

Issue date: August 2007

Review date: July 2010

## **Rituximab for the treatment of rheumatoid arthritis**

**This guidance was developed using the  
single technology appraisal (STA)  
process**

## **NICE technology appraisal guidance 126 Rituximab for the treatment of rheumatoid arthritis**

### **Ordering information**

You can download the following documents from [www.nice.org.uk/TA126](http://www.nice.org.uk/TA126)

- The full guidance (this document).
- A quick reference guide for healthcare professionals.
- Information for people with rheumatoid arthritis 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:

- N1322 (quick reference guide)
- N1323 ('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.

### **National Institute for Health and Clinical Excellence**

MidCity Place  
71 High Holborn  
London  
WC1V 6NA

[www.nice.org.uk](http://www.nice.org.uk)

© National Institute for Health and Clinical Excellence, 2007. All rights reserved. This material may be freely reproduced for educational and not-for-profit purposes. No reproduction by or for commercial organisations, or for commercial purposes, is allowed without the express written permission of the Institute.

## Contents

1	Guidance	4
2	The technology	4
3	The manufacturer's submission	5
4	Consideration of the evidence	13
5	Implementation	18
6	Recommendations for further research	19
7	Related NICE guidance	19
8	Review of guidance	20
	Appendix A. Appraisal Committee members, guideline representative and NICE project team	21
	Appendix B. Sources of evidence considered by the Committee	25

## Guidance

- 1.1 Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) inhibitor therapy.
- 1.2 Treatment with rituximab plus methotrexate should be continued only if there is an adequate response following initiation of therapy. An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more. Repeat courses of treatment with rituximab plus methotrexate should be given no more frequently than every 6 months.
- 1.3 Treatment with rituximab plus methotrexate should be initiated, supervised and treatment response assessed by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

## 2 The technology

- 2.1 Rituximab (MabThera, Roche Products Ltd) is a genetically engineered chimeric monoclonal antibody that depletes the B-cell population by targeting cells bearing the CD20 surface marker. Rituximab in combination with methotrexate is licensed for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other DMARDs, including one or more tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) inhibitor therapies. A course of rituximab consists of two 1000-mg i/v infusions given 2 weeks apart. For further information, see the summary of product characteristics (SPC).

- 2.2 According to the SPC, contraindications for the use of rituximab are hypersensitivity to the active substance; active, severe infections (including tuberculosis, sepsis and opportunistic infections); and severe heart failure or severe uncontrolled cardiac disease. For full details of side effects and contraindications, see the SPC.
- 2.3 The cost to the NHS of 100-mg and 500-mg vials of rituximab is £174.63 and £873.15 respectively, excluding VAT ('British national formulary [BNF]' 53). The cost of a single course of rituximab is £3492 (two 1000-mg i/v infusions). However, 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 approached the decision problem by considering the effects of rituximab within two different treatment strategies following failure of an initial TNF- $\alpha$  inhibitor. In the first scenario, patients receive either rituximab in combination with methotrexate or non-biological DMARDs (that is, not TNF- $\alpha$  inhibitors). In the second scenario, patients receive either rituximab in combination with methotrexate or an alternative TNF- $\alpha$  inhibitor to the one they tried initially. In both scenarios the drugs are used sequentially, with patients who do not respond to rituximab, or any other drug, moving on to the next drug in the sequence. Apart from rituximab, the sequences were the same in both treatment and comparator arms. The manufacturer specified that the population under consideration comprised adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other DMARDs, including one or more TNF- $\alpha$  inhibitors. Several outcome measures were outlined in the decision problem, including physical function, pain, mortality, quality of life and inhibition of

disease progression, using measures including American College of Rheumatology (ACR) response criteria.

- 3.2 The manufacturer's submission presented evidence on the clinical effectiveness of rituximab from a double-blind trial (REFLEX, n = 517) and the open-label extension at 24 weeks to the REFLEX trial (n = 281). The study evaluated the efficacy and safety of rituximab in patients with active rheumatoid arthritis who had experienced an inadequate response to at least one TNF- $\alpha$  inhibitor therapy, because of lack of either efficacy or tolerability. Participants were randomly assigned to either rituximab plus methotrexate or placebo plus methotrexate. The primary efficacy endpoint was a 20% improvement according to ACR response criteria (ACR20) at 24 weeks. Secondary endpoints were 50% and 70% improvements in ACR response criteria (ACR50 and ACR70 respectively), and changes in DAS28 score and EULAR response criteria, at 24 weeks. Additional endpoints included scores on the FACIT-F, health assessment questionnaire (HAQ) and SF-36 instruments, as well as Genant-modified Sharp radiographic scores at 24 weeks.
- 3.3 The ACR response criteria (ACR20, ACR50 and ACR70) require a specified percentage improvement (20, 50 or 70% respectively) in tender joint count, swollen joint count, global assessments, pain, disability and circulating inflammatory markers (for example, erythrocyte sedimentation rate or C-reactive protein). The disease activity score (DAS) is an alternative scoring system developed in Europe. It is calculated using a formula that includes counts for tender and swollen joints (53 and 44 joints respectively), an evaluation of general health by the patient (on a scale of 0 to 100), and a measure of circulating inflammatory markers. DAS28 is similar to DAS as described above but uses only 28 joints for assessment. A DAS28 score greater than 5.1 is considered to be indicative of high disease activity; between 5.1 and 3.2 indicates

moderate disease activity; and less than 3.2 indicates low disease activity. A patient scoring less than 2.6 is defined as being in remission. The European League Against Rheumatism (EULAR) response criteria on drug treatment are based on the DAS measure. A decrease in DAS28 score of 0.6 or less is considered to show a poor response, while decreases greater than 1.2 points indicate a moderate or good response depending on whether a patient's DAS28 score at the end point is above or below 3.2 respectively. The Stanford Health Assessment Questionnaire (HAQ) is one component of the ACR criteria and scores patients' ability to perform daily activities from 0 (least disability) to 3 (most severe disability). The modified Sharp score is a measure of joint damage, as assessed radiographically, and is based on joint-space narrowing and erosions.

- 3.4 The manufacturer's submission presented additional evidence from two randomised controlled trials, the results of which were pooled with those from the REFLEX trial to demonstrate the long-term efficacy of rituximab and to allow analysis of safety data. Both of these trials were excluded from the primary analyses because they included patients who had no prior exposure to TNF- $\alpha$  inhibitors and who had received unlicensed doses of rituximab.
- 3.5 In the REFLEX trial at 24 weeks, 51% of patients in the rituximab group reached an ACR20 response compared with 18% of patients in the placebo group. In the REFLEX trial at 48 weeks, including the open-label extension, 19% of patients in the rituximab group reached an ACR20 response compared with 4% of patients in the placebo group. At 24 and 48 weeks, all secondary efficacy outcomes, including ACR50 and ACR70 responses, were significantly different between the two groups in favour of rituximab ( $p < 0.002$ ). For patients who were randomised to rituximab and were re-treated ( $n = 279$ ), there was a mean time of 307 days between treatments.

- 3.6 The manufacturer did not identify any clinical trials that compared rituximab directly with any of the comparator drugs as specified in the decision problem, and therefore reported an indirect comparison. For the indirect comparison the manufacturer identified 44 trials, six of which were included. All of the included trials were considered to have a common comparator (methotrexate). The manufacturer calculated a weighted average of the placebo ACR response rates from all the included trials. For all treatments included in the indirect comparison, this figure was then used to adjust the specific ACR response rates for each of the included trials. The manufacturer noted the differences between the patient populations in the included trials in terms of disease severity.
- 3.7 For the indirect comparison, efficacy values for DMARDs (including TNF- $\alpha$  inhibitors) adjusted by reference placebo (methotrexate, 26%) were as follows: rituximab plus methotrexate (63%); leflunomide (31%); etanercept plus methotrexate (70%); infliximab plus methotrexate (59%); adalimumab plus methotrexate (60%); abatacept plus methotrexate (60%); gold (26%); ciclosporin (26%).
- 3.8 The manufacturer's submission presented an economic analysis using a microsimulation Markov model based on the REFLEX trial. All patients entered the model at the start of their next treatment option after initial TNF- $\alpha$  inhibitor therapy had failed. Efficacy estimates were adjusted ACR response rates from the indirect comparison. Patient disease progression was tracked within the model according to their HAQ score. Baseline HAQ scores and changes in HAQ scores relative to ACR responses were taken from the REFLEX trial. HAQ scores were transposed into quality-adjusted life years (QALYs) by using the Health Utilities Index (HUI)-3 transformation.
- 3.9 The base-case analysis compared rituximab with a return to non-biological DMARDs following the failure of an initial TNF- $\alpha$  inhibitor

(scenario 1). It resulted in an incremental cost-effectiveness ratio (ICER) for rituximab of £14,690 per additional QALY. A comparison of rituximab with alternative TNF- $\alpha$  inhibitors used sequentially following the failure of an initial TNF- $\alpha$  inhibitor (scenario 2) resulted in an ICER of £11,601 per additional QALY.

- 3.10 Univariate sensitivity analyses of the original submitted model demonstrated that the model was most sensitive to variations in patient age (scenario 1) and the assumed time interval between treatments for those patients who respond to treatment (scenario 2). The sensitivity analysis demonstrated that the ICER for rituximab varied from £5000 to £31,500 per QALY gained.
- 3.11 The ERG reviewed the evidence submitted in relation to clinical and cost effectiveness. The ERG judged that the REFLEX trial was of good methodological quality. The results from the REFLEX trial at 24 and 48 weeks confirmed that rituximab plus methotrexate was more effective than placebo plus methotrexate. Given that the patients in the trial were difficult to treat and had severe disabling disease with marked impairment of quality of life, the results of the REFLEX trial were convincing for this trial population. However, the ERG stated that this evidence cannot be used directly to answer the questions raised in the manufacturer's analysis of the decision problem. This is because rituximab was not compared directly with the stated comparator (a sequence of DMARDs including, in one of two analyses, a second and a third TNF- $\alpha$  inhibitor). Furthermore, the ERG questioned whether the patients in the REFLEX trial were similar enough to the patients described in the rituximab management strategies in the manufacturer's decision problem. This is because 40% of the participants in the REFLEX trial had received at least two TNF- $\alpha$  inhibitors before receiving rituximab.
- 3.12 The ERG considered it appropriate for the manufacturer to conduct the indirect comparison to calculate efficacy rates in the economic model. The ERG stated that although the methodology used by the

manufacturer was computationally sound, it questioned the validity of the adjusted ACR scores presented in the manufacturer's submission, because:

- the inclusion and exclusion criteria for selecting the trials used in the indirect comparison were unclear
- the comparator arms of the included trials were not the same
- no clinical evidence was cited to support the equivalence of methotrexate, gold and ciclosporin
- no rationale was given for the choice of method for the indirect comparison.

3.13 The ERG reviewed the economic model and identified two particular issues of concern regarding its implementation. These were the method of randomisation and the representation of parameter uncertainty in the probabilistic sensitivity analysis. The manufacturer submitted a revised model as requested, which gave very similar results to the original model. Although the revised model did address some of the ERG's criticisms, the ERG considered the algorithm to be very limited in its coverage of parameter uncertainty. Therefore the ERG stated that the probabilistic sensitivity analyses presented by the manufacturer (both original and revised) were unreliable aids to decision-making.

3.14 In addition, the ERG questioned the validity of the manufacturer's assumption for long-term HAQ progression. Specifically, the ERG re-examined studies cited by the manufacturer to support long-term HAQ progression rates of 0.034 per annum while on active treatment and 0.13 per annum while receiving palliative care. The ERG concluded that the manufacturer's analysis of the studies failed both to give an accurate representation of the quoted sources and to recognise the incompatibility of data derived from such studies. The best estimate derived from the studies by the ERG

was an average HAQ progression rate for active treatment and palliative care of 0.012 per annum.

- 3.15 The ERG undertook further analysis to assess predominantly the impact of the alternative interpretation of the evidence on the long-term progression rates for HAQ scores. This additional analysis substantially affected the ICER results. For scenarios 1 and 2, the manufacturer's ICERs increased from £14,694 to £40,873 and from £11,666 to £32,855 per additional QALY respectively.
- 3.16 The ERG also identified other key issues that could potentially influence the model results and undertook sensitivity analyses to show their impact. The 'worse case' amendment for graduated loss of efficacy (50% reduction in HAQ score), applied in conjunction with the analysis explained in section 3.15, increased the ICER from £40,873 to £80,198 per additional QALY for scenario 1, and from £32,855 to £65,558 per additional QALY for scenario 2. The assumption of a longer mean time between re-treatments resulted in slightly improved ICERs for rituximab (a reduction from £40,873 to £37,002 per additional QALY for scenario 1, and from £32,855 to £28,553 per additional QALY for scenario 2).
- 3.17 Following the request of the Committee, the manufacturer carried out analyses of four different variations to the model, as described in sections 3.17.1 to 3.17.4.
- 3.17.1 The first analysis looked at the effect on cost effectiveness of varying the progression rate in HAQ score. Patients receiving rituximab were assumed to have underlying HAQ progression commensurate with the general population (a constant increase of HAQ score indicating worsening functional disability of 0.03 a year). Patients receiving palliative care were assumed to have HAQ progression twice that of the general population, while those on other DMARDs had underlying HAQ progression of 0.045 a year. The manufacturer's analysis concluded that varying the annual

HAQ progression rate as requested produced an ICER for rituximab of £18,823 per additional QALY.

- 3.17.2 The second analysis looked at the effect on cost effectiveness of using a zero HAQ progression rate for rituximab while using the differential rates for DMARDs and palliative care, as described in section 3.17.1. The manufacturer's analysis gave an ICER for rituximab of £12,461 per additional QALY.
- 3.17.3 The third analysis looked at the effect on cost effectiveness of using alternative assumptions about the possible loss of effectiveness of rituximab over time ('rebound effect'). These alternative assumptions were applied in conjunction with the assumptions for HAQ progression rate as described in section 3.17.1. The manufacturer varied the time over which the rebound effect was considered. In this analysis, the ICER for rituximab varied between £18,823 and £21,423 per additional QALY, depending on the time period over which the loss of effectiveness was assumed to occur.
- 3.17.4 The fourth analysis looked at the effect on cost effectiveness of changing the definition of initial response to rituximab treatment used in the economic model to include the following.
- The definition of initial response defined as an improvement in DAS28 of 1.2 points or more. The manufacturer reanalysed the REFLEX trial data using the requested DAS28 criteria. This was carried out in conjunction with varying the HAQ progression rate as described in section 3.17.1. The manufacturer's analysis resulted in an ICER for rituximab of £18,405 per additional QALY.
  - The definition of loss of response (in terms of DAS28) for determining time to repeat treatment with rituximab and the impact of varying this definition on the cost effectiveness of rituximab. The manufacturer reported that the design of the

REFLEX trial does not allow the examination of a modified mean repeat treatment impact on clinical outcomes. Therefore, the analysis undertaken by the manufacturer considered only modifications to costs. This analysis was carried out in conjunction with varying the HAQ progression rate as described in section 3.17.1. The ICER values for rituximab from the manufacturer's DAS28 model varied between £12,214 per additional QALY when repeating treatments every 12 months and £29,810 per additional QALY when repeating treatments every 6 months.

- 3.18 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from [www.nice.org.uk/TA126](http://www.nice.org.uk/TA126)

## **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 severe active rheumatoid arthritis, having considered evidence on the nature of the condition and the value placed on the benefits of rituximab by people with severe active rheumatoid arthritis, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

### ***Clinical effectiveness***

- 4.2 The Committee considered current clinical practice in patients with severe active rheumatoid arthritis. Clinical specialists stated that the pathway of care is dependent on individual patient responses to therapies, and this will influence the number and order of therapies used (including non-steroidal anti-inflammatory drugs, non-biological DMARDs and TNF- $\alpha$  inhibitors). Clinical specialists and patient experts emphasised that rituximab was an important innovation and offered an extra line of treatment for people whose condition has not responded to established therapies. They

believed that, for people in whom TNF- $\alpha$  inhibitor therapy has not been effective, rituximab is a useful option. The clinical specialists reported that, on the basis of clinical deterioration after initial treatment with rituximab, the average time to re-treatment was approximately 9 months, but this could vary widely depending on the individual response.

- 4.3 The Committee noted that the manufacturer's decision problem presented two different management strategies. The Committee heard from clinical specialists and patient experts that there is variation in the management strategies for rheumatoid arthritis, including the nature and number of DMARDs used before introducing biotechnological agents. The Committee considered it appropriate for the manufacturer primarily to examine the clinical effectiveness of rituximab based on the two scenarios presented, while acknowledging the variation in clinical practice.
- 4.4 The Committee reviewed the evidence available on the clinical effectiveness of rituximab as presented in the manufacturer's submission and the ERG critique of the manufacturer's submission. The Committee noted that 40% of the study population in the REFLEX trial had received more than one TNF- $\alpha$  inhibitor. These patients therefore may not be representative of those receiving treatment according to current NICE guidance on TNF- $\alpha$  inhibitors for the treatment of rheumatoid arthritis ('Etanercept and infliximab for the treatment of rheumatoid arthritis'; NICE technology appraisal guidance 36), in that the trial population could represent a particularly severely affected group of patients. The Committee concluded, however, that the study demonstrated the efficacy of rituximab in patients with severe active rheumatoid arthritis.
- 4.5 The Committee noted that a number of efficacy endpoints were reported in the REFLEX trial and that the ACR20 response was the primary outcome measure. The Committee heard from clinical specialists that they do not routinely use the ACR measure in

clinical practice, and prefer to use the DAS28 score for assessment in the clinic. However, they considered the ACR measure to be appropriate for use in clinical trials. The clinical specialists also stated that the HAQ score is used routinely in clinical practice.

- 4.6 The Committee discussed the reported results from the manufacturer's indirect comparisons of rituximab with other DMARDs and biotechnological agents. The Committee discussed whether the trials in the indirect comparison were truly comparable, noting both the manufacturer's and the ERG's comments that only two of the trials (those relating to abatacept and rituximab) were conducted in patients who matched the population of interest, that is, patients in whom TNF- $\alpha$  inhibitors have failed to adequately control symptoms. The Committee considered whether the ACR responses reported for the trials relating to the TNF- $\alpha$  inhibitors and DMARDs may have been overstated, as the trial populations were from a less severely affected population. The Committee concluded that on the basis of the evidence presented, it was unable to determine whether the reported ACR20 responses were overstated, therefore favouring comparator drugs over rituximab. However, the Committee accepted that it was likely that the general direction of the improvements in ACR20 responses reported for all treatments included was clinically credible.

### ***Cost effectiveness***

- 4.7 The Committee considered the cost-effectiveness estimates from the manufacturer and the comments of the ERG on this analysis. The Committee noted that scenario 2 (sequential use of TNF- $\alpha$  inhibitors following previous treatment failure) was outside current NICE guidance.
- 4.8 The Committee noted that the manufacturer had assumed a constant rate of response for the TNF- $\alpha$  inhibitors (and DMARDs) that did not depend on where they were used in the treatment

sequence. The Committee was aware that current evidence from the British Society for Rheumatology (BSR) Biologics Register suggests that although people whose first TNF- $\alpha$  inhibitor therapy had failed during the first 12 months of treatment were likely to respond to a second agent, on average this was a lesser response than to the first. The Committee discussed whether using an alternative assumption of a reduced response for subsequent TNF- $\alpha$  inhibitors would affect the reported ICER for scenario 2. However, the Committee concluded that on the basis of the evidence presented it was unable to determine what effect this may have, and also recognised that the sequential use of TNF- $\alpha$  inhibitors was not within current NICE guidance.

4.9 The Committee examined the manufacturer's assumption of differential long-term disease progression (represented by HAQ score) between active treatment and palliative care, and the reanalysis presented by the ERG. The Committee was persuaded that although there is considerable uncertainty about the assumptions concerning the long-term progression of HAQ score, the use of differential progression rates is plausible and appropriate.

4.10 The Committee considered the cost effectiveness of rituximab for two sets of differential HAQ progression rates presented by the manufacturer in their original submission and in their clarification. The Committee considered it appropriate to examine primarily the estimates of cost effectiveness based on the differential HAQ progression rates presented in the manufacturer's clarification, to ensure consistency with previous appraisals. The Committee concluded that rituximab is cost effective when using differential HAQ progression rates as described in section 3.17.1.

4.11 The Committee noted that the manufacturer in their original submission and the ERG presented two different assumptions about loss of effectiveness over time for rituximab according to the

change in HAQ score in the economic model. The manufacturer assumed instantaneous loss of effectiveness when rituximab was discontinued, whereas the ERG performed an additional sensitivity analysis assuming a gradual loss of effectiveness over time leading up to the point when rituximab was discontinued. The Committee also considered the manufacturer's additional sensitivity analysis. The Committee concluded that differences in the period over which the rebound effect might most plausibly occur would not affect the cost effectiveness of rituximab sufficiently to impact on its decision when also accepting the assumption of differential long-term HAQ progression rates.

- 4.12 The Committee discussed how best to define initial response to therapy. It was mindful of the fact that the definitions used for describing these responder groups in the manufacturer's original submission did not match those used in other technology appraisals of drugs for the treatment of rheumatoid arthritis. The Committee examined the additional analysis provided by the manufacturer in clarification (see section 3.17.4). The Committee concluded that rituximab is a cost-effective use of NHS resources when the initial response is defined as an improvement in DAS28 score of 1.2 points or more.
- 4.13 The Committee considered the time intervals between treatment from the point of view of both clinical effectiveness and cost effectiveness. The Committee was mindful of the results of the REFLEX trial, in which the average time interval between treatments was 307 days, and the recommendations in the marketing authorisation for rituximab, which indicate treatment intervals of between 6 and 12 months. The Committee then examined the sensitivity analysis of time to repeat treatment presented in the manufacturer's economic analysis. The Committee accepted that the manufacturer was unable to determine the clinical impact of varying the mean time to repeat treatment on the

cost effectiveness of rituximab. However, based on the manufacturer's modification of costs associated with more frequent or less frequent repeat treatments, the Committee considered that the time to repeat treatment should not be less than 6 months. The Committee was persuaded that, on the basis of the trial evidence available, people whose condition deteriorates between treatments such that courses of rituximab would need to be administered more frequently than every 6 months could be considered to have had an inadequate response to treatment. The Committee therefore concluded that the repeat treatment interval for rituximab for those patients who respond to initial treatment should not be less than 6 months.

## **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/TA126](http://www.nice.org.uk/TA126)).
- 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 As part of a post-marketing risk management plan, the manufacturer proposes to become a partner in the British Society for Rheumatology Biologics Register. Data collection is recommended from the cohort enrolled in the Register on the measurement of change in HAQ score over time during treatment with rituximab, and on the long-term safety of rituximab.
- 6.2 It is proposed that further research is carried out to examine data on the underlying rate of disease progression in rheumatoid arthritis as measured by HAQ score, and how this varies across treatments.

## **7 Related NICE guidance**

- 7.1 Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 36. Available from: [www.nice.org.uk/TA036](http://www.nice.org.uk/TA036)
- 7.2 NICE is developing the following guidance (details available from [www.nice.org.uk](http://www.nice.org.uk)).
- Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (including a review of technology appraisal guidance 36). NICE technology appraisal guidance (publication date to be confirmed).

- Abatacept for the treatment of rheumatoid arthritis. NICE technology appraisal guidance (publication date to be confirmed).
- Rheumatoid arthritis: the management and treatment of rheumatoid arthritis in adults. NICE clinical guideline (publication expected December 2008).

## **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 July 2010.

Andrew Dillon  
Chief Executive  
August 2007

## **Appendix A. Appraisal Committee members, guideline representative 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.

#### **Dr Jeff Aronson**

Reader in Clinical Pharmacology, Radcliffe Infirmary

#### **Dr Darren Ashcroft**

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

#### **Professor David Barnett (Chair)**

Professor of Clinical Pharmacology, University of Leicester

#### **Dr Peter Barry**

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

#### **Professor Stirling Bryan**

Director of the Health Economics Facility, University of Birmingham

**Professor John Cairns**

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

**Dr Mark Charkravarty**

Head of Government Affairs and NHS Policy, Procter and Gamble  
Pharmaceuticals (UK) Ltd

**Professor Jack Dowie**

Health Economist, London School of Hygiene and Tropical Medicine

**Lynn Field**

Nurse Director, Pan Birmingham Cancer Network

**Professor Christopher Fowler**

Professor of Surgical Education, University of London

**Dr Fergus Gleeson**

Consultant Radiologist, Churchill Hospital

**Ms Sally Gooch**

Former Director of Nursing & Workforce Development, Mid Essex Hospitals  
Services NHS Trust

**Mrs Barbara Greggains**

Company Director, Greggains Management Limited

**Mr Sanjay Gupta**

Former Stroke Services Manager, Basildon and Thurrock Universities  
Hospitals NHS Trust

**Dr Mike Laker**

Medical Director, Newcastle Hospitals NHS Trust

**Mr Terence Lewis**

Mental Health Consultant, National Institute for Mental Health in England

**Professor Gary McVeigh**

Professor of Cardiovascular Medicine, Queens University, Belfast

**Dr Ruairidh Milne**

Senior Lecturer in Health Technology Assessment, National Coordinating  
Centre for Health Technology

**Dr Neil Milner**

General Medical Practitioner, Tramways Medical Centre, Sheffield

**Dr Rubin Minhas**

General Practitioner, CHD Clinical Lead, Medway PCT

**Dr John Pounsford**

Consultant Physician, North Bristol NHS Trust

**Dr Rosalind Ramsay**

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital

**Dr Stephen Saltissi**

Consultant Cardiologist, Royal Liverpool University Hospital

**Dr Lindsay Smith**

General Practitioner, East Somerset Research Consortium

**Mr Cliff Snelling**

Lay Member

**Professor Andrew Stevens**

Professor of Public Health, University of Birmingham

## ***B*** ***Guideline representative***

The following individual, representing the Guideline Development Group responsible for developing the Institute's clinical guideline related to this topic, was invited to attend the meeting to observe and to contribute as an adviser to the Committee.

- Dr Christopher Deighton, National Collaborating Centre for Chronic Conditions

## ***C*** ***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.

### **Nicola Hay and Ruth McAllister**

Technical Leads

### **Janet Robertson**

Technical Adviser

### **Reetan Patel**

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 & Implementation Group, University of Liverpool:

- Bagust A, Boland A, Dundar Y et al. ERG Report: Rituximab for the treatment of rheumatoid arthritis, February 2006.

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. 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 Ltd

### II Professional/specialist and patient/carer groups:

- Arthritis and Musculoskeletal Alliance
- Arthritis Care
- Arthritis Research Campaign
- National Rheumatoid Arthritis Society
- Pain Concern
- Royal Association for Disability and Rehabilitation (RADAR)
- Specialised Healthcare Alliance
- Bone Research Society
- British Association of Spine Surgeons
- British Health Professionals in Rheumatology
- British Institute of Musculoskeletal Medicine
- British Orthopaedic Association
- British Society for Rheumatology
- British Society of Rehabilitation Medicine
- Physiotherapy Pain Association
- Primary Care Rheumatology Society
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians

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

- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- Medicines and Healthcare products Regulatory Agency (MHRA)
- National Public Health Service for Wales
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Scottish Medicines Consortium
- Abbott Laboratories Ltd
- Schering-Plough Ltd
- Wyeth Pharmaceuticals Ltd
- MRC Clinical Trials Unit
- Society for Back Pain Research
- National Coordinating Centre for Health Technology Assessment
- Liverpool Reviews & Implementation Group, University of Liverpool
- National Collaborating Centre for Chronic Conditions

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.

- Dr Tarnya Marshall, nominated by Royal College of Physicians – clinical specialist
- Professor David Isenberg, nominated by British Society for Rheumatology – clinical specialist
- Lynn Love, nominated by National Rheumatoid Arthritis Society – patient expert
- Avril Neerken nominated by National Rheumatoid Arthritis Society – patient expert