NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

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

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

1 Guidance

1.1 Rituximab, in combination with glucocorticoids, is recommended as an option for inducing remission in adults with anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener's] and microscopic polyangiitis), only if:

- further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose; **or**
- cyclophosphamide is contraindicated or not tolerated; **or**
- the person has not completed their family and treatment with cyclophosphamide may materially affect their fertility; **or**
- the disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months; **or**
- the person has had uroepithelial malignancy.

1.2 People currently receiving treatment initiated within the NHS with rituximab that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

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 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 about the efficacy of subsequent courses of rituximab in people 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 people 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 66). 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 reviews of this evidence by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

Manufacturer's original submission

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 anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis or microscopic polyangiitis). RAVE recruited both newly diagnosed and relapsed 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 ANCA-associated vasculitis. The study tested the hypothesis that rituximab was not inferior to (that is, was no worse than) 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 end point 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 end point assessed the superiority of rituximab to cyclophosphamide in patients who had complete remission at 6 months. Tertiary end points included the number of severe flares at 6 months, the number of limited flares at 6 months, and quality of life using Short Form (SF-36) physical component and mental component summary scores. 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. Efficacy data were analysed on an intention-to-treat basis.

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).

3.8 There was no statistically significant difference between the treatment groups in the number of severe or limited flares during the first 6 months. 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.

3.9 The manufacturer explored the effects of various baseline characteristics in relation to the primary end point, including relapsed disease. In patients who had relapsed 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).

RITUXVAS study

3.10 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. 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. Secondary end points included quality of life, assessed by the SF-36 questionnaire between 0 and 12 months. Analyses were performed on an intention-to-treat basis.

3.11 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.

3.12 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.

3.13 There was no statistically significant difference between treatment groups in median change in the physical component SF-36 score (p=0.36). Patients in the cyclophosphamide group had a statistically significantly better mental component 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).

3.14 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.

3.15 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.

3.16 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).

Manufacturer's response to consultation

3.17 In response to consultation, the manufacturer clarified the definition of severe disease. In RAVE, severe ANCA-associated vasculitis was defined as disease activity that threatened the function of the affected organ and had the potential to cause permanent organ damage or to threaten the patient's life unless effective therapy was implemented quickly. Severe disease had previously been referred to as 'generalised', 'generalised organ-threatening' or 'organ-threatening' disease. The manufacturer stated that when RAVE began, the standard of care for inducing remission in people with severe disease was cyclophosphamide and glucocorticoids.

3.18 The manufacturer summarised the 18-month follow-up results from RAVE. The proportion of patients who achieved complete remission (BVAS/WG of 0 on a prednisone dose of 0 mg) at 6 months and who maintained complete remission at 12 and 18 months was similar in the rituximab group and the cyclophosphamide group. The rates of severe and limited flares at 6, 12, and 18 months did not differ significantly between the rituximab group and the cyclophosphamide group. Slightly more flares occurred after 6 months in the rituximab group.

3.19 The manufacturer provided remission rates after re-treatment with rituximab. In RAVE, 16 patients received a second course of rituximab, of whom 7 (44%) entered complete remission.

3.20 The manufacturer provided information about the maximum cumulative dose of cyclophosphamide and its mode of administration in UK clinical practice. The manufacturer advised that the maximum cumulative dose of cyclophosphamide is 25 g

and that intravenous therapy is preferred to oral administration. These statements are consistent with the 2013 draft guidelines from the British Society for Rheumatology on the management of ANCA-associated vasculitis. The manufacturer indicated that 2 courses of intravenous therapy would equate to approximately 23 g of cyclophosphamide, based on a body weight of 78.89 kg.

3.21 The manufacturer defined a subgroup of people for whom it is desirable to avoid cyclophosphamide:

- Women who wish to preserve their fertility.
- People at a higher risk of severe infection, tuberculosis, or chronic infection such as bronchiectasis.
- People with uroepithelial malignancy or dysplasia.
- People with cytopenia or bone marrow insufficiency.
- People with cyclophosphamide allergy or intolerance.

3.22 The manufacturer provided evidence about the long-term safety of rituximab when used as a treatment for rheumatoid arthritis. A global clinical trial programme studied 3595 patients for over 11 years. The patients received up to 20 courses of rituximab. The manufacturer reported there was no evidence of an increased safety risk, an increased risk of malignancy, or increased rates of adverse events after prolonged exposure to rituximab.

3.23 The manufacturer provided evidence that rituximab does not prevent women from conceiving children. A retrospective audit in the USA identified 157 women who received rituximab for ANCA-associated vasculitis. The audit identified 7 women who wanted to have children, of whom 6 became pregnant.

Evidence Review Group's comments on the manufacturer's original submission

3.24 The ERG noted that restricting the systematic review of clinical-effectiveness studies to the population and intervention in the 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.

3.25 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. 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 have been 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 marketing authorisation.

3.26 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 relapsed severe ANCA-associated vasculitis (who had previously received at least 1 dose of cyclophosphamide, methotrexate or azathioprine) and non-inferior to oral cyclophosphamide in patients with newly diagnosed disease. The ERG also highlighted that longer-term efficacy and safety end points 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.

Evidence Review Group's comments on the manufacturer's response to consultation

3.27 The ERG acknowledged that the manufacturer's definition of severe disease was helpful. However, the ERG noted that the clinical evidence submitted by the manufacturer is not relevant for all people with severe ANCA-associated vasculitis. RAVE excluded patients who needed mechanical ventilation because of alveolar haemorrhage or had a serum creatinine level greater than

4.0 mg/100 ml attributed to ANCA-associated vasculitis. RITUXVAS did include patients with more severe disease, but the treatment was rituximab plus cyclophosphamide.

3.28 The ERG reviewed the 18-month follow-up results from RAVE. The ERG advised that, for patients with relapsed disease at baseline, rituximab was superior to cyclophosphamide followed by azathioprine at 6- and 12-month follow-up, but at 18 months the difference in remission rates was not statistically significant.

3.29 The ERG noted that the estimate of remission rates after re-treatment with rituximab provided by the manufacturer was based on small numbers of patients and was at risk of selection bias.

3.30 The ERG acknowledged the value of the 18-month safety data from RAVE, which was submitted by the manufacturer in response to consultation, but noted that these data did not indicate an advantage of rituximab compared with cyclophosphamide. The ERG accepted the relevance of long-term data in rheumatoid arthritis, which suggest that rituximab is well tolerated. The ERG also acknowledged data which indicate that rituximab allows people with ANCA-associated vasculitis to maintain fertility. The ERG advised that the duration of the RAVE study was limited and longer follow-up may be needed to evaluate the safety of rituximab plus glucocorticoids.

Cost effectiveness

Manufacturer's original submission

3.31 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 revised in its clarification response, evaluating the cost effectiveness of rituximab compared with cyclophosphamide in people with ANCA-associated vasculitis. In line with its marketing authorisation, the manufacturer restricted its analysis to inducing remission only and did not look at treating flares or maintenance therapy. The original base case included the population from RAVE, and subgroup analyses investigated people with newly diagnosed disease and with relapsed disease. A separate subgroup analysis estimated the cost effectiveness of rituximab in people 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.

3.32 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.

3.33 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 original 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, received 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 whose disease responded to rituximab could not have re-treatment on relapse because this is outside the scope of the 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.

3.34 The transition probabilities in the manufacturer's original 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 relapsed disease. The same probability of remission 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.

3.35 The costs used in the manufacturer's original 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.

3.36 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.

3.37 The manufacturer's original 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). In its response to clarification, the manufacturer provided the results of scenario analyses, one-way deterministic sensitivity analyses, and probabilistic sensitivity analyses. These original analyses have been superseded by the manufacturer's response to consultation (see sections 3.54 to 3.62).

Evidence Review Group's comments on the manufacturer's original submission

3.38 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 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.

3.39 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.

3.40 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.

3.41 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.

3.42 The ERG was aware that the manufacturer had not modelled different severities of relapse, despite the availability of data from RAVE for minor and severe 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 severe 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 severe 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.

3.43 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. The ERG noted that 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 to 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, in line with clinical specialist advice received by the ERG. The ERG believed that patients in the uncontrolled disease health state would have some disease control, so the health state would have a higher utility score than that assumed by the manufacturer. 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.

3.44 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 impact 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 using the manufacturer's original model

3.45 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, adjusted the numbers at risk of relapse, 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.

3.46 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 CT 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 3.45, 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.

3.47 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 3.48–3.52):

- 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.

3.48 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%.

3.49 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%.

3.50 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 1 course of 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%.

3.51 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%.

3.52 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%.

3.53 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.

Manufacturer's response to consultation

3.54 In response to consultation, the manufacturer provided 2 updated economic models; one for patients who can have cyclophosphamide and one for patients who cannot have cyclophosphamide. Both models incorporated the following changes:

- The minor technical changes proposed in section 3.45.
- The mean body surface area of patients was increased to 1.90 m^2 and the mean weight of patients was increased to 78.89 kg, based on data from 30 patients with vasculitis treated at Manchester Royal Infirmary.
- The model assumed that only severe relapses would be treated with induction therapy.
- The utility value in the uncontrolled disease health state was increased from 0.671 to 0.710.

- The cost of administering methylprednisolone was included. The cost was assumed to be equivalent to the cost of delivering rituximab and cyclophosphamide.
- The cost of an X-ray was updated to £18.56 and the cost of a CT scan was increased to £100.00. It was assumed that 80% of scans received in the modelled population would be X-rays and 20% would be CT scans.
- The model included wastage costs associated with drug delivery.
- There were 4 outpatient visits every 6 months in the uncontrolled disease health state.
- The model included only intravenous administration of cyclophosphamide (whereas the original model assumed 28% of patients would receive oral cyclophosphamide).
- In the uncontrolled disease health state, patients were assumed to receive the recommended dosage of mycophenolate mofetil, methotrexate, or azathioprine. The average cost of the 3 therapies was used in the model. The model assumed no difference in efficacy between treatment arms once patients entered the uncontrolled disease heath state.
- The models did not include any maintenance therapy after induction treatment with rituximab.

3.55 In the manufacturer's updated model for patients who can have cyclophosphamide, the base-case analysis was designed to compare 2 sequences of treatments:

- In the 'standard of care' sequence, patients received intravenous cyclophosphamide as induction therapy. Patients who went into remission with cyclophosphamide received azathioprine as maintenance therapy during remission. Patients who did not go

into remission, or who relapsed, received a second course of intravenous cyclophosphamide.

- In the ‘intervention’ sequence, patients received 1 course of intravenous cyclophosphamide as induction therapy. Patients who went into remission with cyclophosphamide received azathioprine as maintenance therapy during remission. Patients who did not go into remission, or who relapsed, received 2 courses of rituximab. Patients who went into remission with rituximab did not receive any maintenance therapy.

3.56 In the manufacturer’s updated model, the base-case transition probabilities were based on data from RAVE. In both the 'standard of care' sequence and the ‘intervention’ sequence, the probability of achieving remission with the first course of cyclophosphamide was estimated using data from the subgroup of patients in RAVE who had newly-diagnosed disease and were treated with cyclophosphamide.

- In the 'standard of care' sequence, the probability of achieving remission with the second course of cyclophosphamide was estimated using data from the subgroup of patients in RAVE who had relapsed disease and were treated with cyclophosphamide.
- In the ‘intervention’ sequence, the probability of achieving remission with rituximab following a course of cyclophosphamide was estimated using data from the subgroup of patients in RAVE who had relapsed disease and were treated with rituximab. The probability of achieving remission with the subsequent course of rituximab was estimated using data from the subgroup of patients in RAVE who were re-treated with rituximab.

3.57 In the manufacturer’s updated base-case model, the estimate of relapse rates was based on data from patients who had severe flares after receiving cyclophosphamide in RAVE. The same

relapse rate was applied to patients in the rituximab group and patients in the cyclophosphamide group. The relapse rate was assumed to be identical after subsequent lines of therapy.

3.58 The manufacturer's updated model for people with ANCA-associated vasculitis who can have cyclophosphamide produced an ICER for the comparison of rituximab with cyclophosphamide of £18,556 per QALY gained (incremental costs £6117; incremental QALYs 0.330).

3.59 The model for people with ANCA-associated vasculitis who cannot have cyclophosphamide was the same as the updated base-case model for patients who can have cyclophosphamide, except that it compared the following 2 sequences of treatments:

- In the 'standard of care' sequence, patients received a 6-month course of either mycophenolate mofetil or methotrexate. These treatments were assumed to have the same complete remission rates as cyclophosphamide. Patients who went into remission with mycophenolate mofetil or methotrexate received azathioprine as maintenance therapy during remission. The probability of relapse was assumed to be higher than that with cyclophosphamide or rituximab and was set at 0.103.
- In the 'intervention' sequence, patients received 2 courses of rituximab. Patients who went into remission with rituximab did not receive any maintenance therapy. The probability of relapse was 0.086, based on data from RAVE.

3.60 The manufacturer's updated model for people with ANCA-associated vasculitis who cannot have cyclophosphamide produced an ICER for the comparison of rituximab with mycophenolate mofetil or methotrexate of £35,003 per QALY gained (incremental costs £10,186; incremental QALYs 0.291).

3.61 The manufacturer conducted one-way sensitivity analyses to explore the effect of assumptions about key parameters on the results of the base-case model. The following changes, when implemented independently, gave ICERs that were higher than the base case: a higher relapse rate in the rituximab arm, treating both minor and severe relapses with induction therapy, reducing the number of outpatient appointments in the uncontrolled disease health state, and assuming that no patients received a second course of rituximab. When it was assumed that there was less wastage of rituximab, the ICERs were lower than the base case.

3.62 The Committee had requested analyses that incorporated the costs and disutility of the cumulative long-term toxicity of cyclophosphamide. The Committee had also requested analyses that incorporated the inpatient costs associated with non-remission, and separate analyses of the benefit of rituximab for patients who wished to have children. The manufacturer stated that they did not provide these analyses because of time constraints and a lack of data.

Evidence Review Group's comments on the manufacturer's response to consultation

3.63 The ERG advised that the manufacturer's model submitted in response to consultation was incorrect because of several apparent errors:

- The cost of treatment in the uncontrolled disease health state was incorrectly multiplied by 4.
- There were coding errors in the sensitivity analyses that examined re-treatment with rituximab.
- The unit costs for mycophenolate mofetil and methotrexate were incorrect.

3.64 The ERG consulted clinical specialists to assess the plausibility of the treatment sequences in the manufacturer's model for patients who can have cyclophosphamide. The model assumed that only 1 course of cyclophosphamide would be provided in the rituximab arm. The ERG advised that some patients may receive a second course of cyclophosphamide even if rituximab was available. The ERG observed that, in the manufacturer's model, all patients in the rituximab arm received 2 courses of rituximab regardless of the effect of the first course of rituximab. The ERG advised that, at the first Committee meeting, the Committee agreed this assumption was not plausible. The ERG noted that the manufacturer had not modelled all possible treatment sequences as requested by the Committee.

3.65 The ERG acknowledged there is a lack of consensus about the use of maintenance therapy after remission induced by rituximab. The 2013 draft guidelines from the British Society for Rheumatology include 4 options for maintenance therapy. These are, to wait for relapse and then re-treat, to use an immunosuppressive agent (azathioprine or methotrexate), or to use rituximab as maintenance therapy (2 rituximab regimes are described). Only 1 of the options (wait for relapse and then re-treat) was modelled by the manufacturer.

3.66 In the manufacturer's model for patients who cannot have cyclophosphamide, the 'standard of care' arm included only 1 course of mycophenolate mofetil or methotrexate. The ERG stated this may not be realistic. The ERG received clinical advice that cumulative glucocorticoid use is likely to be higher with mycophenolate mofetil or methotrexate than with rituximab, yet this was not reflected in the manufacturer's model.

3.67 In the uncontrolled disease health state, the ERG considered 3 outpatient appointments every 6 months to be a reasonable assumption. The manufacturer's model assumed 4 appointments every 6 months.

3.68 The ERG noted that in RAVE the rate of severe relapse was lower at 18 months than at 6 or 12 months in the cyclophosphamide group, but was increasing in the rituximab group. The ERG advised that it would be relevant to consider scenarios in which the relapse rate was higher in the rituximab group in the long term. The manufacturer's model did not allow relapse rates to alter over time.

3.69 In response to consultation, the manufacturer stated that there were additional QALY gains associated with rituximab because of the preservation of fertility, but these gains were not included in the economic model. The ERG advised that, in the model that included the subgroup of patients who wished to maintain fertility, the comparators were mycophenolate mofetil and methotrexate. The ERG understood that mycophenolate mofetil and methotrexate do not impair long-term fertility. Thus, in the view of the ERG, the manufacturer's argument about QALY gains was not relevant because no fertility advantage had been demonstrated for rituximab compared with mycophenolate mofetil and methotrexate.

3.70 The ERG noted that 2 additional changes, which were included as scenario analyses in the ERG's original report, had not been implemented by the manufacturer. First, cyclophosphamide can be infused more quickly than rituximab and therefore may have a lower administration cost. Second, some patients receive fewer than 10 infusions of intravenous cyclophosphamide. The ERG advised that the ICER associated with rituximab would increase if these 2 amendments were made to the manufacturer's economic model.

Evidence Review Group's exploratory analyses after consultation

3.71 The ERG made the following changes to the manufacturer's model:

- The apparent errors listed in section 3.63 were amended.
- The ERG incorporated uncertainty around the remission rate after re-treatment with rituximab.
- Only patients who entered remission with rituximab were given a second course of rituximab.

3.72 The ERG ran probabilistic sensitivity analyses. The ERG also ran the following scenario analyses for the subgroups who can and cannot have cyclophosphamide:

- The rituximab arm included maintenance therapy with azathioprine.
- There was no re-treatment with rituximab.

3.73 The ERG's exploratory analyses examined the cost effectiveness of rituximab for patients who can have cyclophosphamide.

- Assuming only patients who entered remission with rituximab would be given a second course of rituximab and no maintenance treatment after rituximab, the ICER for the comparison of rituximab with cyclophosphamide was £20,879 per QALY gained (incremental costs £5075; incremental QALYs 0.24). The probability of rituximab being cost effective compared with cyclophosphamide was 40.7% at £20,000 per QALY gained and 56.7% at £30,000 per QALY gained.
- Assuming only patients who entered remission with rituximab would be given a second course of rituximab and azathioprine as maintenance treatment after rituximab, the ICER for the comparison of rituximab with cyclophosphamide was £23,444 per QALY gained (incremental costs £5698; incremental QALYs 0.24). The probability of rituximab being cost effective compared

with cyclophosphamide was 34.8% at £20,000 per QALY gained and 52.8% at £30,000 per QALY gained.

- Assuming no re-treatment with rituximab and no maintenance treatment after rituximab, the ICER for the comparison of rituximab with cyclophosphamide was £20,080 per QALY gained (incremental costs £2790; incremental QALYs 0.14). The probability of rituximab being cost effective compared with cyclophosphamide was 42.0% at £20,000 per QALY gained and 53.7% at £30,000 per QALY gained.

3.74 The ERG's exploratory analyses also examined the cost effectiveness of rituximab for patients who cannot have cyclophosphamide.

- Assuming that only patients who entered remission with rituximab would be given a second course of rituximab and no maintenance treatment after rituximab, the ICER for the comparison of rituximab with mycophenolate mofetil or methotrexate was £60,569 per QALY gained (incremental costs £8345; incremental QALYs 0.14). The probability of rituximab being cost effective compared with mycophenolate mofetil or methotrexate was 13.8% at £20,000 per QALY gained and 25.3% at £30,000 per QALY gained.
- Assuming only patients who entered remission with rituximab would be given a second course of rituximab and azathioprine as maintenance treatment after rituximab, the ICER for the comparison of rituximab with mycophenolate mofetil or methotrexate was £65,700 per QALY gained (incremental costs £9052; incremental QALYs 0.14). The probability of rituximab being cost effective compared with mycophenolate mofetil or methotrexate was 10.9% at £20,000 per QALY gained and 22.4% at £30,000 per QALY gained.

- Assuming no re-treatment with rituximab and no maintenance treatment after rituximab, the ICER for the comparison of rituximab with mycophenolate mofetil or methotrexate was £118,154 per QALY gained (incremental costs £5463; incremental QALYs 0.05). The probability of rituximab being cost effective compared with mycophenolate mofetil or methotrexate was 14.7% at £20,000 per QALY gained and 23.1% at £30,000 per QALY gained.

Manufacturer's response to second consultation

3.75 In response to the second consultation, the manufacturer provided a weighted-average threshold analysis. The aim was to calculate an ICER for rituximab for treating the entire population of people with severely active granulomatosis with polyangiitis and microscopic polyangiitis (including both people who can and people who cannot have cyclophosphamide). For the subgroup of people who can have cyclophosphamide, the manufacturer used an ICER of £12,100 per QALY gained (see section 3.48). Based on the opinion of clinical specialists, the manufacturer assumed that 10% of patients cannot have cyclophosphamide. For the subgroup of people who cannot have cyclophosphamide, the manufacturer used a range of ICERs from £80,000 to £200,000 per QALY gained. The weighted-average ICERs for the entire population of people with severely active granulomatosis with polyangiitis and microscopic polyangiitis ranged from £18,890 to £30,890 per QALY gained.

ERG's response to second consultation

3.76 In response to the second consultation, the ERG provided illustrative analyses based on the manufacturer's updated model for people who cannot have cyclophosphamide; this model

compared 2 courses of rituximab with 1 course of mycophenolate mofetil or methotrexate (see section 3.74). The following changes were made to the 'standard of care' sequence in the model:

- The utility in the remission health state was decreased from 0.84 to 0.79.
- The cost of glucocorticoids in the remission health state was increased from £293 to £439 per 6-month treatment cycle.
- The remission rate was decreased from 0.65 to 0.52.
- Mycophenolate mofetil was the only active treatment in the 'standard of care' sequence.

The changes resulted in an ICER for rituximab compared with mycophenolate mofetil of £26,406 per QALY gained.

3.77 Full details of all the evidence are in the manufacturer's original submission, the manufacturer's responses to consultation, the ERG's original report, the ERG's critique of the manufacturer's response to consultation, and the ERG's response to the second consultation.

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 people with severe ANCA-associated vasculitis, and that this includes people with granulomatosis with polyangiitis and microscopic polyangiitis. The Committee recognised that induction treatment lasts for up to 6 months, and that cyclophosphamide is administered either orally or intravenously with glucocorticoids. The Committee was advised by the clinical specialists that alternatives to cyclophosphamide (such as mycophenolate mofetil, methotrexate and deoxyspergualin) were associated with higher relapse rates and would not normally be used to treat severe disease (unless cyclophosphamide was 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 first. The Committee concluded that cyclophosphamide is the standard of care for people with ANCA-associated vasculitis who can have cyclophosphamide.

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, uroepithelial malignancies) increases with the cumulative dose of cyclophosphamide, and understood from the clinical specialists that the cumulative dose should not exceed 25 g and that they aim to keep it below this level if possible. Draft guidelines from the British Society for Rheumatology also state that the cumulative dose of cyclophosphamide should not exceed 25 g. The Committee was advised by the clinical specialists that people 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 intravenous cyclophosphamide was typically preferred to oral cyclophosphamide, because 1 course of oral cyclophosphamide would result in a cumulative dose of up to 30 g. The Committee concluded that alternative treatments for severe ANCA-associated vasculitis 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 understood that some people with ANCA-associated vasculitis cannot have cyclophosphamide or have disease that is refractory to cyclophosphamide. The Committee heard from the patient experts that currently the only suitable alternative treatment option for these people is rituximab. 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 also 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 marketing authorisation for ANCA-associated vasculitis. 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 people with severe ANCA-associated vasculitis. 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. In response to consultation, the manufacturer provided 18-month follow-up data from RAVE. The Committee acknowledged that rituximab was non-inferior to cyclophosphamide in inducing complete remission at 6, 12, and 18 months. In response to consultation, the manufacturer stated that patients in RAVE had severe disease, meaning the disease threatened the function of the affected organ and had the potential to cause permanent organ damage or to threaten the patient's life unless effective therapy was implemented quickly. The Committee concluded that rituximab was not less effective than cyclophosphamide as an induction treatment for people with severe ANCA-associated vasculitis.

4.6 The Committee discussed the need for maintenance treatment after rituximab induction therapy. The 2013 draft British Society for Rheumatology guidelines include 4 options for maintenance treatment (see section 3.65). The Committee was aware of a difference of opinion between clinical specialists about the use of maintenance treatment. Some specialists stated that maintenance treatments such as azathioprine would be given after rituximab induction therapy, whereas others stated that azathioprine would not normally be given and is not supported by clinical trial evidence.

In response to consultation, several specialists stated that rituximab would be used as maintenance treatment. The Committee recalled that the marketing authorisation was specifically for inducing 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 maintenance treatment. It further noted that the summary of product characteristics for rituximab states that the efficacy and safety of rituximab as maintenance treatment have not been established. The Committee 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 people were likely to experience a greater treatment benefit. The Committee was aware that, at 6-month follow-up from RAVE, the complete remission rate for the subgroup with relapsed disease was statistically significantly higher in patients who received rituximab compared with patients who received cyclophosphamide. The Committee noted that the 18-month follow-up results for this subgroup, submitted in response to consultation, showed no significant difference in remission rates between the treatment groups. The Committee observed that, at 6-month follow-up for the subgroup with newly diagnosed disease, there was no significant difference in remission rates between the treatment groups. The Committee concluded that, over a period of 18 months, rituximab and cyclophosphamide have similar effectiveness in inducing remission in both newly diagnosed and relapsed patients.

4.8 The Committee considered whether there were additional patient subgroups who might experience a greater treatment benefit. The Committee heard from the clinical specialists that there may be a

small subgroup of people who would benefit from avoiding cyclophosphamide. In response to consultation, the manufacturer defined this subgroup (see section 3.21). The Committee noted that the manufacturer's definition is broadly in agreement with draft guidelines from the British Society for Rheumatology. Both the manufacturer and the British Society for Rheumatology stated that patients at risk of infection would benefit from avoiding cyclophosphamide. However, the Committee observed that the summary of product characteristics states that rituximab should not be used for patients with active, severe infection. In response to the second consultation, clinical specialists advised that there is evidence from case series to support the use of rituximab for people who cannot have cyclophosphamide. The Committee concluded that, for the purposes of this guidance, 'people who cannot have cyclophosphamide' refers to people:

- for whom cyclophosphamide is contraindicated (as defined in the summary of product characteristics) or not tolerated; or
- who have not completed their family and whose fertility may be materially affected by treatment with cyclophosphamide; or
- with disease that has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months; or
- with a previous uroepithelial malignancy.

4.9 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. In response to consultation, the manufacturer submitted evidence of the long-term safety of rituximab as a treatment for rheumatoid arthritis, and evidence that rituximab does not prevent women from conceiving children. The Committee concluded that the safety profiles of rituximab and cyclophosphamide seemed broadly similar in the short term, and there was uncertainty about any long-term safety benefits of rituximab because of a lack of data from patients with ANCA-associated vasculitis.

4.10 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 concluded that this benefit was important to patients.

Cost effectiveness

4.11 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 excluding some comparators and some end points). The Committee concluded that the outlined economic analysis was acceptable for assessing the cost effectiveness of rituximab in treating ANCA-associated vasculitis.

4.12 The Committee considered the comparators included in the manufacturer's economic analysis. The clinical specialists, and responses to consultation, confirmed that cyclophosphamide is the standard of care for inducing remission in people who can have cyclophosphamide; typically administered intravenously. The Committee noted that there was a lack of consensus about the appropriate comparator for people who cannot have cyclophosphamide. The Committee recalled that the ERG's exploratory analyses for this subgroup, based on the manufacturer's original model, used a comparator of best supportive care. The Committee was uncertain whether best supportive care was a realistic comparator. The Committee was aware that the manufacturer's updated model for this subgroup used a comparator of either mycophenolate mofetil or methotrexate. Clinical specialists at the meeting advised that neither of these drugs is a treatment of choice for people with severe disease, and methotrexate is unsuitable for people with renal disease. Also, the British Society for Rheumatology draft guidelines recommend mycophenolate mofetil or methotrexate for patients with low disease activity who are not at risk of organ damage. The Committee heard from the manufacturer that the clinical specialists it consulted advised that mycophenolate mofetil or methotrexate would be used as an induction treatment for people who cannot have cyclophosphamide. The Committee concluded that it was appropriate to include intravenous cyclophosphamide as the comparator in the economic analysis for people who can have cyclophosphamide, and that there was uncertainty about the appropriate comparator for people who cannot have cyclophosphamide.

4.13 The Committee evaluated the treatment sequences used in the manufacturer's original economic analysis. It considered the

treatment sequences to be incomplete and unsuitable because they did not enable fully incremental analyses for all populations of interest. Also, 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 using the manufacturer's original model were more comprehensive and therefore more appropriate. However, the Committee agreed that it needed additional analyses for all possible treatment sequences for the different subgroup populations, with ICERs presented in a fully incremental analysis and as pairwise comparisons. The Committee then evaluated the treatment sequences used in the manufacturer's updated economic analysis, submitted in response to consultation. The Committee observed that the updated model did not consider all treatment sequences and assumed that all patients received a second course of rituximab. The results were not presented in a fully incremental analysis. The Committee concluded that these issues with the manufacturer's updated economic analysis added considerable uncertainty to the cost-effectiveness estimates.

4.14 The Committee discussed the uncontrolled disease health state in the manufacturer's original economic model. It noted the ERG's concerns that patients in the model spent 60–70% of their average lifespan in the uncontrolled disease state and heard from the clinical specialists that this was not 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 agreed that the utility value had been underestimated and costs had been overestimated for the uncontrolled disease health state in the manufacturer's original model. The Committee noted that, in response to consultation, the manufacturer submitted an updated model with a higher utility value and lower costs in the uncontrolled disease health state. It heard from the manufacturer and the ERG that the revised utility value was based on extrapolation from the utility values in the remission and non-remission health states. The Committee noted that the utility value could have been estimated using data from patients in RAVE who had not entered remission during the trial, but this analysis had not been presented. The Committee concluded that the revised utility value in the uncontrolled disease health state was more plausible than the value in the original model, but was still a source of some uncertainty.

4.15 The Committee discussed how adverse events and disease consequences had been incorporated into the manufacturer's original model. It noted that disutilities for cyclophosphamide's cumulative long-term toxicity had not been included in the analyses by the manufacturer, and that the costs of managing long-term toxicity could be substantial (for example, treating uroepithelial cancer or fertility problems). The Committee noted that the long-term toxicity of rituximab also had not been modelled and was not 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 manufacturer's updated model, submitted in response to consultation, did not include disutilities for long-term toxicity, inpatient costs, or the costs of disease consequences. The Committee concluded that the manufacturer's original and updated

models had not captured all relevant costs and disutilities, which added some uncertainty to the cost-effectiveness estimates.

4.16 The Committee reviewed how the manufacturer had estimated relapse rates in its original economic model and noted that the model assumed that both minor and severe relapses would need induction treatment. The Committee noted from the manufacturer's submission that, when possible, minor relapses in RAVE were managed by increasing the glucocorticoid dose. It understood from the clinical specialists that this would generally be the first approach in UK clinical practice (unless, for example, it was considered that there was a high risk of progression to a severe relapse). 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. It agreed with the ERG's opinion that the relapse rates derived from RAVE had been poorly estimated. In response to consultation, the manufacturer submitted an updated model which assumed that only severe relapses would need induction treatment. The Committee continued to have concerns about the manufacturer's use of summary statistics and concluded that the relapse rates in the manufacturer's updated model were a source of uncertainty.

4.17 The Committee then considered the manufacturer's updated models submitted in response to the first consultation (see sections 3.54–3.62). The Committee noted that the manufacturer had not provided all the analyses requested at consultation. The manufacturer's response did not include all treatment sequences, pairwise and incremental comparisons, incorporate the costs and disutility of the cumulative long-term toxicity of cyclophosphamide, or include inpatient costs associated with non-remission. The ERG

identified several errors in the manufacturer's models (see section 3.63). The Committee then considered the manufacturer's weighted-average threshold analysis submitted in response to the second consultation (see section 3.75). It was aware that one of the reasons the manufacturer used this analysis was that another Committee had agreed to consider a whole-population weighted-ICER analysis in Omalizumab for treating severe persistent allergic asthma (NICE technology appraisal guidance 278). However, the Committee noted that the circumstances were different to the current appraisal. For example, the omalizumab appraisal considered subgroups created by an arbitrary cut-off between age groups whereas the current appraisal considered 2 clinically distinct subgroups (people who can and cannot have cyclophosphamide). The Committee recalled that NICE's Guide to the methods of technology appraisal states that estimates of clinical and cost effectiveness should be provided separately for each relevant subgroup of patients. The Committee concluded that the manufacturer's models submitted in response to the first consultation, and the manufacturer's weighted-average threshold analysis submitted in response to the second consultation, did not provide a suitable basis for decision-making.

4.18 The Committee considered the ERG's exploratory analyses using the manufacturer's updated model for people who can have cyclophosphamide (see section 3.73). The Committee noted that the ERG had corrected the errors identified in the manufacturer's updated model. The Committee also noted the ERG's exploratory analysis allowed re-treatment of patients who responded to rituximab rather than re-treatment of all patients in the manufacturer's updated model. It also considered the treatment sequence, which was 1 course of cyclophosphamide followed by 2 courses of rituximab compared with 2 courses of

cyclophosphamide in the comparator arm. The Committee noted that there was no incremental analysis of rituximab in different places in the treatment pathway. Therefore, the ICER of £20,900 per QALY gained from the ERG's exploratory analyses did not reflect the true cost effectiveness of rituximab given after 1 course of cyclophosphamide compared with cyclophosphamide. The Committee then discussed the ERG's exploratory analyses using the manufacturer's original model (see section 3.48), because these incremental analyses explored the use of rituximab in different places in the treatment pathway. The Committee was aware that a treatment sequence of 2 courses of cyclophosphamide followed by 1 course of rituximab compared with 2 courses of cyclophosphamide resulted in an ICER of £12,100 per QALY gained. It noted that using rituximab after 1 course of cyclophosphamide (compared with using it after 2 courses of cyclophosphamide) or as a first-line treatment (compared with using rituximab after 1 course of cyclophosphamide), resulted in ICERs of £69,700 and £127,500 per QALY gained respectively (see section 3.48). The Committee agreed that the ICERs for rituximab after 1 course of cyclophosphamide or as a first-line treatment were outside the range normally considered a cost-effective use of NHS resources. The Committee noted that these exploratory analyses included maintenance treatment with azathioprine after rituximab, which may not reflect UK clinical practice (see section 4.6). The Committee heard from the ERG that, based on previous exploratory analyses (see section 3.73), including maintenance treatment with azathioprine was likely to have a small impact on the ICER. The Committee concluded that the most plausible ICER on which to base its decision for people who can have cyclophosphamide was £12,100 per QALY gained, provided by the comparison of 2 courses of cyclophosphamide

followed by 1 course of rituximab with 2 courses of cyclophosphamide.

4.19 The Committee considered the cumulative dose provided by 2 courses of intravenous cyclophosphamide. Based on the manufacturer's response to consultation, the Committee was persuaded that 2 courses of intravenous cyclophosphamide provides a cumulative dose of approximately 23 g on average, which is within the limit of 25 g advised by draft guidelines from the British Society for Rheumatology. The Committee further noted that approximately 23 g cyclophosphamide represented 10 infusions (the maximum number that would be administered per course of treatment) and that, according to the clinical specialists, some patients would respond with fewer infusions per cycle. The Committee noted that when possible, giving 2 courses of cyclophosphamide before rituximab would represent a more cost-effective option than giving 1 course of cyclophosphamide before rituximab. The Committee concluded that rituximab could be recommended as a cost-effective use of NHS resources in people with severe ANCA-associated vasculitis who can have cyclophosphamide, only if further treatment with cyclophosphamide would exceed the maximum cumulative dose (25 g) of cyclophosphamide.

4.20 The Committee discussed the ERG's exploratory analyses using the manufacturer's updated model for people who cannot have cyclophosphamide (see section 3.74). The treatment sequence included 2 courses of rituximab compared with 1 course of either mycophenolate mofetil or methotrexate and the ERG's exploratory analysis of the manufacturer's updated model gave an ICER of £60,600 per QALY gained. The Committee was aware of substantial uncertainty about the assumptions in the model, such

as the utility of the remission health state, the cost and disutility associated with glucocorticoids, and the remission and relapse rates. Therefore, the Committee agreed that the ICER of £60,600 per QALY gained was not plausible. The Committee considered the ERG's illustrative analyses, submitted in response to the second consultation (see section 3.76). The ERG's illustrative analyses changed some assumptions in the model and gave an ICER of £26,400 per QALY gained for the comparison of 2 courses of rituximab with 1 course of mycophenolate mofetil. The Committee heard from the ERG that the analyses illustrate the uncertainty in the estimates of cost effectiveness for people who cannot have cyclophosphamide. The Committee was aware that the clinical specialists did not agree about the use of mycophenolate mofetil or methotrexate as an induction treatment in people who cannot have cyclophosphamide (see section 4.12). The Committee then discussed the ERG's exploratory analyses using the manufacturer's original model for people who cannot have cyclophosphamide (see section 3.52), because these analyses included an alternative comparator. The Committee noted that 1 course of rituximab compared with best supportive care gave an ICER of £11,300 per QALY gained. The Committee agreed that there was a lack of consensus about the appropriate comparator for people who cannot have cyclophosphamide. The Committee concluded there was substantial uncertainty about the cost effectiveness of rituximab for people who cannot have cyclophosphamide, but on balance the ICER was likely to be lower than £30,000 per QALY gained.

4.21 The Committee discussed whether rituximab was innovative in its potential to make a significant and substantial impact on health-related benefits. The Committee was aware that, in response to the second consultation, clinical specialists and patient experts stated

that rituximab was 'scene-changing' in the treatment of ANCA-associated vasculitis. Consultees also advised that rituximab was the first new effective treatment since the introduction of cyclophosphamide in the 1970s, and rituximab may be the first of a new generation of treatments. In addition, consultees advised that people who cannot have cyclophosphamide have the highest unmet need because no alternative treatments are as effective as rituximab. 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 was aware that the manufacturer had provided evidence that rituximab does not prevent women from conceiving children. The Committee concluded that rituximab was an innovative treatment.

4.22 In summary, for people who cannot have cyclophosphamide, the Committee considered the manufacturer's original and updated analyses, the ERG's exploratory and illustrative analyses, and comments received during consultation. The Committee took into account the estimates of cost effectiveness and noted the uncertainty associated with them. The Committee also recognised that rituximab is an innovative treatment and the high unmet need for treatment options for people who cannot have cyclophosphamide. Having taken into account all of the evidence submitted and the comments received during consultation and noting the NICE Social Value Judgements, the Committee concluded that rituximab was a cost-effective use of NHS resources for treating people with severe ANCA-associated vasculitis who cannot have cyclophosphamide, as defined in section 4.8.

4.23 The Committee considered whether its recommendations were associated with any issues related to the equality legislation and the requirement for fairness. The Committee noted that the manufacturer stated that cyclophosphamide reduces fertility in both men and women. The Committee was also aware that the manufacturer had provided evidence that rituximab does not prevent women from conceiving children and that no evidence was presented regarding the effect of rituximab on male fertility. Based on the available evidence, the Committee considered that it was appropriate to accept that rituximab was likely to have a less detrimental effect on male fertility than cyclophosphamide. The Committee considered that, in this context, guidance that only recommended rituximab for women who had not completed their family would potentially constitute unlawful sex discrimination. The Committee concluded that it was appropriate to recommend rituximab for men and women who have not completed their family and whose fertility may be materially affected by treatment with cyclophosphamide.

4.24 The Committee further considered issues related to the equality legislation. Considering that the guidance in section 1.1 recommends rituximab for people who have not completed their family and whose fertility may be materially affected by treatment with cyclophosphamide, the Committee was aware that this recommendation would affect access for post-menopausal women whereas younger women and men of all ages could potentially receive rituximab. The Committee discussed whether this could be regarded as indirect discrimination. The Committee noted that any differential treatment of post-menopausal women arises from the different physiological features of fertility in men and women. The Committee noted that rituximab and cyclophosphamide have similar effectiveness as induction treatments for severe ANCA-

associated vasculitis (see section 4.7), so an effective induction treatment will also be available for post-menopausal women. Therefore, the Committee agreed that its recommendations do not constitute detrimental treatment of post-menopausal women. The Committee noted that the safety profiles of rituximab and cyclophosphamide are broadly similar in the short term, and there was uncertainty about any long-term safety benefits of rituximab compared with cyclophosphamide (see section 4.9). The Committee concluded that the guidance would permit an effective induction treatment for all groups of people, and there was no evidence that some groups would experience more adverse effects of treatment than other groups, and therefore there was no unfairness.

4.25 In considering the potential equalities issues, the Committee took into account the size and characteristics of the overall population of people with ANCA-associated vasculitis and the subgroup of people who would be affected by the recommendation relating to fertility. The Committee was aware that around 1200 people are diagnosed with ANCA-associated vasculitis each year in England and Wales and the peak age of onset is between 60 and 70 years. Therefore, the Committee concluded that the number of people with ANCA-associated vasculitis who have not completed their family is likely to be small.

4.26 The Committee further discussed issues related to the equality legislation. Consultees suggested that children should be included in the population, but the marketing authorisation specifies ‘adults’ so this is not an equality issue that falls within the remit of a NICE technology appraisal. The Committee concluded that its decision on the use of rituximab would not have a disproportionate impact on any group with a protected characteristic that cannot be

objectively justified, and that therefore there was no need to alter or add to its 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		
Rituximab, in combination with glucocorticoids, is recommended as an option for inducing remission in adults with anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener's] and microscopic polyangiitis), only if: • further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose; **or** • cyclophosphamide is contraindicated or not tolerated; **or** • the person has not completed their family and treatment with cyclophosphamide may materially affect their fertility; **or** • the disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months; **or** • the person has had uroepithelial malignancy.		1.1
The Committee concluded that a plausible treatment sequence for people who can have cyclophosphamide was 2 courses of cyclophosphamide followed by 1 course of rituximab. The Committee noted that 2 courses of cyclophosphamide would provide a cumulative dose of 23 g on average, which is within the limit of 25 g advised by draft guidelines from the British Society for Rheumatology. The Committee noted that using rituximab earlier in the treatment sequence, either as a first-line treatment or after 1 course of cyclophosphamide, was not cost effective. It concluded that, for patients for whom further cyclophosphamide treatment would exceed the maximum cumulative dose, rituximab is a cost-effective use of NHS resources and therefore should be recommended.		4.18, 4.19
The Committee concluded there was substantial uncertainty regarding the cost effectiveness of rituximab for people who cannot have cyclophosphamide, but on balance the ICER was likely to be lower than £30,000 per QALY gained. The Committee recognised that rituximab is an innovative treatment and the high unmet need of treatment options for people who cannot have cyclophosphamide. Therefore, the Committee concluded that rituximab was a cost-effective use of NHS resources for treating people with severe ANCA-associated vasculitis who cannot have cyclophosphamide, as defined in section 4.8.		4.8, 4.20–4.22
Current practice		
Clinical need of patients, including the	The Committee heard from the clinical specialists that induction treatment with cyclophosphamide is	4.1–4.3

availability of alternative treatments	the standard of care for people with severe ANCA-associated vasculitis, and that alternative treatments such as mycophenolate mofetil, methotrexate and deoxyspergualin were associated with higher relapse rates and would not normally be used to treat severe disease (unless cyclophosphamide was unsuitable). The Committee recognised that the risk of long-term toxicity (for example, uroepithelial malignancies) increases with the cumulative dose of cyclophosphamide and understood that the cumulative dose should not exceed 25 g. The Committee concluded that alternative treatments for ANCA-associated vasculitis would be welcomed by clinicians and patients.	
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. The Committee was aware that clinical specialists and patient experts stated that rituximab was 'scene-changing' in the treatment of ANCA-associated vasculitis. Consultees also advised that rituximab was the first new effective treatment since the introduction of cyclophosphamide in the 1970s, and rituximab may be the first of a new generation of treatments. The manufacturer noted that cyclophosphamide reduces fertility in men and women, stated that the benefit of maintaining fertility while treating the disease effectively cannot be captured in the QALY, and provided evidence that rituximab does not prevent women from conceiving children. The Committee agreed that rituximab was an innovative treatment and therefore the Committee would consider an ICER at the top end of the range that would normally be considered a cost-effective use of NHS resources (£20,000–30,000 per QALY gained).	2.1 4.21
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 people 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	4.9

	that there were long-term adverse events associated with cyclophosphamide (such as bladder cancer and loss of fertility). It was aware of evidence of the long-term safety of rituximab as a treatment for rheumatoid arthritis, and evidence that rituximab does not prevent women from conceiving children. The Committee concluded that the safety profiles of rituximab and cyclophosphamide seemed broadly similar in the short term, and there was uncertainty about any long-term safety benefits of rituximab because of a lack of data from patients with ANCA-associated vasculitis.	
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 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 British Society for Rheumatology draft guidelines include 4 options for maintenance treatment, but clinical specialists did not agree about which options would be used in routine practice. The Committee concluded that maintenance treatment with rituximab was outside the scope of the appraisal because it was not included in the marketing authorisation.	4.6
Uncertainties generated by the evidence	The Committee concluded there was uncertainty about any long-term safety benefits of rituximab compared with cyclophosphamide because of a lack of data from people with ANCA-associated vasculitis.	4.9
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee noted that rituximab was superior to cyclophosphamide in inducing remission in patients with relapsed disease at 6-month follow-up, but the difference between treatments was not significantly different at 18-month follow-up. The Committee heard from the clinical specialists that there may be a small subgroup of people who would benefit from avoiding cyclophosphamide,	4.7 4.8

	and that there is evidence from case series to support the use of rituximab for this subgroup. The Committee concluded that, for the purposes of this guidance, 'people who cannot have cyclophosphamide' refers to people: • for whom cyclophosphamide is contraindicated (as defined in the summary of product characteristics) or not tolerated; or • who have not completed their family and whose fertility may be materially affected by treatment with cyclophosphamide; or • with disease that has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months; or • with a previous uroepithelial malignancy.	
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, 12, and 18 months. The Committee concluded that the RAVE and RITUXVAS studies provided adequate evidence for assessing rituximab for inducing remission of ANCA-associated vasculitis and were generalisable to UK clinical practice.	4.4, 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 excluding some comparators and end points). The Committee concluded that the outlined economic analysis was acceptable for assessing the cost effectiveness of rituximab in treating ANCA-associated vasculitis.	4.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee identified several reasons for uncertainty in the results of the manufacturer's updated economic models submitted in response to the first consultation. The reasons included: not all treatment sequences were modelled, no incremental analyses were reported, not all costs and consequences were included, there were concerns about the way relapse rates were calculated, there were errors in the model, and there was uncertainty about utility values. The	4.12–4.17

	Committee then considered the manufacturer's weighted-average threshold analysis submitted in response to the second consultation. It was aware that another Committee had agreed to consider a whole-population weighted-ICER analysis in Omalizumab for treating severe persistent allergic asthma (NICE technology appraisal guidance 278), but the circumstances were different to the current appraisal. The Committee recalled that NICE's Guide to the methods of technology appraisal states that estimates of clinical and cost effectiveness should be provided separately for each relevant subgroup of patients. The Committee concluded that the manufacturer's models submitted in response to the first consultation, and the manufacturer's weighted-average threshold analysis submitted in response to the second consultation, did not provide a suitable basis for decision-making. Some of the Committee's concerns had been resolved in the ERG's exploratory analyses. Accordingly, the Committee was able to identify the most plausible ICER for people who can have cyclophosphamide. For people who cannot have cyclophosphamide, the Committee considered the manufacturer's original and updated analyses, and the ERG's exploratory and illustrative analyses. The Committee agreed that, for people who cannot have cyclophosphamide, there was a lack of consensus about the appropriate comparator treatment. The Committee concluded there was substantial uncertainty about the cost effectiveness of rituximab for people who cannot have cyclophosphamide, but on balance the ICER was likely to be lower than £30,000 per QALY gained.	4.18 4.20
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	The Committee noted that, in the manufacturer's updated models, the utility value in the uncontrolled disease health state was based on extrapolation from the utility values in the remission and non-remission health states. It concluded that that the revised utility value in the uncontrolled disease health state was more plausible than the value in the original model, but was still a source of some uncertainty. The Committee noted that the economic model did not include disutilities for cyclophosphamide's cumulative long-term toxicity or the costs of	4.14 4.15

considered?	managing long-term toxicity. It agreed that these issues added some uncertainty to the cost-effectiveness estimates.	
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee agreed that rituximab was cost effective for adults with ANCA-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener's] and microscopic polyangiitis), only if: • further cyclophosphamide treatment would exceed the maximum cumulative dose (25 g) of cyclophosphamide; or • the person cannot have cyclophosphamide (as specified in section 4.8).	4.18, 4.19 4.8
What are the key drivers of cost effectiveness?	The Committee was aware from the ERG's exploratory analyses based on the manufacturer's original model that the ICER substantially increased when the number of outpatient appointments was reduced. The Committee also noted that the ICERs presented by the manufacturer and the ERG were sensitive to changes in treatment sequence.	3.46, 3.48
Most likely cost-effectiveness estimate (given as an ICER)	The Committee agreed that the most plausible ICER on which to base its decision for people who can have cyclophosphamide was £12,100 per QALY gained, provided by the comparison of 2 courses of cyclophosphamide followed by 1 course of rituximab with 2 courses of cyclophosphamide. The Committee concluded there was substantial uncertainty about the cost effectiveness of rituximab for people who cannot have cyclophosphamide, but on balance the ICER was likely to be lower than £30,000 per QALY gained.	4.18 4.20
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	For people who cannot have cyclophosphamide, the Committee considered the evidence, the comments received during consultation, and the NICE Social Value Judgements. The Committee took into account the estimates of cost	4.22

	effectiveness and noted the uncertainty associated with them. The Committee also recognised that rituximab is an innovative treatment and the high unmet need for treatment options for people who cannot have cyclophosphamide. The Committee concluded that rituximab was a cost-effective use of NHS resources for treating people with severe ANCA-associated vasculitis who cannot have cyclophosphamide, as defined in section 4.8.	
	The Committee considered whether its recommendations were associated with any issues related to the equality legislation. The Committee noted that the manufacturer stated that cyclophosphamide reduces fertility in both men and women. The Committee was aware of evidence that rituximab does not prevent women from conceiving children but no evidence had been presented regarding the effect of rituximab on male fertility. The Committee considered that it was appropriate to accept that rituximab was likely to have a less detrimental effect on male fertility than cyclophosphamide. The Committee concluded that it was appropriate to recommend rituximab for men and women who have not completed their family whose fertility may be materially affected by treatment with cyclophosphamide.	4.23
	The Committee was aware that the recommendation regarding fertility would affect access for post-menopausal women whereas younger women and men of all ages could potentially receive rituximab. The Committee discussed whether this could be regarded as indirect discrimination. The Committee noted that rituximab and cyclophosphamide have similar effectiveness as induction treatments for severe ANCA-associated vasculitis. The Committee also noted that the safety profiles of rituximab and cyclophosphamide are broadly similar in the short term, and there was uncertainty about any long-term safety benefits of rituximab compared with cyclophosphamide. The Committee concluded that the guidance would permit an effective induction treatment for all groups of people, and there was no evidence that some groups would experience more adverse effects of treatment than other groups, and therefore there was no unfairness. The Committee also concluded that the number of people with ANCA-associated vasculitis who have not completed their family is likely to be small.	4.24, 4.25

5 Implementation

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.

5.1 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 ANCA-associated vasculitis and the doctor responsible for their care thinks that rituximab is the right treatment, it should be available for use, in line with NICE's recommendations.

5.2 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.

7 Review of guidance

7.1 The guidance on this technology will be considered for review in March 2017. 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

January 2014

8 Appraisal Committee members 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

Dr Brian Shine (Vice Chair)
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Andrew Black
General Practitioner, Mortimer Medical Practice, Herefordshire

Professor David Bowen
Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

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 Martin Duerden

Assistant Medical Director, Betsi Cadwaladr University Health Board, North Wales

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

Professor Peter Jones

Emeritus Professor of Statistics, Keele University

Professor Steven Julious

Professor in Medical Statistics, University of Sheffield

Dr Tim Kinnaird

Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Terrance Lewis

Lay Member

Warren Linley

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

Professor Jonathan Michaels

Professor of Clinical Decision Science, University of Sheffield

Malcolm Oswald

Lay Member

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 Lindsay Smith

General Practitioner, Westlake Surgery

Dr Murray Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie

Lay Member

Dr Alison Talbot-Smith

Consultant in Public Health, Herefordshire Clinical Commissioning Group

Charles Waddicor

Formerly Chief Executive, NHS Berkshire West

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 and Rosie Lovett

Technical Leads

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
- Pfizer
- 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 Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Lorraine Harper, Professor of Nephrology, nominated by the Renal Association – clinical specialist
- Dr Peter Lanyon, nominated by the British Society for Rheumatology – 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