first-line therapy. The Committee considered that it was necessary to be cautious about the assumption that rituximab is as efficacious in patients who had already received it as in patients who are rituximab-naïve. The clinical specialists stated that the evidence indicated that follicular non-Hodgkin's lymphoma could be re-treated with rituximab with little or no loss of efficacy. Although it noted this as an area of uncertainty, the Committee accepted that this was biologically plausible given its mechanism of action. The Committee noted that rituximab maintenance therapy was associated with similar increases in progression-free survival in patients who had received rituximab at induction as in those who had only chemotherapy for induction. It also noted that the use of rituximab maintenance therapy following induction with chemotherapy alone resulted in a greater reduction in the risk of progression compared with rituximab maintenance therapy following induction with combined chemotherapy plus rituximab. However, the Committee was aware that the trial was not powered or designed to evaluate the relative efficacy of rituximab maintenance in patients who had or had not received rituximab at induction. The Committee was therefore unable to draw firm conclusions on the relative efficacy of rituximab maintenance therapy in patients who had and had not received rituximab for induction.

4.6 The Committee also queried the extent to which induction therapy with CHOP was representative of the comparator treatments used in the NHS. The clinical specialists stated that CHOP was the main chemotherapy used in follicular non-Hodgkin's lymphoma patients at this stage but that fludarabine-containing regimens are also used to some extent. The Committee was also aware that the GLSG trial, using a fludarabine-based regimen, showed a similar magnitude of benefit as the EORTC trial, which used CHOP. However, the regimen of fludarabine used in the GLSG trial differed from that commonly used in the NHS and the trial population included people with other indolent lymphomas. The Committee considered it appropriate to focus its considerations on CHOP as the most important comparator within the NHS.

Cost effectiveness

4.7 The Committee considered the manufacturer's economic model and the critique of it by the ERG. In particular, it discussed the costs included in the model and the approach to survival modelling and extrapolation. The Committee considered the changes to the costs in the manufacturer's model suggested by the ERG. It thought that it was appropriate to calculate costs at progression by aggregating treatments into categories, and it agreed with the ERG's assumptions as to how these would vary across the treatment strategies. It heard from clinical and patient specialists that, although the duration of second and subsequent infusions can sometimes be reduced to as little as 2 hours, for the most part, approximately 4 hours are necessary. The Committee also understood that the practice of rapid administration of rituximab was increasingly followed because its safety was now accepted by clinicians. The Committee concluded that it would currently be more appropriate to cost administration of rituximab as a day-case procedure than as an outpatient visit. The Committee also

concluded with the ERG's approach of adding a terminal-care cost to the model and that the amounts assumed were appropriate. The Committee was not satisfied that the survival modelling adopted by the manufacturer was optimal and regarded the estimates resulting from the manufacturer's initial model as unreliable and requiring further analysis (see 3.14).

4.8 The Committee first considered the cost effectiveness of rituximab when used as maintenance therapy. When considering rituximab monotherapy as maintenance, it was mindful that the clinical and patient specialists had strongly supported this use based on its potential to prolong remission, and the lack of alternative therapies for doing so. The Committee considered the results of the exploratory analysis performed by the ERG, which did not use model-based extrapolation but limited the analysis to 1500 days of the Kaplan-Meier estimates and made changes to costs as suggested by the ERG above (see 4.7). The Committee agreed that this approach overcame some of the concerns regarding the initial survival modelling. Based on this approach, the use of rituximab as maintenance only when compared with no use at all was associated with an ICER of approximately £13,000 per QALY gained. The Committee noted that the limited time horizon used in this approach could result a higher ICER than if a longer time horizon was used. The Committee concluded that, despite its concern that the EORTC population (from whom these calculations were derived) was not fully representative of UK patients (see 4.5), the use of rituximab for maintenance therapy following induction of remission with chemotherapy was likely to be a cost-effective use of NHS resources.

4.9 Having accepted that rituximab maintenance therapy following induction with chemotherapy was likely to be a cost-effective use of NHS resources, the Committee then considered the use of

rituximab as induction with chemotherapy. Given that patient experts and clinical specialists identified maintenance therapy as the clinical priority and that this is cost effective when compared with current standard treatment, the cost effectiveness of rituximab at induction was considered as an additional strategy over its use as maintenance alone. It is expected that rituximab maintenance will become standard therapy following this appraisal, and the Committee agreed that the appropriate comparator for the dual-use strategy was the next best use of resources – single use of rituximab as maintenance therapy as opposed to no use of rituximab.

- 4.10 The Committee therefore considered the use of rituximab in combination with chemotherapy for induction in addition to use for maintenance. It noted that the use of rituximab in induction increased the proportion of patients who entered remission and became eligible for rituximab maintenance. It also noted that the ERG's exploratory analysis suggested an ICER of approximately £43,000 per QALY gained when compared with chemotherapy only for induction followed by rituximab maintenance therapy. However, the Committee was aware that this figure resulted from a curtailed time horizon and required further analysis to obtain more reliable estimates. The Committee was also aware that there were a number of concerns with the manufacturer's survival modelling raised by the ERG (see 4.7) and that further analysis (see 4.11) was required before obtaining reliable estimates of cost effectiveness.
- 4.11 The manufacturer's original approach to the modelling of survival did not take account of the initial zero-hazard period, although there was a protocol-driven event-free period in the data. The Committee did not accept this approach because excluding the event-free period when fitting distributions could change the goodness-of-fit of

any distribution fitted to trial data and influence the outcome of the cost-effectiveness analysis. The Committee noted that the additional analyses by the manufacturer excluded the event-free period when fitting functions and this resulted in an ICER of £21,379 using the Weibull model, with the exponential model being the best fit and resulting in an ICER of £16,183 per QALY gained (see 3.14). These analyses were calculated over a lifetime horizon, assuming a duration of treatment benefit of 5 years, which the Committee considered to be reasonable.

- 4.12 The Committee also discussed that, in initially fitting the Weibull model to the RCT data, the manufacturer had made the assumption of proportional hazards such that the only difference between the fitted distributions was as a result of a treatment effect. The Committee requested further analysis because this strong assumption had not been substantiated by RCT data and could have resulted in an overestimation of the clinical and cost effectiveness of rituximab. The Committee noted that relaxing the proportional hazards assumption and independently fitting Weibull functions caused the ICERs to decrease to £15,775 per QALY gained (see 3.14). It also noted that, in the further analysis from the manufacturer, terminal-care costs were not included, but it was aware that including such a cost made little difference to the ICERs. The Committee considered the ICERs of approximately £16,000 per QALY using extrapolation from distributions that had been shown to be a good fit to clinical data to be the most appropriate of those presented in the manufacturer's reanalysis. It was, however, mindful that this figure could be an underestimate of the cost per QALY gained because in practice patients would not usually be rituximab-naive, whereas those in the evidence base were. On balance, the Committee concluded that the use of

rituximab in combination with chemotherapy as induction therapy was likely to be a cost-effective use of resources.

5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA137).
- Costing report and costing template to estimate the savings and costs associated with implementation.

- Audit support for monitoring local practice.

6 Related NICE guidance

Published

Rituximab for the treatment of follicular lymphoma. NICE technology appraisal guidance 110 (2006). Available from www.nice.org.uk/TA110

Rituximab for aggressive non-Hodgkin's lymphoma. NICE technology appraisal guidance 65 (2003). Available from www.nice.org.uk/TA065

7 Review of guidance

- 7.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 7.2 The guidance on this technology will be considered for review in December 2010.

Andrew Dillon
Chief Executive
February 2008

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is a standing advisory committee of the Institute. Its 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. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

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

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

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr David W Black

Director of Public Health, Derbyshire County PCT

Mr Brian Buckley

Chairman, Incontact

Dr Carol Campbell

Senior Lecturer, University of Teesside

Professor Mike Campbell

Professor of Medical Statistics, University of Sheffield

Professor David Chadwick

Professor of Neurology, Liverpool University

Dr Peter Clarke

Consultant Medical Oncologist, Clatterbridge Centre for Oncology,
Merseyside

Ms Jude Cohen-Phillips

Special Projects Consultant, UK Council for Psychotherapy

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R & D Unit

Dr Mike Davies

Consultant Physician, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic

Dr Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Mrs Eleanor Grey

Lay member

Dr Catherine Jackson

Clinical Lecturer in Primary Care Medicine, Alyth Health Centre

Dr Peter Jackson

Clinical Pharmacologist, Sheffield Teaching Hospitals NHS Foundation Trust

Professor Peter Jones

Professor of Statistics and Dean, Faculty of Natural Sciences, Keele
University

Ms Rachel Lewis

Practice Development Facilitator, Manchester PCT

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Professor Andrew Stevens

Professor of Public Health, University of Birmingham and Chair of Appraisal Committee C

Dr Cathryn Thomas

GP and Associate Professor, University of Birmingham

B ***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.

Elangovan Gajraj

Technical Lead

Helen Chung

Technical Adviser

Chris Feinmann

Project Manager

Appendix B: Sources of evidence considered by the Committee

- A The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group:
- Bagust A et al, Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, August 2007.
- B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II gave their expert views on rituximab by providing a written statement to the Committee. Organisations listed in I and II have the opportunity to appeal against the final appraisal determination.
- I Manufacturer/sponsor:
- Roche Products (rituximab)
- II Professional/specialist and patient/carer groups:
- Cancer Research UK
 - Cancerbackup
 - Department of Health
 - East Riding of Yorkshire PCT
 - Leukaemia Care Society
 - Lymphoma Association
 - Macmillan Cancer Relief
 - Royal College of Nursing
 - Royal College of Pathologists

- Royal College of Physicians Medical Oncology Joint Special Committee
- UK Oncology Nursing Society

III Other:

- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- Liverpool Reviews and Implementation Group, University of Liverpool
- Medicines and Healthcare products Regulatory Agency (MHRA)
- MRC Clinical Trials Unit, Cancer Division
- National Collaborating Centre for Cancer
- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement Scotland
- Schering Healthcare (fludarabine)
- Schering Plough (doxorubicin)

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

- Professor Terry J Hamblin, Professor of Immunohaematology, nominated by the Royal College of Pathologists – clinical specialist
- Professor Barry Hancock, Professor in Clinical Oncology, nominated by the UK Oncology Nursing Society – clinical specialist

- Ms Catriona Gilmour-Hamilton, Medical Writer/Medical Liaison, nominated by the Lymphoma Association – patient expert
- Mr Philip McIntyre, Regional Manager, nominated by the Lymphoma Association – patient expert