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Rituximab for the treatment of follicular lymphoma

**This guidance was developed using the
Single Technology Appraisals process**

NICE technology appraisal guidance 110 Rituximab for the treatment of follicular lymphoma

Ordering information

You can download the following documents from www.nice.org.uk/TA110

- The full guidance (this document).
- A quick reference guide for healthcare professionals.
- Information for people with follicular 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 the NHS Response Line on 0870 1555 455 and quote:

- N1124 (quick reference guide)
- N1125 ('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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1 Guidance

- 1.1 Rituximab within its licensed indication (that is, in combination with cyclophosphamide, vincristine and prednisolone) is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients.

2 The technology

- 2.1 Rituximab (Roche Products) is a genetically engineered monoclonal antibody that causes lysis of normal and malignant pre-B and mature B lymphocytes. Rituximab is licensed for the treatment of previously untreated patients with stage III and IV follicular lymphoma in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy.
- 2.2 Rituximab is associated with infusion-related reactions including severe cytokine release syndrome and hypersensitivity. Both typically occur within 2 hours of the first administration and are characterised by severe dyspnoea together with fever, chills, rigors, urticaria and angioedema. The summary of product characteristics (SPC) notes that because of this, care should be taken when using rituximab to treat patients with high tumour burden or a high number of circulating malignant cells, and that rituximab should only be used when all other therapeutic alternatives have been exhausted in those patients. Full blood cell counts should be performed regularly, as rituximab in combination with CVP has also been associated with worse neutropenia than CVP alone. For full details of side effects and contraindications, see the SPC.
- 2.3 Rituximab is administered by intravenous (IV) infusion on day 1 of each chemotherapy cycle (21 days/cycle) following the IV administration of the corticosteroid component (prednisolone) of CVP. The SPC recommends 8 cycles of rituximab treatment at a dose of 375 mg/m² body surface area. Rituximab is available in 10-ml or 50-ml vials containing 10 mg of rituximab per ml. The net price of a 10-ml and 50-ml vial is £174.63 (excluding VAT) and £873.15 (excluding VAT), respectively (BNF 51). Assuming vial wastage

and an average body surface area of 1.75 m², the cost per dose of rituximab is £1222.41 (excluding VAT) and the cost per course is £9779.28 (excluding VAT). Costs may also 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 Both the clinical effectiveness and the cost effectiveness evidence in the manufacturer's submission were based on the registration study M39021. This study compared rituximab plus CVP with CVP alone in 322 patients with previously untreated stage III and IV follicular lymphoma. In this study the median age of the participants was 53 years. Approximately one third were diagnosed with grade 1 lymphoma, half with grade 2 lymphoma and 10% with grade 3 lymphoma. The primary end point in the trial was time to treatment failure (TTF), a composite outcome based on the time to the first of: progressive disease or relapse after response, death, new antilymphoma treatment, and stable disease after cycle 4 of treatment.
- 3.2 The registration study M39021 showed a statistically significant difference in median TTF after a median of 42 months follow-up (range 1.5–60 months). The median TTF in the rituximab plus CVP arm was 27 months compared with 6.6 months in the CVP-alone arm (risk reduction 66%, 95% confidence interval 55 to 74%). The median overall survival was not estimable for either arm, but Kaplan–Meier estimates for overall survival at 36 months were 89% in the rituximab plus CVP arm and 81% in the CVP arm ($p = 0.07$). In the rituximab plus CVP arm, 71% of patients experienced an adverse event in the first 24 hours of treatment compared with 51% of patients in the CVP arm. The manufacturer's submission states that this difference was mainly attributable to rituximab-related infusion reactions. In addition, a greater

proportion of patients in the rituximab plus CVP arm experienced neutropenia as compared to patients in the CVP arm (24.1% compared with 14.5%, respectively).

- 3.3 Four additional studies (GLSG, MMHSG, OSHO39 and FL-2000) were included in the manufacturer's submission as supporting evidence. These all investigated the impact of rituximab as a first-line therapy for patients with follicular lymphoma, but not within the licensed indication of rituximab plus CVP. In all four studies patients were given an anthracycline-containing chemotherapy regimen either with or without rituximab. One of the four studies (MMHSG) also included a third arm of patients who received rituximab monotherapy. Three of the four studies (GLSG, OSHO39, FL-2000) showed statistically significant differences in measures of survival without disease favouring the addition of rituximab, and two of the four (GLSG, OSHO39) showed statistically significant differences in measures of overall survival, again favouring the rituximab-containing arms.
- 3.4 The economic analyses provided by the manufacturer were modelled using a three-state Markov model with a life time horizon. Progression-free survival following first-line therapy was taken from the registration study M39021, and was assumed to translate into a gain in overall survival. The initial age of the cohort entering the model was assumed to be 53 years, reflecting the median age of the participants in the registration study. Survival following first-line relapse was modelled using data taken from the Scottish and Newcastle lymphoma group (SNLG) database and was assumed to be the same for both the rituximab plus CVP and the CVP arms. Rituximab as a second-line or subsequent therapy was not included as a treatment option in either the rituximab plus CVP or the CVP arm. Cost data for first-line therapy were not taken from trial M39021 but were sourced from published literature. Cost data for second-line and subsequent therapies were sourced from a single study which investigated the average lifetime cost of treating a patient with follicular lymphoma. Utilities were sourced from a study of 215 patients with follicular

lymphoma commissioned by the manufacturer. Neither costs nor disutilities associated with adverse events were included in the model.

- 3.5 The manufacturer provided a cost-effectiveness estimate of £8290 per incremental quality-adjusted life year (QALY) gained. One-way sensitivity analyses gave estimates of cost effectiveness ranging from £6790 to £26,602 per incremental QALY gained. A sensitivity analysis including the costs of chlorambucil but assuming equal efficacy with CVP gave an estimate of £9752 per incremental QALY gained.
- 3.6 The ERG identified no further studies of rituximab for the treatment of first-line stage III and IV follicular lymphoma. They noted that CVP is one of a number of possible comparators for rituximab plus CVP, and that treatment options include alkylator-based regimens, anthracycline-based regimens and fludarabine-based regimens. The ERG assessed the characteristics of the patients included in the registration trial and concluded that they were representative of the general population of patients in England and Wales, except that they tended to be relatively younger than might be expected for patients with follicular lymphoma.
- 3.7 The ERG analysed the manufacturer's model. Initially, they made adjustments to minor assumptions in the model and some model formulae. These adjustments only marginally altered the cost per incremental QALY, which remained approximately £8500. In addition to these minor adjustments the ERG explored key assumptions firstly around the age of the cohort and secondly around the translation of gains in progression-free survival into overall survival. The first of these analyses suggested that if the initial age of the cohort included in the model was 60 years, 70 years or 75 years rather than 53 years, the costs per incremental QALY gained would be approximately £9000, £11,000 and £17,000, respectively. The second set of analyses, which assumed that 0%, 30% and 50% of progression-free survival translated into overall survival, gave estimates of the cost per incremental QALY gained of approximately £27,500, £14,500 and £12,000, respectively.

- 3.8 Full details of all the evidence are in the manufacturer's submission and ERG report, which are available from www.nice.org.uk/TA110

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 previously untreated patients with follicular lymphoma, having considered evidence on the nature of the condition and the value placed on the benefits of rituximab by people with follicular 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 considered current standard practice for the treatment of follicular lymphoma in England and Wales. The Committee accepted that there was only one study (the registration study M39021) that investigated the benefits of rituximab within its licensed indication, and that this study compared rituximab in combination with CVP to CVP alone. However, the Committee was aware of evidence in the manufacturer's submission indicating that there were a wide range of treatments being used in clinical practice. The Committee heard from a clinical specialist that patients who presented as asymptomatic were usually managed initially with a strategy of 'watchful waiting' until symptoms of the follicular lymphoma occurred. The Committee noted statements from clinical specialists and patient experts that once a patient started experiencing symptoms of follicular lymphoma, the treatments most frequently used were chlorambucil, CVP and the combination of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). They heard from a clinical specialist that although fludarabine was used frequently in Europe it did not tend to be used as a first-line treatment in England and Wales. The Committee was therefore satisfied that the comparison made in the registration study was appropriate. However, they felt that chlorambucil and CHOP should also be considered as treatment options in their deliberations and that because of the 'watchful waiting' strategy

described above the guidance should refer to the use of rituximab in patients with symptomatic follicular lymphoma.

- 4.3 The Committee considered the evidence for the clinical effectiveness of rituximab plus CVP. They noted that the registration study demonstrated that the addition of rituximab to CVP had resulted in a statistically significant improvement in TTF over CVP alone. They also noted that gains in overall survival had been observed, but these had not reached statistical significance. They were, however, mindful that the long natural history of follicular lymphoma and relatively short duration of trial follow-up may explain why a statistically significant survival benefit was not observed.
- 4.4 The Committee accepted that there was no direct evidence comparing rituximab plus CVP with either chlorambucil or CHOP. They understood from the clinical specialists' and patient experts' statements that the duration of progression-free survival and overall survival for chlorambucil and CHOP were believed to be comparable with those seen for CVP, although response rates following treatment with CHOP may be higher. The Committee was also aware from the manufacturer's submission of a randomised controlled trial (RCT) comparing CVP and chlorambucil, which showed no significant differences in effect. The Committee heard from a clinical specialist that while they were not aware of any RCTs that had compared CVP and CHOP, rates of remission measured at the molecular level had been shown to be comparable between CVP and CHOP. The Committee also noted that the (unlicensed) combination of rituximab and CHOP was more effective, in terms of TTF, than CHOP alone (the GLSG study). The Committee was therefore persuaded that it was likely (although this was associated with uncertainty) that a comparable improvement in treatment outcomes would be observed if rituximab plus CVP was compared with chlorambucil or CHOP.
- 4.5 The Committee discussed the assumptions in the manufacturer's economic model, and noted that the age of the patients in the economic model reflected the median age of the patients in the registration study. They heard from the

ERG that this was relatively younger than the age of patients with lymphoma typically receiving chemotherapy in England and Wales, and that this may underestimate the cost per QALY gained because death rates from causes other than lymphoma would be higher for an older population than for a younger population. The Committee was also mindful that this effect may be further exacerbated both by the way in which mortality was incorporated in the model and by the use of utility values which remain constant regardless of age. The Committee examined analyses undertaken by the ERG using the manufacturer's model which adjusted the age of the patient cohort and the way in which mortality was included. These analyses suggested that the estimates of the cost per QALY gained remained below £20,000 regardless of the age cohort. However, while acknowledging that this additional analysis helped to reduce uncertainty, the Committee believed the estimates should be interpreted with some caution, as the model structure did not separate the risk of death from lymphoma from death from other causes, and the utility estimates may not accurately reflect the health-related quality of life of patients with follicular lymphoma.

- 4.6 The Committee considered the assumption in the manufacturer's economic model that gains in progression-free survival translated into gains in overall survival. The Committee considered evidence from studies of CVP with and without rituximab, and CHOP with and without rituximab, which demonstrated that gains in progression-free survival did in part translate into gains in overall survival. This was also supported by clinical opinion. In addition, the ERG analyses suggested that only when the increase in progression-free survival did not translate into any incremental gain in survival did the cost per QALY gained rise above £20,000. The Committee was of the opinion that, based on the evidence available, it was likely that gains in progression-free survival would translate at least partially into a gain in overall survival. They were therefore satisfied that although this remained an area of uncertainty, it did not in itself lead to increases in the estimates of cost per QALY gained that were incompatible with the best use of NHS resources.

- 4.7 The Committee was aware of additional uncertainties in the model which may also have underestimated the cost per QALY gained. Particular concern was noted about the exclusion of the costs and consequences of receiving rituximab as a last-line therapy, and the exclusion from the economic model of adverse events which, although not occurring at a rate which was statistically significant, occurred with greater frequency in the rituximab plus CVP arm in the clinical trial. The Committee believed this latter concern could underestimate the costs and overestimate the QALYs associated with rituximab plus CVP treatment. In addition the Committee raised concerns about the source and reliability of the cost data for the progressed health state, which could also underestimate the cost per QALY gained. However, the Committee was also aware that the assumption in the model that all patients received 8 treatment cycles may overestimate the cost per QALY gained, as some patients may have treatment withdrawn if they experienced an adverse event or lack of response, and in clinical practice six cycles may be given instead of eight.
- 4.8 The Committee accepted that the economic modelling provided by the manufacturer was associated with a number of uncertainties as a result of the structure and assumptions made in the model. They were aware that not all of these could be adjusted by the ERG, but that the group's analyses had helped to explore uncertainties around the estimates of cost effectiveness. Although the Committee acknowledged that in some respects the assumptions in the model (such as 8 treatment cycles for every patient) could overestimate the cost per QALY gained, overall the Committee was mindful of the possibility that the manufacturer's economic model underestimated the cost per QALY gained of adding rituximab to CVP.
- 4.9 The Committee was of the opinion that the manufacturer had presented evidence most strongly for the use of rituximab plus CVP where CVP would otherwise have been the preferred treatment option, but that greater uncertainty existed where chlorambucil or CHOP would have been the preferred treatment option. However, the Committee considered that, on

balance, rituximab in combination with CVP had been demonstrated to be a cost-effective use of NHS 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 which 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/TA110).
- Local costing template incorporating a costing report to estimate the savings and costs associated with implementation.
 - Audit criteria to monitor local practice.

6 Recommendations for further research

- 6.1 Randomised control trials including patients with stage III/IV follicular lymphoma which investigate the effect of rituximab plus CVP compared with other frequently used first-line therapies (such as chlorambucil or CHOP).
- 6.2 Studies that examine the health-related quality of life of patients with follicular lymphoma.

7 Related guidance

- 7.1 NICE has issued the following related technology appraisal guidance and cancer service guidance.

Guidance on the use of rituximab for recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma. *NICE technology appraisal guidance* no. 37 (March 2002). Available from: www.nice.org.uk/TA37

Rituximab for aggressive non-Hodgkin's lymphoma. *NICE technology appraisal guidance* no. 65 (September 2003). Available from: www.nice.org.uk/TA65

Improving outcomes in haematological cancers. *NICE cancer service guidance* (October 2003). Available from: www.nice.org.uk/csgho

8 Review of guidance

- 8.1 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.
- 8.2 The guidance on this technology will be considered for review in June 2009.

Andrew Dillon
Chief Executive
September 2006

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 twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice chair and a number of other members attending meetings of both branches. 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.

Dr Jane Adam

Radiologist, St George's Hospital, London

Professor A E Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Dr Amanda Adler

Consultant Physician, Addenbrooke's Hospital, Cambridge

Dr Tom Aslan

General Practitioner, Stockwell, London

Professor David Barnett (Vice Chair)

Professor of Clinical Pharmacology, University of Leicester

Mrs Elizabeth Brain

Lay Member

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer in Health Economics, School of Medicine Health Policy and Practice,
University of East Anglia

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital,
Blackpool

Dr Paul Ewings

Statistician, Taunton and Somerset NHS Trust, Taunton

Professor John Geddes

Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin

Health Outcomes Manager, Johnson & Johnson Medical Ltd

Ms Linda Hands

Consultant Surgeon, John Radcliffe Hospital

Dr Rowan Hillson

Consultant Physician, Diabeticare, The Hillingdon Hospital

Dr Catherine Jackson

Clinical Senior Lecturer in Primary Care Medicine, University of Dundee

Professor Richard Lilford

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

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Ms Judith Paget

Chief Executive, Caerphilly Local Health Board, Wales

Dr Katherine Payne

Health Economist, The North West Genetics Knowledge Park, The University of Manchester

Dr Ann Richardson

Independent Research Consultant

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Dr Debbie Stephenson

Head of HTA Strategy, Eli Lilly and Company

Professor Andrew Stevens (Chair)

Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

General Practitioner, and Associate Professor, Department of Primary Care and General Practice, University of Birmingham

Simon Thomas

Consultant Physician, General Medicine and Clinical Pharmacology, Newcastle Hospitals NHS Trust

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Professor Mary Watkins

Professor of Nursing, University of Plymouth

Dr Paul Watson

Medical Director, Essex Strategic Health Authority

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), and a project manager.

Zoe Garrett

Technical Lead

Alana Miller

Project Manager

Appendix B. Sources of evidence considered by the Committee

A The following manufacturer provided a submission for this appraisal.

- Roche Products Ltd

B The evidence review group report for this appraisal was prepared by the Liverpool Reviews and Implementation Group

- Dundar Y, Hounsom J, McLeod C, Bagust A, Boland A, Davis H, Walley T, Dickson R (April 2006) Rituximab for the first line treatment of stage III–IV follicular non-Hodgkin’s lymphoma.

C The following individuals were selected from clinical specialist and patient expert nominations from the professional/specialist and patient/carer groups. They gave their expert personal view on rituximab by providing written evidence to the Committee:

- Dr Andrew McMillan, Consultant Haematologist, nominated by the British Society of Haematology – clinical specialist
- Mrs Tracey Murray, Lymphoma Clinical Nurse Specialist, nominated by the Royal College of Nursing – clinical specialist
- Chris Hatton, Consultant Haematologist, nominated by the Lymphoma Association – clinical specialist
- Catriona Gilmour Hamilton, nominated by the Lymphoma Association – patient expert
- Mrs Jacquelyn Williams Durkin, nominated by CancerVoices – patient expert

D The following individual gave her expert personal view on the use of rituximab by providing oral evidence to the Committee:

- Dr Ruth Pettengell, Senior Lecturer in Haemato-Oncology, Department of Haematology, St George's Hospital Medical School, London

Appendix C. List of organisations involved in this appraisal

The following organisations are consultees/commentators in this appraisal.

Consultees are also invited to appeal against the Final Appraisal Determination.

I Professional/specialist and patient/carer groups

- British Oncology Pharmacy Association
- British Society of Haematology
- Cancer Research UK
- Cancerbackup
- Department of Health
- Leukaemia Care Society
- Lymphoma Association
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians of Edinburgh
- Royal College of Physicians' Medical Oncology Joint Special Committee
- Royal College of Radiologists
- Royal Pharmaceutical Society
- Tenovus Cancer Information Centre
- Welsh Assembly Government

II Commentator organisations (without the right of appeal)

- British National Formulary
- Institute of Cancer Research
- Liverpool Reviews and Implementation Group
- National Collaborating Centre for Cancer
- National Coordinating Centre for Health Technology Assessment