NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using rituximab in the NHS in England and Wales. The Appraisal Committee has considered the evidence submitted by the manufacturer and the views of non-manufacturer consultees and commentators, and clinical specialists and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the evaluation report). [hyperlink 'the evaluation report']

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using rituximab in the NHS in England and Wales.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 12 August 2013

Second Appraisal Committee meeting: 28 August 2013

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 The Committee is minded not to recommend rituximab in combination with glucocorticoids within its marketing authorisation, that is, for inducing remission in adults with anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener's] and microscopic polyangiitis).

1.2 The Committee recommends that NICE requests further clarification and analyses from the manufacturer, which should be made available for the second Appraisal Committee meeting, and should include the following:

- The definition of severe disease.
- Any available longer-term data from the RAVE study (including data from patients who were re-treated with rituximab).
- Any further information about UK clinical practice relating to maximum cumulative cyclophosphamide dose, and route and frequency of its administration.
- A definition of a subgroup for whom avoiding cyclophosphamide is desirable, according to clearly described patient characteristics.
- A revised economic model incorporating:
  - the changes suggested by the Evidence Review Group (ERG) (see sections 3.42 and 3.43) that were considered appropriate by Committee (see section 4.16) (including those to weight

and body surface area, and to the uncontrolled disease health state)
  - any further information relating to maximum cumulative cyclophosphamide dose, and route and frequency of its administration in UK clinical practice
  - the assumption that only severe relapses are treated with induction therapy assuming the relapse rates based on the RAVE study for each treatment group, and:
    - ◊ scenario analyses to explore the same relapse rate for each treatment (as part of modelling maintenance treatment with azathioprine for all patients after induction treatment)
    - ◊ scenario analyses to explore the effect of not limiting induction treatment to severe relapses.
  - the costs and disutility of the cumulative long-term toxicity of cyclophosphamide
  - inpatient costs associated with non-remission (including treating infections)
  - a clinically plausible frequency of outpatient appointments for each health state
  - scenario analyses showing the effect of azathioprine maintenance treatment after induction therapy with rituximab.
- Cost-effectiveness estimates for all possible appropriate treatment sequences, including the treatment sequences in the ERG's exploratory analyses (see sections 3.44–3.49), using cyclophosphamide (1 or 2 courses of cyclophosphamide in total), rituximab, other treatments for ANCA-associated vasculitis (such as azathioprine, methotrexate, and mycophenolate [in combination with glucocorticoids]) and best supportive care.
- Cost-effectiveness estimates for all populations, comprising newly diagnosed people, people with relapsed disease, people who are intolerant to cyclophosphamide, people for whom

cyclophosphamide is inappropriate and people for whom avoiding cyclophosphamide would be desirable.

- Pairwise comparisons and incremental analyses for the cost-effectiveness estimates for the treatment sequences for all populations.

2 The technology

2.1 Rituximab (MabThera, Roche Products) is a genetically engineered chimeric (mouse/human) monoclonal antibody that depletes B cells by targeting cells bearing the CD20 surface marker. Within its European marketing authorisation, rituximab in combination with glucocorticoids is indicated for 'the induction of remission in adult patients with severely active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)'. The summary of product characteristics states that limited data preclude any conclusions regarding the efficacy of subsequent courses of rituximab in patients with granulomatosis with polyangiitis and microscopic polyangiitis. The summary of product characteristics also states that continued immunosuppressive therapy may be considered to prevent relapse, and may be especially appropriate in patients at risk of relapse (for example, in people who have had previous relapses), but that the efficacy and safety of rituximab in maintenance therapy has not been established.

2.2 The summary of product characteristics lists the following adverse events occurring at an incidence of 10% or greater in patients receiving rituximab to treat granulomatosis with polyangiitis and microscopic polyangiitis: diarrhoea, peripheral oedema, muscle spasms, arthralgia, back pain, dizziness, tremor, insomnia, cough, dyspnoea, epistaxis and hypertension. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Rituximab is priced at £174.63 per 10 ml vial and £873.15 per 50 ml vial (excluding VAT; British national formulary [BNF] edition 65). The recommended dosage for treating granulomatosis with polyangiitis and microscopic polyangiitis (2 types of anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis) is 375 mg/m^2 body surface area, administered intravenously once weekly for 4 weeks (4 infusions in total). The manufacturer's estimate of the average cost of a course of treatment is £4889.64 (based on 1.79 m^2 body surface area and no vial sharing). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of rituximab and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The manufacturer's systematic review identified 2 relevant randomised controlled trials for inclusion in its submission: RAVE and RITUXVAS. Seven non-randomised controlled trials were identified but the manufacturer judged that they contained insufficient data to be useful to the decision problem. The manufacturer explained that its submission focused on efficacy data from RAVE, complemented by the RITUXVAS results. Both RAVE and RITUXVAS compared rituximab with cyclophosphamide in patients with ANCA-associated vasculitis (granulomatosis with polyangiitis or microscopic polyangiitis). RAVE recruited both newly diagnosed and relapsing patients, whereas RITUXVAS recruited newly diagnosed patients with renal involvement.

RAVE study

3.2 RAVE was a randomised, multicentre, double-blind, double-dummy, placebo-controlled trial conducted in the USA and the Netherlands, which compared rituximab with conventional therapy (cyclophosphamide and azathioprine) in patients with severe anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The study tested the hypothesis that rituximab was not inferior to conventional therapy in its ability to induce disease remission in ANCA-associated vasculitis at 6 months. Eligible patients had either granulomatosis with polyangiitis or microscopic polyangiitis, had tested positive for ANCA at screening, and had evidence of severe disease and a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 3 or more. BVAS/WG scores range from 0 to 68, with higher scores indicating more active disease. A 6-month remission induction phase was followed by a 12-month remission maintenance phase. In both groups, patients who went into remission before 6 months of treatment were eligible to switch to maintenance treatment from month 4 onwards.

3.3 At the start of the study, all patients received an intravenous glucocorticoid pulse (methylprednisolone 1 g, or an equivalent dose of an alternative drug) followed by an oral prednisone taper (dosage starting at 1 mg/kg/day and not exceeding 80 mg/day). Patients in the rituximab group (n=99) received remission induction treatment consisting of once weekly infusions of rituximab 375 mg/m^2 for 4 weeks plus daily oral placebo and daily oral prednisone for 3–6 months. For the remission maintenance treatment, patients then switched to oral placebo as maintenance treatment until 18 months. Patients in the cyclophosphamide group (n=98) received remission induction treatment consisting of daily oral prednisone, oral cyclophosphamide 2 mg/kg/day plus placebo

infusions for 3–6 months to induce remission. Remission maintenance treatment consisted of oral azathioprine 2 mg/kg/day until 18 months. Patients who had a severe flare (BVAS/WG of 3 or more, or a major BVAS/WG item that needed cyclophosphamide after remission [BVAS/WG of 0]) in the first 6 months could cross over to the other treatment group and receive the other induction regimen in full. Limited flares (new occurrence or worsening of 1 or more minor BVAS/WG items) were managed by restarting or increasing the glucocorticoid dose. Patients whose BVAS/WG had not decreased by at least 1 point at 1 month or who had a new manifestation of disease were considered as having early treatment failure. These patients discontinued their assigned treatments and were treated according to best medical judgement.

3.4 RAVE's primary outcome was the induction of complete remission at 6 months, defined as a BVAS/WG of 0 and successful completion of the prednisone taper (that is, prednisone dose was reduced to 0 mg). A secondary analysis of the primary outcome assessed the superiority of rituximab to cyclophosphamide in patients who had complete remission at 6 months. Tertiary outcomes were cumulative BVAS/WG area under the curve for 6 months; BVAS/WG of 0 on prednisone less than 10 mg/day at 6 months; partial remission (BVAS/WG of 2 or less and no prednisone at 6 months); cumulative glucocorticoid dose at 6 months; number of severe flares at 6 months; number of limited flares at 6 months; and quality of life using Short Form (SF-36) Physical Component Summary and Mental Component Summary scores. Additionally, the study protocol stated that laboratory markers of inflammation (erythrocyte sedimentation rate and C-reactive protein) were measured. Disease damage was measured using the Vasculitis Damage Index (range 0–64, with higher scores indicating more severe damage). End points for the assessment of

efficacy up to 18 months included duration of complete remission and time to limited and/or severe flare after complete remission.

3.5 Baseline demographic and disease characteristics in RAVE were generally similar between the treatment groups except for creatinine clearance, which was lower in the rituximab group. At the time of screening, 96 (48.7%) patients were newly diagnosed. There were 82 (83%) of the 98 patients remaining in the rituximab group and 79 (81%) of the 95 patients remaining in the cyclophosphamide group who completed the 6-month remission induction phase without crossover or change to treatment by best medical judgement. A similar proportion of patients in the 2 groups completed 18 months on randomised treatment (62% in the rituximab group and 63% in the cyclophosphamide group).

3.6 Sixty-three (64.3%) patients in the rituximab group were in complete remission at 6 months, compared with 52 (54.7%) patients in the cyclophosphamide group. The absolute difference in rate of remission between the 2 groups was 9.5% (95% confidence interval [CI] −4.30% to 23.40%). This showed that rituximab was not inferior to cyclophosphamide in inducing complete remission because the lower limit of the 95% CI (−4.30%) was higher than the predetermined non-inferiority margin (−20%). After estimating missing data by worst case imputation, 63.6% of the 99 patients in the rituximab group achieved complete remission at 6 months compared with 53.1% of the 98 patients in the cyclophosphamide group (absolute treatment difference 10.6% [95% CI −3.18% to 24.33%]).

3.7 The complete remission rate at 6 months in the rituximab group was not statistically significantly superior to the cyclophosphamide group (95% CI for the between-group difference −4.30% to 23.40%; p=0.177). The outcome was similar using worst case imputation (95% CI for the between-group difference −3.2% to

24.3%; p=0.132). In a prespecified analysis, the manufacturer concluded that survival with rituximab was superior to expected survival rates for untreated patients using historical control data generated from a study by Walton et al. (1958), which described a cohort of 56 largely untreated patients with granulomatosis with polyangiitis.

3.8 There was no statistically significant difference between the treatment groups in the cumulative BVAS/WG area under the curve during the first 6 months, remission on less than 10 mg/day prednisone at 6 months, partial remission, severe or limited flares, or median cumulative dose of prednisone from randomisation to 6 months. In an exploratory analysis that investigated the rate of remission, regardless of prednisone use, a statistically significantly greater proportion of patients in the rituximab group than in the cyclophosphamide group had a BVAS/WG of 0 (80.8% compared with 66.3%; p=0.021).

3.9 Quality-of-life scores improved in both groups; there was no significant difference between treatment groups in the change in quality-of-life scores or their rate of change from baseline to 6 months. From baseline to 6 months, scores on the Vasculitis Damage Index increased by 1.3 points in the rituximab group and 1.5 points in the cyclophosphamide group (p=0.62).

3.10 The manufacturer explored the effects of various baseline characteristics in relation to the primary outcome, including relapsing disease. In patients who had relapsing disease at baseline, a statistically significantly higher proportion in the rituximab group went into complete remission at 6 months than in the cyclophosphamide group (66.7% compared with 42.0%, p=0.013). Complete remission rates in patients with new disease were similar in the 2 treatment groups (60.4% compared with 64.6%, p=0.673).

3.11 The manufacturer presented results for subgroup analyses of the primary end point according to ANCA subtype at baseline. Complete remission rates at 6 months were similar in both treatment groups in patients with myeloperoxidase antibodies (treatment difference −3.0% [95% CI −26.53% to 20.47%, p=0.800]). For patients with proteinase-3 antibodies at baseline, complete remission rates were statistically significantly higher in the rituximab group, with a treatment difference of 17.5% (95% CI 0.66% to 34.25%, p=0.044).

RITUXVAS study

3.12 RITUXVAS was a phase II, open-label, randomised controlled trial conducted in Europe and Australia. It compared the efficacy and safety of rituximab plus cyclophosphamide as induction therapy with cyclophosphamide plus azathioprine in 44 patients with newly diagnosed, severe ANCA-associated vasculitis and renal involvement. Patients were randomised to rituximab plus cyclophosphamide (n=33) or cyclophosphamide (n=11) and both groups received intravenous methylprednisolone (1 g) and an oral glucocorticoid (1 mg/kg/day initially, reducing to 5 mg/day at the end of 6 months). Patients in the rituximab group received infusions of rituximab (375 mg/m^2 weekly, for 4 weeks), and intravenous cyclophosphamide (15 mg/kg with the first and third rituximab infusions). A further dose of intravenous cyclophosphamide (15 mg/kg) was permitted for patients who had progressive disease within the first 6 months. Patients in the rituximab group received no maintenance treatment. Patients in the control group received intravenous cyclophosphamide (15 mg/kg for 3–6 months; 6–10 doses in total), followed by azathioprine maintenance (2 mg/kg/day). Further treatment with rituximab or cyclophosphamide was permitted if patients in either group relapsed.

3.13 The primary end points for RITUXVAS were sustained remission at 12 months (defined as BVAS of 0 maintained for at least 6 months) and severe adverse events. Major secondary and tertiary end points were time to remission (BVAS=0), BVAS area under the curve, change in glomerular filtration rate, prednisolone dose, and quality of life and disease damage (assessed by the SF-36 questionnaire and Vasculitis Damage Index between 0 and 12 months). Analyses were performed on an intention-to-treat basis.

3.14 There were no major imbalances in baseline characteristics between the 2 groups, except for a greater proportion of patients with renal-limited vasculitis in the cyclophosphamide group and a greater proportion of patients needing dialysis in the rituximab plus cyclophosphamide group. No patients were lost to follow-up.

3.15 Sustained remission occurred in 76% of patients in the rituximab plus cyclophosphamide group and 82% of patients in the cyclophosphamide group. The absolute difference in sustained remission with rituximab plus cyclophosphamide compared with cyclophosphamide was −6% (95% CI −33 to 21). Among patients who were still in the study at 12 months, 93% of patients in the rituximab plus cyclophosphamide group and 90% of patients in the cyclophosphamide group were in sustained remission. Of the 9 patients dependent on dialysis at study entry, 6 out of 8 patients in the rituximab plus cyclophosphamide group were in sustained remission (5 of whom became dialysis independent) and the 1 patient from the cyclophosphamide group died shortly after study entry.

3.16 Remission (defined as BVAS of 0 for 2 months) occurred in 91% of patients in each of the treatment groups. There were no statistically significant differences between treatment groups in median time to remission (p=0.87), prednisolone dose at 12 months (p=0.78),

median estimated glomerular filtration rate (p=0.14 for the comparison of medians), median change in the Vasculitis Damage Index (p=0.38) or physical composite SF-36 score (p=0.36). Median BVAS fell from 19 (interquartile range 14 to 24) at entry to 0 (interquartile range 0 to 1.5) at 3 months in the rituximab plus cyclophosphamide group and 18 (interquartile range 12 to 25) at entry to 0 (interquartile range 0 to 0) at 3 months in the cyclophosphamide group. Patients in the cyclophosphamide group had a statistically significantly better mental composite SF-36 score compared with the rituximab plus cyclophosphamide group (p=0.04), but excluding outlying data for 2 patients eliminated the statistical significance (p=0.32).

3.17 The manufacturer did not do any indirect comparisons or meta-analyses and advised that the economic evaluation was based solely on the RAVE results. It stated that RAVE reflected the marketing authorisation and scope of the appraisal, whereas the way rituximab was given in RITUXVAS was fundamentally different.

3.18 The manufacturer's submission described rituximab's safety profile using the Summary of Clinical Safety provided to the European Medicines Agency to support the marketing authorisation application for rituximab for treating severe ANCA-associated vasculitis. The Summary of Clinical Safety summarised exposure to rituximab in the rituximab group of RAVE (n=99) after 18 months' follow-up. In addition, the rituximab plus cyclophosphamide group in RITUXVAS (n=33) was followed for up to 24 months, and 162 patients in other investigator-initiated studies were followed for between 3 and 55 months.

3.19 The manufacturer reported that overall safety at 6 and 18 months was comparable between the rituximab and cyclophosphamide groups in RAVE, including the incidences and rates per patient-year of any adverse event, selected adverse events, adverse

events that were grade 3 or higher, serious adverse events, and serious infections. The manufacturer stated that although the data are limited, safety in the other published studies was consistent with RAVE. Overall death rates and causes of death in RAVE and RITUXVAS were similar in the rituximab and cyclophosphamide groups. The most commonly reported type of serious adverse event in all studies was infection, with similar incidences between rituximab and cyclophosphamide groups in the controlled studies. The incidences and rates of serious adverse events were comparable between the rituximab and cyclophosphamide groups in RAVE at 6 months (33.3% compared with 33.7%) and 18 months (46.5% compared with 41.8%), and in RITUXVAS at 12 months (42% compared with 36%). There was no statistically significant difference between treatment groups in RITUXVAS in incidence rates of severe adverse events (p=0.77).

Evidence Review Group's comments

3.20 The ERG noted that restricting the systematic review of clinical-effectiveness studies to the population and intervention in the European marketing authorisation meant that it did not fulfil the scope or decision problem specified by NICE. The ERG did not identify any further randomised controlled trials directly comparing rituximab with the comparators in the NICE scope and decision problem in patients with ANCA-associated vasculitis. However, it did identify 5 ongoing or published trials that could potentially have enabled an indirect comparison or mixed treatment comparison of rituximab with the comparators other than cyclophosphamide that were specified in the NICE scope and decision problem.

3.21 The ERG broadly agreed with the treatment pathway described by the manufacturer but noted some uncertainties:

- A high cumulative dose of cyclophosphamide indicates increased risk of adverse events, and although there is no consensus on a specific lifetime maximum dose of cyclophosphamide, the ERG indicated that a cumulative dose of 20–30 g appears to provide a range that should not be exceeded. The ERG noted that giving the drug intravenously rather than orally may offer the opportunity to reduce the cumulative dose, or allow more courses to be given. A complete course of oral cyclophosphamide (2 mg/kg/day for 6 months) would be 31 g for a patient weighing 85 kg (the mean weight in RAVE). Conversely, a complete course of intravenous cyclophosphamide (15 mg/kg × 10 over a 6-month period) for a patient weighing 85 kg would be 12.75 g. The ERG judged this method of reducing the cumulative dose of cyclophosphamide to be inadequately explored by the manufacturer.
- The ERG believed that the manufacturer's submission did not adequately consider alternative treatments to cyclophosphamide that may be used to induce remission.
- The ERG observed that the European Vasculitis Study Group guidelines recommend maintenance treatment after remission, and received clinical specialist advice that not receiving any maintenance treatment after remission with rituximab was unrealistic. The ERG also noted that relapse is not inevitable with appropriate maintenance treatment.
- The ERG stated that a 2 × 1000 mg dosage of rituximab is used more often in UK clinical practice to treat ANCA-associated vasculitis than the 4 × 375/mg^2 dosage recommended in the European marketing authorisation.

3.22 In the ERG's view, the evidence suggested that rituximab was superior to oral cyclophosphamide (p=0.01) in inducing remission in the subgroup of patients with relapsing severe ANCA-associated vasculitis (who had previously received at least 1 dose of

cyclophosphamide, methotrexate or azathioprine) and non-inferior in patients with newly diagnosed disease. The ERG also highlighted that longer-term efficacy and safety outcomes of rituximab in treating ANCA-associated vasculitis are unknown, and that there are some potential questions concerning effects on fertility and certain adverse events, especially rates of mortality and malignancies.

Cost effectiveness

3.23 The manufacturer's systematic review did not identify any studies that reported on the cost effectiveness of treatment for ANCA-associated vasculitis. The manufacturer therefore submitted a de novo model, which it subsequently updated in its clarification response, evaluating the cost effectiveness of rituximab compared with cyclophosphamide in patients with ANCA-associated vasculitis. In line with its European marketing authorisation, the manufacturer restricted its analysis to inducing remission only and did not look at treating flares or maintenance therapy. The base case included the population from RAVE, and subgroup analyses investigated patients with newly diagnosed disease and with relapsing disease. A separate subgroup analysis estimated the cost effectiveness of rituximab in patients for whom cyclophosphamide was not considered to be the standard of care (because this group was not represented in RAVE). The analysis was conducted from an NHS and personal and social services perspective. A lifetime time horizon was used and a 3.5% discount rate was adopted for health benefits and costs.

3.24 The manufacturer developed a Markov model with a similar design to that used in another NICE technology appraisal (Tocilizumab for the treatment of rheumatoid arthritis [NICE technology appraisal guidance 247]). It consisted of 4 different health states: non-

remission, complete remission, uncontrolled disease and death. 'Complete remission' reflected treatment success as assessed in RAVE, 'non-remission' reflected non-attainment of remission and 'uncontrolled disease' reflected a state of worse health that patients enter after the simulated treatment options have been exhausted.

3.25 Patients entered the model in the non-remission health state, received induction therapy and either moved to the complete remission health state (if they went into remission) or remained in the non-remission health state (if they did not go into remission). During each 6-month cycle, moving from 1 treatment to the next in each arm's sequence was triggered either by failing to attain complete remission or by the patient eventually relapsing. After receiving all possible treatment options, patients entered the uncontrolled disease health state. The base-case analysis was designed to compare 2 sequences of treatments:

- In the 'standard of care' sequence, patients received cyclophosphamide as induction therapy. Patients who went into remission with cyclophosphamide switched to azathioprine during remission. Patients who did not go into remission, or who relapsed, receive another course of cyclophosphamide. Clinical specialist advice to the manufacturer was that a maximum of 2 courses of cyclophosphamide would be used in standard clinical practice. The manufacturer assumed that 72% of patients received cyclophosphamide intravenously, with the remainder receiving it orally.
- In the ‘intervention’ sequence, patients received rituximab as a first-line induction treatment. Patients who went into remission did not receive any further treatment until relapse. Patients who did not go into complete remission received a further course of rituximab (this is based on expert opinion, because RAVE did not investigate the effects of re-treatment). Patients who

responded to rituximab were not eligible for re-treatment on relapse because this is outside the scope of the European marketing authorisation. After relapse following 1 or 2 cycles of rituximab, patients received 1 course of cyclophosphamide (it was assumed that 72% of patients received cyclophosphamide intravenously, with the remainder receiving it orally).

If patients received all available induction treatments in the treatment sequence and relapsed, they entered the 'uncontrolled disease' health state and received best supportive care.

3.26 The transition probabilities in the manufacturer's base-case model were based on the primary endpoints from RAVE. A constant rate of relapse was applied in the model and it was assumed that the second course of treatment was associated with a lower probability of achieving remission than the first course. The manufacturer estimated the probability of achieving remission with the second course of treatment using RAVE results from the subgroup of patients with relapsing disease. The same relative risk was used for re-treatment with rituximab and with cyclophosphamide. Transition probabilities for adverse events were also based on RAVE data. Disease-specific mortality risks in the manufacturer's economic model were derived from a retrospective cohort study of UK patients with ANCA-associated vasculitis.

3.27 The costs used in the manufacturer's economic model comprised treatment-associated costs plus health state costs. Cost data (excluding drug costs) were largely derived from National Reference Costs. Drug costs were derived from the British national formulary (BNF) edition 64. Average drug costs per cycle were £4689.78 for rituximab, £99.15 for oral cyclophosphamide, £110.84 for intravenous cyclophosphamide, £44.17 for azathioprine, £28.01 for methylprednisone, £1497.96 for prednisone and £21.38 for trimethoprim. Treatment administration costs per cycle were

£721.16 for rituximab and £1802.89 for intravenous cyclophosphamide, and it was assumed that these included monitoring costs. Monitoring costs for oral cyclophosphamide and azathioprine were £108. The per-cycle cost of best supportive care for patients with uncontrolled disease was £4415.73. Health state costs were £778.10 for the remission health state and £6309.01 for the non-remission and uncontrolled disease health states.

3.28 The manufacturer's systematic review did not identify any relevant studies that reported usable utility values. Health-related quality of life data were collected in RAVE using the SF-36 questionnaire, which was administered at baseline and at 6 months. The SF-36 scores were converted from the non-remission and remission health states to the EQ-5D in a post-hoc analysis using a published model (Ara and Brazier 2008) and adjusted for age. Disutility adjustments were applied for adverse events.

3.29 The manufacturer's updated base-case results, provided after the request for clarification, showed that treating ANCA-associated vasculitis with rituximab increased the cost of treatment but was associated with more quality-adjusted life years (QALYs) than cyclophosphamide. The manufacturer's incremental cost-effectiveness ratio (ICER) for the comparison of rituximab with cyclophosphamide in patients with ANCA-associated vasculitis was £8544 per QALY gained (incremental costs £1391; incremental QALYs 0.1628).

3.30 In its response to clarification, the manufacturer provided updated cost-effectiveness results for the comparison of rituximab and cyclophosphamide from its subgroup analyses on patients with newly diagnosed ANCA-associated vasculitis and patients with relapsing disease. Using the base-case number of cyclophosphamide cycles (2 cycles for standard of care and 1 cycle for intervention), the ICERs were £55,175 per QALY gained for the

newly diagnosed subgroup and £43,003 per QALY gained for the subgroup with relapsing disease.

3.31 The manufacturer performed probabilistic sensitivity analyses to explore uncertainty around the model's key variables in the base case, and estimated in its original submission that the probability of rituximab being cost effective compared with cyclophosphamide in patients with ANCA-associated vasculitis was 57.8% at £20,000 per QALY gained and 64.6% at £30,000 per QALY gained. The manufacturer did not give the probability of cost effectiveness in its clarification response.

3.32 The manufacturer did one-way deterministic sensitivity analyses to explore the structural uncertainty associated with the model. The manufacturer reported that its economic model was robust to changes in the main parameters such as health state costs, patient characteristics, the proportion of patients receiving cyclophosphamide intravenously rather than orally, and assuming equal remission rates for rituximab and cyclophosphamide. It indicated that the assumed offset of future costs was a key driver of the model (because of costs in the uncontrolled disease state).

3.33 The manufacturer presented results for its scenario analysis and noted that the cost-effectiveness estimates were particularly sensitive to changes in treatment sequence because of the small differences in costs and benefits:

- The ICER increased from £8544 per QALY gained to £23,634 per QALY gained when it was assumed that patients in the standard of care sequence had 1 course of cyclophosphamide and that patients in the intervention sequence did not receive any courses of cyclophosphamide.
- When it was assumed that all patients, regardless of treatment-sequence arm, received 2 courses of cyclophosphamide,

rituximab dominated cyclophosphamide (that is, was more effective and less costly).

- Rituximab also dominated cyclophosphamide when it was assumed that all patients received 1 course of cyclophosphamide.
- However, rituximab was dominated by cyclophosphamide (that is, was less effective and more costly) when it was assumed that patients in the intervention sequence did not receive any cyclophosphamide courses and patients in the standard of care sequence received 2 cyclophosphamide courses.

3.34 In its response to clarification, the manufacturer provided scenario analyses for the subgroups of patients with newly diagnosed ANCA-associated vasculitis and patients with relapsing disease. When it was assumed that all newly diagnosed patients received 2 courses of cyclophosphamide (regardless of treatment-sequence arm), the ICER decreased to £1274 per QALY gained. When it was assumed that patients with relapsing disease would be unable to tolerate additional cyclophosphamide courses, the ICER decreased to £12,556 per QALY gained. Incremental costs and QALYs were not reported for these analyses. The manufacturer advised that the results should be interpreted with a degree of caution because of low patient numbers (approximately 50 in each arm). The manufacturer confirmed that rituximab dominated best supportive care (that is, it was more effective and less costly) in patients who were unable to tolerate cyclophosphamide (incremental costs −£4885; incremental QALYs 0.5386).

Evidence Review Group's comments

3.35 The ERG found that the manufacturer's economic model generally followed NICE's reference case, but noted that not all comparators had been included, and that it may have been more appropriate to

consider intravenous cyclophosphamide as the primary comparator because of its lower adverse-event risk, and because its lower cumulative dose could potentially allow additional courses of treatment. The ERG described some uncertainties in the population in the manufacturer's base case. It considered the manufacturer's decision to focus on severe granulomatosis with polyangiitis and microscopic polyangiitis to be appropriate given that this is the population specified in the European marketing authorisation and given the populations in RAVE and RITUXVAS. However, the ERG was aware that there is no clear definition of severe disease, and that the definition of severity used in RAVE was closer to that classified as generalised disease in treatment guidelines. The ERG also noted that RAVE excluded patients with severe renal disease and other life-threatening forms of the disease, so the clinical evidence submitted by the manufacturer did not cover the full population with severe disease. The ERG was also concerned that the manufacturer had used values for weight and body surface area that would be likely to underestimate those of the UK population with ANCA-associated vasculitis.

3.36 The ERG noted that treatment sequences depend on the patient population under consideration (for example, previous treatment with cyclophosphamide will limit its further use). Consequently, different sequences are available for newly diagnosed patients, patients with relapsed disease, and patients who cannot receive or cannot tolerate cyclophosphamide. The ERG expressed concerns about the treatment sequences used in the manufacturer's economic model:

- The ERG questioned the assumption in the manufacturer's model that all patients in the standard care group would receive 2 courses of cyclophosphamide, given that 28% of cyclophosphamide treatment was given orally, which would result in a high cumulative dose.

- The ERG had concerns about the assumption that after receiving 2 courses of cyclophosphamide, patients would receive only best supportive care.
- The ERG was unsure why rituximab was only considered as the first induction treatment in the manufacturer's economic model. It believed it was relevant to consider the relative cost effectiveness of rituximab used before and after cyclophosphamide in the treatment pathway. It noted that the NHS Commissioning Board recommended rituximab as first-line treatment in newly diagnosed patients only when avoiding cyclophosphamide is desirable.
- Clinical specialist advice received by the ERG suggested that it would be unlikely that patients who did not respond to an initial course of rituximab would receive a second course (because of a lack of evidence) and they would instead receive an alternative treatment.

Based on clinical specialist advice, the ERG believed that the results presented by the manufacturer should be approached with considerable caution because other more appropriate treatment sequences exist, and these have not been modelled by the manufacturer.

3.37 Clinical specialist advice to the ERG suggested that it was very unlikely that patients who go into remission after treatment with rituximab would not receive subsequent maintenance therapy. The ERG noted that it would seem appropriate to assume that patients who go into remission after rituximab would then receive maintenance therapy with azathioprine or methotrexate. However, in its economic model the manufacturer did not include maintenance treatment for patients who go into remission after receiving rituximab.

3.38 The ERG had concerns about how the relapse rates used in the manufacturer's model had been derived from RAVE, and believed they had been poorly estimated. It noted that exponential model distributions were fitted to data from patients who went into complete remission at 6 months in order to estimate the time-to-event for relapse, and was aware that the manufacturer had used summary statistics rather than individual patient-level data. It noted that the Kaplan–Meier time to relapse curves for the rituximab and cyclophosphamide groups crossed, indicating that the proportional hazards assumption did not hold and that applying a constant relapse rate to each treatment group was unlikely to be appropriate. It further noted that the relapse rate for the cyclophosphamide group had potentially been overestimated. The ERG concluded that it appeared highly likely that an alternative parametric model (for example, Weibull, Gompertz, log normal or log-logistic) would have provided a better fit to the relapse data, but that these would not be suitable for use with the standard Markov model structure, so the standard Markov model may not have been an appropriate choice. The ERG was unable to assess the relative fit of the exponential models for the subgroup relapse data, and noted the manufacturer's statement that these were less precise than the all-patient data.

3.39 The ERG was aware that the manufacturer had not modelled different severities of relapse, despite the availability of data from RAVE for minor and major flares. The ERG's clinical specialists advised that treatment options and the subsequent disease pathway depend critically upon severity of relapse. The ERG noted that the manufacturer had assumed that all relapses lead to immediate re-treatment with cyclophosphamide or rituximab because it believed almost all minor relapses would lead to major relapses needing re-treatment. However, the ERG received clinical specialist advice that minor relapses may be controlled in other

ways (for example, an increase in glucocorticoid dose) and that not all patients would progress to a major relapse. The ERG anticipated that modelling severe relapse rates for the subgroups of patients with newly diagnosed or relapsed disease would be likely to be highly uncertain because of very low event numbers, and suggested it may be preferable to assume similar relapse rates in these 2 subgroups.

3.40 The ERG believed it would be more appropriate to have included a health state for non-complete remission (that is, when glucocorticoids and other less immunosuppressive treatments are still used). It considered that the failure to model different levels of treatment response and unrealistically high relapse rates may have led to patients in both treatment sequences entering the uncontrolled disease state too quickly. Furthermore, the ERG had concerns about how the manufacturer had modelled treatment for patients who had completed treatment sequences with rituximab and cyclophosphamide and progressed to the uncontrolled disease state. The ERG noted that in the manufacturer's model, patients in the standard of care sequence spent 70.7% of their discounted mean life expectancy in this health state, compared with 63.2% of patients in the intervention sequence. However, clinical specialist advice to the ERG suggested that it is very rare for patients with severe ANCA-associated vasculitis be in this health state because a treatment strategy can usually be identified that offers some disease control. The ERG stated that ideally the manufacturer's model would have included additional lines of treatment, such as mycophenolate mofetil, leflunomide, azathioprine and methotrexate, because clinical specialist advice received by the ERG suggested that these treatments are likely to be included in the lifetime treatment sequences for patients with severe ANCA-associated vasculitis. The ERG also believed that these patients would have disease that was partially controlled through treatment

and that the health state would involve a higher utility score than that assumed by the manufacturer for uncontrolled disease. The ERG indicated that costs for this health state would be lower than those assumed by the manufacturer because it was unlikely patients would have outpatient appointments to receive specialist palliative care every 1.5 weeks.

3.41 The ERG described several concerns about the costs used in the manufacturer's economic model. It stated that health state costs were the largest proportion of total costs generated by the manufacturer's economic model (93% for the cyclophosphamide group and 89% for the rituximab group in the manufacturer's base-case analysis) and noted the importance of these on the cost-effectiveness results. The ERG noted that certain costs (including some tests and the total number of outpatient appointments) were not realistic and believed that these costs were substantially overestimated by the manufacturer, creating a significant bias in favour of rituximab. The ERG also considered that the manufacturer's approach to estimating the drug costs may be biased in favour of the rituximab group (by overestimating the amount of oral cyclophosphamide used in a typical treatment course), and noted that wastage costs from part-used vials had not been included in the manufacturer's base-case analysis.

Evidence Review Group's exploratory analyses

3.42 The ERG corrected several apparent technical errors in the manufacturer's economic model, which included using costs of prednisolone instead of prednisone in line with UK clinical practice. Other cost changes were for cyclophosphamide, trimethoprim and blood tests. The ERG also adjusted the utility value for pneumonia, the relapse rate numbers at risk, used normal distributions for cost parameters, included distributions for standardised mortality rates and outpatient appointments in the probabilistic sensitivity

analyses, and adjusted the mortality risk for patients aged 91 years and older in the uncontrolled disease health state. Cumulatively, these changes decreased the ICER for the comparison of rituximab with cyclophosphamide for all patients with ANCA-associated vasculitis. The ERG's corrected ICER was £6006 per QALY gained (incremental costs £986; incremental QALYs 0.1642) compared with the manufacturer's base-case ICER of £8544 per QALY gained (incremental costs £1391; incremental QALYs 0.1628). Replacing the cost of prednisone with the cost of prednisolone had the greatest impact.

3.43 In further exploratory analyses, the ERG altered several parameter values in the manufacturer's economic model:

- Body surface area and weight were increased to better reflect patients in RAVE.
- It was assumed that patients who went into remission after receiving rituximab would receive azathioprine maintenance treatment at the same dosage as patients who went into remission after receiving cyclophosphamide.
- Relapse rates were re-estimated based on data from patients who had severe flares after receiving cyclophosphamide in RAVE, to reflect the assumption that only severe flares would lead to renewed induction treatment. Given the assumption that patients receiving rituximab induction treatment also received azathioprine maintenance, the same relapse rate was applied to patients in the rituximab group and patients in the cyclophosphamide group.
- Costs and utility values in the uncontrolled disease state were amended to reflect that patients in this state are likely to have some disease control.
- The number and costs of routine tests were amended to reflect recommendations in published guidelines.

- Methylprednisolone administration costs were increased.
- The costs of X-rays and computerised tomography scans were taken from NHS reference costs.
- Wastage costs were included.
- The number of outpatient appointments was reduced.

When these changes in the manufacturer's economic model were added to those described in section 3.42, the ERG's cumulative ICER increased to £26,347 per QALY gained (incremental costs £5704; incremental QALYs 0.2165) for the comparison of rituximab with cyclophosphamide for the full population of patients with ANCA-associated vasculitis. The ERG noted that reducing the number of outpatient appointments (especially) in the uncontrolled disease health state substantially decreased the benefits associated with the rituximab treatment sequence.

3.44 The ERG modelled several treatment sequences that it considered to be more appropriate than those in the manufacturer's submission for the different populations (described in sections 3.45–3.49):

- the full population in the manufacturer's economic model
- patients with newly diagnosed ANCA-associated vasculitis
- patients with relapsed ANCA-associated vasculitis who could have further treatment with cyclophosphamide
- patients with relapsed ANCA-associated vasculitis who could not have further cyclophosphamide treatment
- patients who are unable to tolerate cyclophosphamide.

3.45 The ERG investigated how different treatment sequences could impact on the cost-effectiveness estimates for the full patient population with ANCA-associated vasculitis in the manufacturer's economic model:

- Adding rituximab to the treatment sequence after 2 courses of cyclophosphamide gave an ICER of £12,075 per QALY gained (incremental costs £3894; incremental QALYs 0.32).
- Using rituximab after 1 course of cyclophosphamide increased the ICER to £69,710 per QALY gained (incremental costs £355; incremental QALYs 0.0051) compared with using it after 2 courses.
- Using rituximab as first-line treatment further increased the ICER to £127,456 per QALY gained (incremental costs £579; incremental QALYs 0.0045) compared with using rituximab as second-line treatment.

At £30,000 per QALY gained, the probability of rituximab being cost effective after 2 courses of cyclophosphamide was 58.3%. The probability that excluding rituximab from the treatment sequence was cost effective was 11.7%.

3.46 The ERG did exploratory analyses for the population with newly diagnosed ANCA-associated vasculitis:

- Adding rituximab to the treatment sequence after 2 courses of cyclophosphamide gave an ICER of £12,851 per QALY gained (incremental costs £3783; incremental QALYs 0.29).
- Using rituximab after 1 course of cyclophosphamide increased the ICER to £81,604 per QALY gained (incremental costs £364; incremental QALYs 0.0045) compared with using rituximab after 2 courses of cyclophosphamide.
- The ICER for using rituximab as a first-line treatment further increased the ICER to £317,038 per QALY gained (incremental costs £843; incremental QALYs 0.0027) compared with using rituximab as second-line treatment.

At £30,000 per QALY gained, the probability that using rituximab after 2 courses of cyclophosphamide was cost effective in

patients with newly diagnosed disease was 59.7%. The probability that excluding rituximab from the treatment sequence was cost effective was 13.9%.

3.47 The ERG did exploratory analyses on the population of patients with relapsed ANCA-associated vasculitis who could have further treatment with cyclophosphamide:

- Adding rituximab to the treatment sequence after cyclophosphamide gave an ICER of £11,129 per QALY gained (incremental costs £4702; incremental QALYs 0.4225).
- The ICER for rituximab as first-line treatment was £51,842 per QALY gained (incremental costs £325; incremental QALYs 0.0063) compared with rituximab as second-line treatment.

The probability of rituximab being cost effective after 1 course of cyclophosphamide was 51.3% at £30,000 per QALY gained. The probability that excluding rituximab from the treatment sequence was cost effective was 10.4%.

3.48 The ERG did exploratory analyses on the population of patients with relapsed ANCA-associated vasculitis who could not have further cyclophosphamide treatment. Using rituximab instead of best supportive care gave an ICER of £10,699 per QALY gained (incremental costs £5385; incremental QALYs 0.5033). The ERG assumed that patients who could not tolerate further cyclophosphamide treatment and were receiving best supportive care moved directly to a low-grade disease health state (with partial disease control), and explained that this assumption limited the analysis because active comparators were excluded. At £30,000 per QALY gained, the probability of rituximab being cost effective was 90.4%. The probability that excluding rituximab from the treatment sequence was cost effective was 9.6%.

3.49 The ERG did an exploratory subgroup analysis on patients who were unable to tolerate cyclophosphamide. This subgroup did not necessarily have relapsed disease, but could not take cyclophosphamide for a reason other than exceeding the maximum recommended lifetime cumulative dose. Model parameter inputs were based on the full patient population in RAVE. Using rituximab instead of best supportive care gave an ICER of £11,277 per QALY gained (incremental costs £5437; incremental QALYs 0.48). The ERG assumed that patients who could not tolerate further cyclophosphamide treatment and were receiving best supportive care moved directly to a low-grade disease health state (with partial disease control), and explained that this assumption limited the analysis because active comparators were excluded. At £30,000 per QALY gained, the probability of rituximab being cost effective in patients who cannot tolerate cyclophosphamide was 90.5%. The probability that excluding rituximab from the treatment sequence was cost effective was 9.5%.

3.50 After receiving feedback from clinical specialists on its exploratory analyses, the ERG did other scenario analyses on the data from the full patient population to further explore uncertainty associated with some parameters used in the economic model. The parameters tested were: reduced administration costs for methylprednisone and cyclophosphamide (because of shorter infusion time); substituting co-trimoxazole for trimethoprim; fewer cyclophosphamide infusions (6 instead of 10); and increased weight and body surface (to reflect the UK population with ANCA-associated vasculitis). These amendments had little cumulative impact on the ICER associated with adding rituximab to the treatment sequence after 2 courses of cyclophosphamide treatment compared with best supportive care after 2 courses of cyclophosphamide treatment, which increased slightly from £12,075 per QALY gained (ERG's base-case ICER) to £12,670 per

QALY gained. However, the cumulative ICERs for using rituximab earlier in the treatment sequence increased more markedly because of reduced costs for intravenous cyclophosphamide and increased costs for rituximab (owing to higher body surface area). The ICER for using rituximab after 1 course of cyclophosphamide was £117,545 per QALY gained compared with after 2 courses of cyclophosphamide, and the ICER for using rituximab as first-line treatment was £191,013 per QALY gained compared with using it as second-line treatment. The ERG anticipated that these findings using the full patient population would be mirrored in the subgroups of patients who were newly diagnosed or had relapsed disease.

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

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of rituximab, having considered evidence on the nature of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and the value placed on the benefits of rituximab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.1 The Committee discussed the current clinical pathway of care for people with ANCA-associated vasculitis. It heard from the clinical specialists that induction treatment with cyclophosphamide is the standard of care for patients with severe ANCA-associated vasculitis, and that this includes patients with severe granulomatosis with polyangiitis and microscopic polyangiitis. The Committee recognised that induction treatment lasted for up to 6 months, that cyclophosphamide was administered either orally or intravenously with glucocorticoids, and that the method of

administration varied across treatment centres. The Committee was advised by the clinical specialists that alternatives to cyclophosphamide (such as mycophenolate mofetil, methotrexate and deoxyspergualin) were associated with reduced remission rates and would not normally be used to treat severe disease (unless cyclophosphamide was highly unsuitable). The Committee heard from the clinical specialists that after going into remission with cyclophosphamide, the glucocorticoid dose is tapered and patients switch to maintenance treatment (such as azathioprine) for up to 2 years to reduce the likelihood of relapse. The Committee learned from clinical specialists that minor relapses would likely be managed with an increased dose of glucocorticoid in the first instance.

4.2 The Committee reviewed the safety of treatments currently used in UK clinical practice to induce remission in severe ANCA-associated vasculitis. It recognised that the risk of long-term toxicity (for example, uro-epithelial malignancies) increases with the cumulative dose of cyclophosphamide, and understood from the clinical specialists that the cumulative dose should not exceed 36 g and that they aim to keep it well below this level (at around 20 g) if possible. The Committee was then advised by the clinical specialists that patients would receive 6–10 cycles of intravenous cyclophosphamide to induce remission, that the cumulative dose administered would depend on body weight, and would generally be 10–15 g for 10 cycles. It further heard that a cyclophosphamide course administered orally would result in a higher cumulative dose and could be more than 30 g. The Committee learned from the clinical specialists that rituximab is currently used in the UK following relapse after 1 course of cyclophosphamide, as a way to delay further courses of cyclophosphamide (and consequently reduce the cumulative dose). The Committee concluded that alternative treatments for ANCA-associated vasculitis that avoided

using cyclophosphamide would be welcomed by clinicians and patients.

4.3 The Committee heard from the patient experts about the demands of living with ANCA-associated vasculitis and its treatment. It learned how each relapse can cause further progressive damage to the body and that this may be permanent, and how considerable stress results from the fear of relapse. The Committee further heard about the effects of cyclophosphamide's long-term toxicity. The Committee acknowledged that ANCA-associated vasculitis has a significant impact on patients' quality of life and that cyclophosphamide treatment can be associated with a range of adverse events that could in turn impair their quality of life.

Clinical effectiveness

4.4 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of rituximab. It noted that the evidence was primarily from the RAVE study and this was complemented by the RITUXVAS study. The Committee reviewed the suitability of the clinical trial evidence and noted that only RAVE used the regimen recommended in the European marketing authorisation. Overall, the Committee concluded that the studies provided adequate evidence for assessing rituximab for inducing remission of ANCA-associated vasculitis and were generalisable to UK clinical practice.

4.5 The Committee discussed the clinical effectiveness of rituximab compared with cyclophosphamide as induction therapy in patients with severe ANCA-associated vasculitis. The Committee was aware that the disease severity in RAVE was closer to that classified as generalised disease in treatment guidelines. It accepted that the RAVE results showed rituximab was non-inferior to cyclophosphamide in inducing complete remission in the full

study population at 6 months, but was uncertain if the treatment benefit persisted because of the short duration of RAVE. The Committee concluded that rituximab was not less effective at 6 months than cyclophosphamide as induction treatment for patients with severe ANCA-associated vasculitis, and that further data were necessary to show benefit in the longer term.

4.6 The Committee discussed the need for maintenance treatment after rituximab induction therapy. The Committee was aware of a difference of opinion between the clinical specialists consulted by the Evidence Review Group (ERG) and those attending the appraisal meeting. It noted that clinical advice received by the ERG stated that maintenance treatment (for example, with azathioprine) would normally be given after induction treatment, including rituximab, and that maintenance treatment was recommended in the British Society of Rheumatology guidelines. The Committee noted that these guidelines, which were published in 2007, referred primarily to maintenance after cyclophosphamide. It was aware that the guidelines had concluded that there was insufficient evidence to recommend the routine use of rituximab in induction or maintenance regimens at that time, and that the results from RAVE had been published after the guidelines. The Committee heard from the clinical specialists at the meeting that they would not currently use maintenance treatments such as azathioprine after rituximab, that there was no clinical trial evidence to support this practice, and that the British Society of Rheumatology guidelines are currently under review. The Committee was advised by the clinical specialists that in clinical practice some patients may receive additional ‘top-up’ infusions of rituximab in the months after completing induction treatment, but recalled that the European marketing authorisation was specifically for the induction of remission (with a recommended dosage of 375 mg/m^2 administered as an intravenous infusion once weekly for 4 weeks)

and did not include rituximab being used as a maintenance treatment. It further noted that the summary of product characteristics for rituximab states that the efficacy and safety of rituximab as a maintenance treatment has not been established. Based on the opinion of the clinical specialists at the meeting, the Committee concluded that maintenance treatments such as azathioprine would not be routinely given in UK clinical practice after induction of remission with rituximab, and also concluded that maintenance treatment with rituximab was outside the scope of the appraisal.

4.7 The Committee reviewed the subgroups presented by the manufacturer to identify which patients were likely to experience a greater treatment benefit. The Committee was aware that the complete remission rate in the subgroup with relapsed disease was statistically significantly higher in patients who had received rituximab compared with patients who received cyclophosphamide, but there was no difference between treatment groups in patients with newly diagnosed disease. The Committee understood from the clinical specialists that this represented a clinically plausible subgroup on which to base treatment decisions. However, the Committee was aware that 60% of patients with relapsing disease had previously received cyclophosphamide, which could potentially influence the findings if some patients' disease was partially refractory to cyclophosphamide. The Committee noted that in the subgroup of patients who tested positive for proteinase-3, the patients receiving rituximab were statistically significantly more likely to go into complete remission than the patients receiving cyclophosphamide. However, it heard from the clinical specialists that treatment decisions would not be based on type of ANCA at baseline in UK clinical practice and that these did not represent clinically plausible subgroups. The Committee also heard from the clinical specialists that there may be a small subgroup of newly

diagnosed patients who would benefit from avoiding cyclophosphamide, such as patients wishing to preserve their fertility, patients who have had a previous uro-epithelial malignancy, and patients with an active bacterial infection being treated in an intensive care unit. The Committee concluded that basing patient subgroups on previous treatment was clinically plausible and suitable for informing treatment decisions. It further concluded that there may be a subgroup of newly diagnosed patients for whom avoiding cyclophosphamide may be desirable, but that this subgroup had not been clearly defined in the manufacturer's submission and no clinical evidence had been provided.

4.8 The Committee discussed the safety of rituximab compared with cyclophosphamide. It was aware that intravenous administration of cyclophosphamide is associated with a more favourable adverse-event profile than oral administration. The Committee noted that the frequency and severity of short-term adverse events were broadly comparable for rituximab and cyclophosphamide in RAVE (in which cyclophosphamide was administered orally) and RITUXVAS (in which cyclophosphamide was administered intravenously). The Committee noted that there were long-term adverse events associated with cyclophosphamide (such as bladder cancer and loss of fertility), but that it was not possible to form any conclusions on the long-term safety profile of rituximab because the data in the manufacturer's submission only extended to a maximum of 18 months. The Committee concluded that the safety profile of rituximab compared with cyclophosphamide seemed broadly similar in the short term, but that there was uncertainty about any long-term safety benefits of rituximab (such as a lack of effect on fertility or reduced risk of malignancy compared with cyclophosphamide) because there was no evidence for this, and that further data were necessary to show benefit in the longer term.

4.9 The Committee discussed potential advantages associated with rituximab that were not related to its efficacy or safety. It heard from the clinical specialists and patient experts that induction treatment with rituximab was 4 weeks instead of up to 6 months with cyclophosphamide, which was more convenient for patients. The Committee understood that patients who had received rituximab as induction therapy would not subsequently receive maintenance treatment, whereas patients who had received cyclophosphamide would then have maintenance treatment and would likely experience associated adverse events. The Committee concluded that these potential benefits were important to patients.

Cost effectiveness

4.10 The Committee discussed the manufacturer's approach to developing its economic model. It noted that the ERG considered the manufacturer's approach to be generally in line with the NICE reference case, but that the manufacturer's decision problem did not match the final NICE scope in all areas (notably the exclusion of all comparators except cyclophosphamide and of some outcomes). The Committee concluded that the outlined structure was acceptable for assessing the cost effectiveness of rituximab in treating ANCA-associated vasculitis.

4.11 The Committee considered the comparators included in the manufacturer's economic model. The clinical specialists confirmed that cyclophosphamide was the standard of care for inducing remission and that this would be administered orally or intravenously. The Committee then heard that a lack of evidence meant it was not possible to confirm the relative proportions for oral and intravenous cyclophosphamide administration, but that the manufacturer's estimate in the model was not unreasonable. It noted that the manufacturer had not considered comparators other

than cyclophosphamide, and recalled that it had been advised by the clinical specialists that other treatments (such as methotrexate and deoxyspergualin) would be given to induce remission if a patient could not have cyclophosphamide. It was aware that although these alternative treatments would be expected to have lower efficacy than cyclophosphamide and rituximab, they would offer some degree of disease control. The Committee concluded that although cyclophosphamide was the standard of care, the manufacturer's model and analyses did not fully represent the management of severe ANCA-associated vasculitis in the UK because it had excluded other comparators that would be used when cyclophosphamide was not suitable.

4.12 The Committee evaluated the treatment pathway used in the manufacturer's economic model. In addition to omitting comparators other than cyclophosphamide, it considered the treatment sequences in the manufacturer's economic model to be incomplete and inappropriate because they did not enable fully incremental analyses for all populations of interest (that is, patients who were newly diagnosed, patients with relapsed disease who could have further cyclophosphamide, patients with relapsed disease who could not have further cyclophosphamide and patients who could not tolerate cyclophosphamide). Furthermore, the Committee learned from clinical specialists that the manufacturer's assumption that patients who had not responded to a first course of rituximab would then receive a second course did not reflect UK clinical practice. The Committee agreed that the treatment sequences used by the ERG in its exploratory analyses were more comprehensive and therefore more appropriate, but noted that these were based on clinical specialist advice that differed from the opinion of the clinical specialists attending the Committee meeting. The Committee noted that the ICERs presented by the manufacturer and the ERG for the different populations were

sensitive to changes in treatment sequence. To fully inform its decision-making, the Committee concluded that it needed additional analyses for all possible treatment sequences, with ICERs presented in a fully incremental analysis and as pairwise comparisons, for the different subgroup populations.

4.13 The Committee discussed the uncontrolled disease health state in the manufacturer's economic model. It noted the ERG's concerns that 60–70% of patients in the model reached the uncontrolled disease state and heard from the clinical specialists that this was not clinically realistic. The Committee was aware that this health state was associated with a low utility value and understood from the clinical specialists that patients would be expected to have some disease control with treatments other than cyclophosphamide. It noted the ERG's opinion that the costs for this health state had been overestimated and was advised by the clinical specialists that the number of outpatient appointments was not plausible. The Committee noted from the ERG's exploratory analyses that the ICER substantially increased when the number of outpatient appointments in the uncontrolled disease state was reduced. The Committee concluded that the utility value had been underestimated and costs had been overestimated for the uncontrolled disease health state in the manufacturer's model, and that this health state should reflect a degree of disease control that would be expected with alternative treatments.

4.14 The Committee discussed how adverse events and disease consequences had been incorporated into the manufacturer's model. It noted that disutilities for cyclophosphamide's cumulative long-term toxicity had not been included in the analyses by the manufacturer or the ERG, and that the costs of managing long-term toxicity could be substantial (for example, treating uro-epithelial cancer or fertility problems). The Committee noted that the long-

term toxicity of rituximab also had not been modelled and was not presently fully established. It was aware that the manufacturer's model did not include inpatient costs (such as treating infections) or the costs of disease consequences (for example, managing renal disease). The Committee concluded that the manufacturer's model had not captured all relevant costs and disutilities relating to treatment-associated adverse events and disease consequences, which had added some uncertainty to the cost-effectiveness estimates generated by the model.

4.15 The Committee reviewed how the manufacturer had estimated relapse rates in its economic model. It noted that the final NICE scope included severity of relapses as an outcome, but that this had not been included by the manufacturer in its decision problem, even though minor and major relapses were reported in RAVE and had been included as part of the clinical evidence in its submission. It noted from the manufacturer's submission that, when possible, minor relapses in RAVE were managed by increasing the glucocorticoid dose (unless cyclophosphamide was considered to be necessary). It understood from the clinical specialists that this would generally be the approach taken in UK clinical practice in the first instance (unless, for example, it was considered that there was a high risk of progression to a major relapse). The Committee heard from the clinical specialists that not all minor relapses progress to major relapses needing induction treatment, and therefore it considered the manufacturer's approach of modelling all relapses to be inappropriate. The Committee was aware that the manufacturer had used summary statistics rather than individual patient-level data, and noted the poor fit of the exponential distributions to the Kaplan–Meier relapse curves for the rituximab and cyclophosphamide groups. It agreed with the ERG's opinion that the relapse rates derived from RAVE had been poorly estimated. Furthermore, the Committee considered that the number

of severe relapses in the patient subgroups would be low and therefore relapse rates based on these limited events would be highly uncertain. The Committee concluded that the relapse rates in the manufacturer's model were not appropriate, adding considerable uncertainty to the cost-effectiveness estimates.

4.16 The Committee attempted to identify the most plausible incremental cost-effectiveness ratio (ICER) for the comparison of rituximab and cyclophosphamide for treating severe ANCA-associated vasculitis. The Committee agreed that it was unable to identify the most plausible ICER because it did not have the necessary information to inform a decision on the cost effectiveness of rituximab. It noted several reasons for uncertainty in the results provided by the manufacturer using its economic model:

- incomplete or inappropriate treatment sequences for all populations of interest
- no incremental analysis
- partial responses were not modelled (that is, when patients were in remission but still taking glucocorticoids at 6 months)
- uncertainty in model parameters (largely as described in the ERG report and summarised in sections 3.35–3.36 and 3.38–3.41 of this document)
- unrealistic outpatient costs and utility values in the uncontrolled disease health state
- uncertainty in treating minor relapses in the same way as major relapses
- uncertainty in estimating the probability of relapse.

The Committee agreed that most, but not all, of the adjustments to the model parameters in the exploratory analyses by the ERG were appropriate. It did not accept the following amendments:

- maintenance treatment after induction therapy with rituximab (given the uncertainty over present UK clinical practice as described in section 4.6)
- the number of outpatient appointments after complete remission (after hearing from clinical specialists that patients would attend more than 2 appointments in 6 months).

4.17 The Committee concluded that none of the ICERs presented by the manufacturer and the ERG provided an accurate cost-effectiveness estimate for rituximab for treating ANCA-associated vasculitis, and that it needed additional analyses to inform its decision-making. Therefore, the Committee was minded not to recommend rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis as a cost-effective use of NHS resources. The Committee requested further analyses from the manufacturer that address the issues identified (see section 1.2 and 4.11–4.16), and which should be made available for the second Appraisal Committee meeting.

4.18 The Committee discussed whether rituximab was innovative in its potential to make a significant and substantial impact on health-related benefits. The manufacturer noted that cyclophosphamide reduces fertility in men and women, and stated that the benefit of maintaining fertility while treating the disease effectively cannot be captured in the QALY. The Committee noted that there was no evidence showing rituximab has benefit in this regard. On the basis of currently available evidence, the Committee did not consider rituximab to be a step change in managing ANCA-associated vasculitis. The Committee concluded that there were no additional QALYs associated with rituximab that had not been incorporated into the economic model and the cost-effectiveness estimates.

4.19 The Committee considered whether NICE's duties under the equality legislation required it to alter or to add to its preliminary recommendations. Consultees suggested that children should be included in the population, but the European marketing authorisation specifies 'adults' so this is not an equality issue that falls within the remit of a NICE technology appraisal. No other equality issues were raised during scoping, in any of the consultees' submissions or during the Committee meeting, that fell within the remit of a NICE technology appraisal. The Committee concluded that its decision on the use of rituximab would not have a particular impact on any group with a protected characteristic and that there was no need to alter or add to its preliminary recommendations.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis	Section
Key conclusion		
The Committee is minded not to recommend rituximab in combination with glucocorticoids within its marketing authorisation, that is, for inducing remission in adults with anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener's] and microscopic polyangiitis). The Committee agreed that it was unable to identify the most plausible ICER because it did not have the necessary information to inform a decision on the cost effectiveness of rituximab. The Committee recommends that NICE requests further clarification from the manufacturer, which should be made available for the second Appraisal Committee meeting.		1.1, 4.16, 4.17

Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical specialists that induction treatment with cyclophosphamide is the standard of care for patients with severe ANCA-associated vasculitis, and that alternative treatments such as mycophenolate mofetil, methotrexate and deoxyspergualin) were associated with reduced remission rates and would not normally be used to treat severe disease (unless cyclophosphamide was highly unsuitable).The Committee recognised that the risk of long-term toxicity (for example, uro-epithelial malignancies) increases with the cumulative dose of cyclophosphamide. The Committee concluded that alternative treatments for ANCA-associated vasculitis that avoided the use of cyclophosphamide would be welcomed by clinicians and patients.	4.1–4.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Rituximab (MabThera, Roche Products) is a genetically engineered chimeric (mouse/human) monoclonal antibody that depletes B cells by targeting cells bearing the CD20 surface marker. Although the manufacturer had noted that cyclophosphamide reduces fertility in men and women, and stated that the benefit of maintaining fertility while treating the disease effectively cannot be captured in the QALY, the Committee was not aware of any evidence showing rituximab has benefit in this regard. On the basis of currently available evidence, the Committee did not consider rituximab to be a step change in managing ANCA-associated vasculitis. The Committee concluded that there were no additional QALYs associated with rituximab that had not been incorporated into the economic model and the cost-effectiveness estimates.	2.1, 4.18
What is the position of the treatment in the pathway of care for the condition?	The Committee assessed the clinical effectiveness of rituximab compared with cyclophosphamide as induction therapy in patients with severe ANCA-associated vasculitis.	4.5

Adverse reactions	The Committee noted that the frequency and severity of short-term adverse events were broadly comparable for rituximab and cyclophosphamide in RAVE and RITUXVAS. The Committee noted that there were long-term adverse events associated with cyclophosphamide (such as bladder cancer and loss of fertility), but that it was not possible to form any conclusions on the long-term safety profile of rituximab because the data in the manufacturer's submission only extended to a maximum of 18 months.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee considered the evidence from RAVE and RITUXVAS presented by the manufacturer and noted that only RAVE used the regimen recommended in the European marketing authorisation. The Committee concluded that the studies provided adequate evidence for assessing rituximab for inducing remission of ANCA-associated vasculitis and were generalisable to UK clinical practice.	4.4
Relevance to general clinical practice in the NHS	The Committee discussed the need for maintenance treatment after rituximab induction therapy. It was aware that clinical advice received by the ERG stated that maintenance treatment (for example, with azathioprine) would normally be given after induction treatment, including rituximab, but heard from the clinical specialists at the meeting that they would not currently use maintenance treatment with drugs such as azathioprine after rituximab. The Committee concluded that maintenance treatments such as azathioprine would not be routinely given in UK clinical practice after induction of remission with rituximab, and also concluded that maintenance treatment with rituximab was outside the scope of the appraisal because it was not included in rituximab's European marketing authorisation.	4.6
Uncertainties generated by the evidence	The Committee accepted that the RAVE results showed rituximab was non-inferior to cyclophosphamide in inducing complete remission in the full study population at 6 months, but was uncertain if the treatment benefit persisted because of the short duration of RAVE.	4.5

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee was aware that the complete remission rate in the subgroup with relapsed disease was statistically significantly higher in patients who had received rituximab compared with patients who received cyclophosphamide, but there was no difference between treatment groups in patients with newly diagnosed disease. The Committee concluded that basing patient subgroups on previous treatment was suitable for informing treatment decisions. The Committee heard from the clinical specialists that there may be a small subgroup of newly diagnosed patients for whom avoiding cyclophosphamide may be desirable, such as patients wishing to preserve their fertility, but noted that this subgroup had not been clearly defined in the manufacturer's submission and no clinical evidence had been provided.	4.7
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee accepted that the RAVE results showed rituximab was non-inferior to cyclophosphamide in inducing complete remission in the full study population at 6 months, but was uncertain if the treatment benefit persisted because of the short duration of RAVE. The Committee concluded that rituximab was not less effective at 6 months than cyclophosphamide as induction treatment for patients with severe ANCA-associated vasculitis, and that further data were necessary to show benefit in the longer term.	4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee observed that the manufacturer's approach was generally in line with the NICE reference case, but that the manufacturer's decision problem did not match the final NICE scope in all areas (notably the exclusion of all comparators except cyclophosphamide and of some outcomes). The Committee concluded that the outlined structure was acceptable for assessing the cost effectiveness of rituximab in treating ANCA-associated vasculitis.	4.10

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee identified several reasons for uncertainty in the results using manufacturer's economic model including: uncertainty in model parameters, unrealistic outpatient costs and utility values in the uncontrolled disease health state, uncertainty in estimating the probability of relapse and in how relapses are treated. The Committee concluded that although cyclophosphamide was the standard of care, the manufacturer's model and analyses did not fully represent the management of severe ANCA-associated vasculitis in the UK because it had excluded other comparators that would be used when cyclophosphamide was not suitable. Additionally, it considered the treatment sequences in the manufacturer's economic model to be incomplete and inappropriate, and did not accept the manufacturer's assumption that patients who had not responded to a first course of rituximab would then receive a second course because this did not reflect UK clinical practice. The Committee also concluded that the relapse rates in the manufacturer's model were not appropriate. Taking all these factors into account, the Committee concluded that none of the ICERs presented by the manufacturer and the ERG provided an accurate cost-effectiveness estimate for rituximab for treating ANCA-associated vasculitis, and that it needed additional analyses to inform a decision on the cost effectiveness of rituximab.	4.11, 4.12, 4.15–4.17
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee concluded that the utility value had been underestimated for the uncontrolled disease health state in the manufacturer's model, and that this health state should reflect a degree of disease control that would be expected with alternative treatments. It noted that disutilities for cyclophosphamide's cumulative long-term toxicity had not been included, and that the costs for managing long-term toxicity could be substantial (for example, treating uro-epithelial cancer), which added some uncertainty to the cost-effectiveness estimates generated by the model.	4.13, 4.14

Are there specific groups of people for whom the technology is particularly cost effective?	The Committee was aware that the complete remission rate in the subgroup with relapsed disease was statistically significantly higher in patients who had received rituximab compared with patients who received cyclophosphamide and concluded that basing patient subgroups on previous treatment was clinically plausible and suitable for informing treatment decisions. However, the Committee concluded that none of the ICERs presented by the manufacturer and the ERG provided an accurate cost-effectiveness estimate for rituximab for treating ANCA-associated vasculitis, and that it needed additional analyses for all possible treatment sequences for the different subgroup populations to inform its decision-making.	4.7, 4.12, 4.17
What are the key drivers of cost effectiveness?	The Committee was aware from the ERG's exploratory analyses that the ICER substantially increased when the number of outpatient appointments in the uncontrolled disease state was reduced and concluded that the costs for the uncontrolled disease health state had been overestimated in the manufacturer's model. The Committee also noted that the ICERs presented by the manufacturer and the ERG for the different populations were sensitive to changes in treatment sequence. The Committee concluded that the treatment sequences in the manufacturer's economic model were incomplete and requested additional analyses for all possible treatment sequences for the different subgroup populations to inform its decision-making.	4.12, 4.13
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that none of the ICERs presented by the manufacturer and the ERG provided an accurate cost-effectiveness estimate for rituximab for treating ANCA-associated vasculitis, and that it needed additional analyses to inform its decision-making.	4.17
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	

Equalities considerations and social value judgements	No equality issues that fell within the remit of a NICE technology appraisal were raised. The Committee concluded that its decision on the use of rituximab would not have a particular impact on any group with a protected characteristic and that there was no need to alter or add to its preliminary recommendations.	4.19

5 Implementation

[NICE to amend this section as needed after consultation]

5.1 [Please delete this paragraph if the technology is not recommended] Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

OR

Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within [insert number] months of its date of publication. The normal period of compliance, of 3 months, has been extended for this technology because [insert reason]. This extension is made under Section 7(5) of the Regulations.

5.2 [Please delete this paragraph if the technology is not recommended] When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set

out in the paragraph above. This means that, if a patient has [indication] and the doctor responsible for their care thinks that [technology name] is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

There is no related guidance for this technology at the time of consultation.

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive in October 2016. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh

Chair, Appraisal Committee

July 2013

8 Appraisal Committee members, guideline representatives and NICE project team

8.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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

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

Professor Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Professor Jonathan Michaels (Vice Chair)
Professor of Clinical Decision Science, University of Sheffield

Dr Matthew Bradley
Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Ian Campbell
Honorary Consultant Physician, Llandough Hospital, Cardiff

Dr Ian Davidson
Lecturer in Rehabilitation, University of Manchester

John Dervan

Lay Member

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Christopher Earl

Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital

Gillian Ells

Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Professor John Henderson

Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Dr Paul Hepple

General Practitioner, Muirhouse Medical Group

Dr Tim Kinnaird

Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Terrance Lewis

Lay Member

Warren Linley BSc

Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

Professor Femi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust and MBC

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Paddy Storrie

Lay Member

Dr Alison Talbot-Smith

Consultant in Public Health, Herefordshire Clinical Commissioning Group

8.2 NICE project team

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

Linda Landells

Technical Lead

Sally Doss

Technical Adviser

Kate Moore

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR), University of Sheffield:

- Latimer N, et al. Rituximab in combination with corticosteroids for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis, May 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- Roche Products

II. Professional/specialist and patient/carer groups:

- Vasculitis UK
- British Association of Dermatologists
- British Association for Paediatric Nephrology
- British Society for Rheumatology
- British Society for Paediatric and Adolescent Rheumatology
- British Thoracic Society
- Primary Care Rheumatology Society
- Renal Association
- Royal College of Nursing
- Royal College of Pathologists

- Royal College of Physicians

III. Other consultees:

- Department of Health
- Bournemouth and Poole, and Dorset PCT Cluster
- Welsh Government

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

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Arthritis Research UK
- Vasculitis Rare Disease Working Group of the UK and Ireland
- School of Health and Related Research (ScHARR)
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on rituximab in combination with glucocorticoids by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Professor Lorraine Harper, Professor of Nephrology, nominated by the Renal Association – clinical specialist
- Dr Richard Watts, nominated by Vasculitis Rare Disease Working Group of UK and Ireland – clinical specialist
- John Mills, nominated by Vasculitis UK – patient expert
- Lisa Ranyell, nominated by vasculitis UK – patient expert

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

- Roche Products