NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Roche Products	In section 4.21 of the ACD, the Committee considered they were unable to recommend RTX for patients who cannot have CYC. While we recognise there is limited published randomised clinical evidence in this patient population, UK clinicians have significant experience in treating these patients who cannot receive CYC. We know that these patients have the highest unmet need, and represent a small proportion of the entire eligible patient population. Without clear national guidance for this small subgroup, we believe regional variations will dictate access to RTX for the small subgroup of patients where CYC treatment is not appropriate.	Comment noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document. 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. See final appraisal determination (FAD) section 1.1, 4.8 and 4.20–4.22.

Consultee	Comment	Response
Roche Products	We have provided a weighted average cost per QALY result for RTX in GPA and MPA. This weighted average represents the cost-effectiveness of RTX in the entire GPA and MPA licensed population and has been presented as a consequence of the precedent set in TA278. In January 2013, NICE accepted the weighted average approach in the assessment of omalizumab for severe asthma [TA278, 2013]. In doing so, the Committee was able to approve the small but extremely important subgroup of children within the overall recommendation. Below are the weighted average estimates using the approved base case ICER of £12,100, and the assumption that 10% of patients cannot receive CYC. Expert clinical opinion was used to inform the proportion of patients unable to receive CYC. Accepting the base case ICER, in order for the weighted ICER to exceed £30,000 per QALY, the subgroup ICER would need to exceed £200,000. *[Table received but not reproduced here.]* We would ask that the Committee reconsiders the recommendation not to approve the subgroup of patients who cannot receive CYC. These patients have the highest unmet need for an effective alternative therapy.	Comment noted. The Committee considered the manufacturer's weighted-average threshold analysis. 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 weighted-average threshold analysis did not provide a suitable basis for decision-making (see FAD sections 3.75 and 4.17).
Roche Products	*Description of problem (section in ACD)* 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. *Description of proposed amendment* Add: and 15 of 16 patients (94%) achieved remission (BVAS/WG=0). *Justification for amendment* This gives a complete representation of the evidence provided by the manufacturer.	Comment noted. The evidence referred to in the proposed amendment was not included in the manufacturer's response to the first appraisal consultation document. The original text reflects the evidence received by NICE in response to the first consultation. No action required.

Consultee	Comment	Response
Roche Products	*Description of problem (section in ACD)* 3.22 The manufacturer provided information on the long-term safety of rituximab when used as a treatment for rheumatoid arthritis. *Description of proposed amendment* Change to: The manufacturer provided published data on the long-term safety of rituximab when used as a treatment for rheumatoid arthritis. *Justification for amendment* Data have been published in a peer-reviewed abstract. This is a higher grade of evidence than “the manufacturer provided information”.	Comment noted. Section 3.22 of the FAD has been amended to read, ’The manufacturer provided evidence about the long-term safety of rituximab when used as a treatment for rheumatoid arthritis.’
Roche Products	*Description of problem (section in ACD)* 3.23 The manufacturer provided evidence that women can conceive after treatment with rituximab. *Description of proposed amendment* Add: there is no evidence to show that RTX has an adverse effect on fertility. *Justification for amendment* As written, the sentence may imply that there could be an underlying issue related to use of RTX and infertility. It is important to note that there are no data to suggest that RTX has an adverse effect on fertility.	Comment noted. Section 3.23 of the FAD has been amended to read, ‘The manufacturer provided evidence that rituximab does not prevent women from conceiving children.’
Roche Products	*Description of problem (section in ACD)* 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, and although there is no consensus on a specific lifetime maximum dose of cyclophosphamide, the ERG indicated that a cumulative dose of 20–30g appears to be the range that should not be exceeded. *Description of proposed amendment* Change to clarify that there is clinical consensus on the max lifetime dose of CYC. *Justification for amendment* Direct contraindication with 3.20 which states that the 2013 draft guidelines from the British Society for Rheumatology on the management of ANCA-associated vasculitis states a maximum cumulative dose of 25g of CYC.	Comment noted. The reference to the maximum dose of cyclophosphamide has been removed from section 3.25 of the FAD.

Consultee	Comment	Response
Roche Products	*Description of problem (section in ACD)* 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* at 6 and 12-month follow-up, but at 18 months the difference in remission rates was not statistically significant. *Description of proposed amendment* Consider adding: “superior to cyclophosphamide followed by azathioprine” *Justification for amendment* For long-term efficacy endpoints, it is important to remember that it is a comparison of a single course of rituximab with conventional immunosuppression with cyclophosphamide followed by azathioprine.	Comment noted. Section 3.28 of the FAD has been amended accordingly.
Roche Products	*Description of problem (section in ACD)* 3.29 Based on the published 18-month results from RAVE (Specks et al. 2013) the ERG suggested that, for patients in RAVE who had not had treatment before, the rate of severe relapse at 18 months may have been higher in the rituximab group than in the cyclophosphamide group. The ERG could not be certain because these data were not included in the manufacturer’s response to consultation or in the published study results. *Description of proposed amendment* Consider removing this statement as no data are available. *Justification for amendment* Data are not available, so this is speculation and not an evidence based consensus.	Comment noted. This section has been removed from the FAD.

Consultee	Comment	Response
Roche Products	*Description of problem (section in ACD)* 3.70 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. *Description of proposed amendment* Consider adding: Additional QALYs remain unaccounted for within the analyses. *Justification for amendment* Patients wishing to preserve their fertility may indeed receive mycophenolate as an alternative; the ERG is right in this instance that no additional QALYs need to be accounted for. However, a proportion of patients wishing to start a family will make the difficult decision to treat their disease with the most effective induction agent available today, CYC. Therefore, it is reasonable to consider that within the 'base case analysis' a proportion of patients forgo the opportunity of having children as a result of the adverse effect of CYC. This detrimental effect is not captured in any analysis.	Section 3.70 (which has been moved to section 3.69 in the FAD) reports the ERG's independent review of the manufacturer's response to consultation and so does not need to be amended. Section 4.21 summarises comments from Roche Products regarding the additional QALYs which remain unaccounted for within the analyses: '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.' No action required.
Roche Products	*Description of problem (section in ACD)* 4.9 The Committee concluded that the safety profile of rituximab compared with cyclophosphamide seemed broadly similar in the short term and that some women maintain fertility after treatment with rituximab. *Description of proposed amendment* Re-write: data have not shown there to be any apparent fertility issues in women after treatment with RTX. *Justification for amendment* The sentence is misleading as it implies that most women lose fertility after treatment with RTX.	Comment noted. Section 4.9 has been amended to: '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.'
Roche Products	*Description of problem (section in ACD)* 4.22 The Committee noted that there was only limited evidence showing rituximab does not affect fertility. *Description of proposed amendment* Change: "there is no evidence to show that RTX has an adverse effect on fertility". *Justification for amendment* It is important to note that there are no data to suggest that RTX has an adverse effect on fertility.	Comment noted. The relevant sentence has been amended and moved to section 4.21.

Consultee	Comment	Response
Roche Products	*Are the provisional recommendations sound and a suitable basis for guidance to the NHS?* We believe the provisional recommendation is a suitable basis for guidance within the NHS, however, as outlined in section II of our response, we believe there is an opportunity to reconsider the subgroup of patients with the highest unmet need should the Committee utilise the approach taken in TA278. We know that this group will have a minor impact on the cost of implementing this guidance within the NHS.	Comment noted. The Committee considered all the consultation comments and concluded that rituximab could be recommended for people who cannot have cyclophosphamide (see FAD section 1.1).
Roche Products	*Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?* No.	Comment noted. No action required.
A joint response was received from several organisations and individuals. The contributors are listed at the end of this table.	This is a response on behalf of representatives of a consortium of professional organisations and vasculitis experts (Appendix). It includes comments on the NICE appraisal (referenced by section number). **Summary** • The introduction of rituximab has been 'scene changing' in the management of ANCA associated vasculitis, of major benefit to patients, and it is re-shaping approaches to AAV therapy. Rituximab is currently indicated for relapsing or refractory disease and when cyclophosphamide is contra-indicated and has been routinely used for these indications in expert centres since 2005. • There is a high level of consensus among vasculitis physicians concerning patient subgrouping, the treatment pathway and the current indications for rituximab, reflected by the 2013 BSR management guidelines for AAV and the 2013 NHS England Clinical Commissioning Policy. • Improving AAV patient outcomes by cyclophosphamide avoidance has been a focus of AAV clinical researchers for two decades. Rituximab achieves both of these goals. • This response represents the views of a consortium of six professional organisations and the majority of expert vasculitis physicians within the UK. • The provisional recommendation is not sound, would change current best practice, and is not a suitable guidance for the NHS.	Comment noted. The Committee considered the consultation comments and concluded that rituximab could be recommended for people who cannot have cyclophosphamide (see FAD sections 1.1, 4.8, and 4.20–4.22).

Consultee	Comment	Response
Joint response	**Introduction** Expert clinical opinion is pleased to note that there has been a change in the preliminary recommendations for the use of rituximab in ANCA-associated vasculitis (AAV) following consultation. However, NICE now recommend use of rituximab for patients with AAV once the maximum cumulative cyclophosphamide dose is exceeded and for those patient currently receiving cyclophosphamide, who are intolerant of cyclophosphamide or resistant to therapy, may continue to receive it. NICE has decided not to support the use of rituximab as primary therapy for those patients where cyclophosphamide should be avoided. These recommendations as stated differ from expert use of rituximab in current NHS practice.	Comment noted. The Committee considered the consultation comments and concluded that rituximab could be recommended for people who cannot have cyclophosphamide (see FAD sections 1.1, 4.8, and 4.20–4.22).
Joint response	Rituximab was originally introduced for the treatment of patients with refractory AAV or those patients where cyclophosphamide should be avoided, with the first case report of use published in 2001. Since then use has increased with over 160 publications in the literature and 700 patients treated. Data, collected from experts in the treatment of AAV in the UK, suggests that approximately 20% of patients have received rituximab, such that it is now part of routine practice in restricted circumstances as recommended by the 2011 UK consensus statement for use of rituximab in AAV.	Comment noted. No action required.

Consultee	Comment	Response
Joint response	This has been recognised by NHS England (the commissioner of care for these patients), as reflected in Clinical Commissioning Policy (A13/p/a) which indicates that Rituximab is commissioned for us in AAV for 1) those patients with relapsing disease, 2) with primary treatment failure or with 3) adverse reactions or contra-indications to cyclophosphamide, which reflects the consensus statement on use of rituximab in AAV published in 2011 (Guerry 2011 Rheum). As outlined in the Policy, NHS England considered the place of rituximab in current clinical practice, whether research supported benefit for patients and whether its use represented best use of NHS resources, for the small numbers of patients (estimated in the policy as only 20-25 patients in each region per annum) who will require treatment with rituximab. The BSR guidelines for treatment of AAV have adopted a similar position. BSR guidelines recommend use of RTX for remission induction of AAV in *de novo* patients for whom CYC is indicated but its avoidance is desirable where: (1) Fertility preservation required (a) There is no time for egg harvesting due to the fulminant nature of vasculitis (b) Male fertility is also affected by cyclophosphamide (2) Severe infection, including infection requiring hospitalization, and chronic infections, such as, tuberculosis, bronchiectasis; and opportunistic infection (3) Uro-epithelial malignancy or dysplasia (4) Cytopaenia/bone marrow insufficiency (5) CYC allergy/intolerance Expert clinical opinion urges NICE to recommend use of rituximab that is in line with both current clinical consensus, national Specialist Society guidelines [1](BSR 2013) and current NHS England Commissioning Policy.	Comment noted. The Committee considered the consultation comments and concluded that rituximab could be recommended for people who cannot have cyclophosphamide (see FAD sections 1.1, 4.8, and 4.20–4.22).

Consultee	Comment	Response
Joint response	**Key conclusion** *1. The NICE recommendation is for rituximab only to be used in those patients who have exceeded the maximum recommended dose of cyclophosphamide and that a treatment sequence of 2 courses of cyclophosphamide should be received before use of rituximab (1.1, 4-17-4.19).* This was based on the most plausible ICER of £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. Despite the BSR guidelines stating that cyclophosphamide use should not exceed 25g, there is no evidence for 25g of cyclophosphamide as a safe limit. It is acknowledged there is a continuum of toxicity associated with cyclophosphamide usage with no evidence for a safe minimum dose. The BSR guideline of a lifetime exposure to cyclophosphamide of 25g is based on level C evidence[1]. Recent publications support the view of no minimum safe limit. Malignancy rates in patients recruited to the European Vasculitis Study Group clinical trials, where the median dose of cyclophosphamide was <20g and reflects current CYC usage, are increased with a standardised incidence ratio of 1.6 at five years[2]. This study had a median follow up of 5 years and is likely to have under-estimated the risk of malignancy, especially bladder cancer that has reported latency periods of up to 15-19 years following cyclophosphamide treatment. A further study based on 467 patients with detailed information on cumulative cyclophosphamide dosing suggested a significant increased risk of bladder cancer for every 10g incremental dose of cyclophosphamide, contributing to the argument that 25g cyclophosphamide is not a safe and that further reductions in exposure below current 'maximum' levels are desirable. Further arguments to reduce current cyclophosphamide exposure are provided by evidence that there may also be an increased risk of malignancy *per se* in patients with Granulomatosis with polyangiitis[3, 4]. Expert clinical opinion is agreed that one course of cyclophosphamide (maximum 10 pulses over 6 months at 15mg/kg dependent on age and renal function) would be the treatment sequence and best reflects current routine practice.	Comment noted. The views of clinical specialists were considered by the Appraisal Committee when formulating its recommendations. Sections 4.2 and 4.19 of the FAD describe the Committee's discussion of the maximum cumulative dose of cyclophosphamide. No action required.

Consultee	Comment	Response
Joint response	**Key conclusion** *[continued]* *2. The Committee have concluded that there is no evidence to support the use of rituximab in the small group of patients that should avoid cyclophosphamide as primary therapy (4.2, 4.8, 4.21).* *Clinical experts note that although the small group of patients that should avoid cyclophosphamide have been excluded from clinical trials, there is substantial evidence from case series* that rituximab is as effective in those individuals where cyclophosphamide should be avoided (e.g. [5]) (4.8). Clinical experts would support development of a database to report the outcome of rituximab use in AAV patients. Expert clinical opinion considers that the model proposed comparing use of methotrexate or mycophenolate as alternative induction agents for those that cannot have cyclophosphamide is not appropriate. The BSR guidelines suggest these agents should only be used for induction therapy where there is no organ threatening disease. Within current practice rituximab has replaced the use of other alternative immunosuppressant agents for those where cyclophosphamide should be avoided and is welcomed by patients and clinicians[1] (4.1-4.3).	Comment noted. The Committee considered the consultation comments and concluded that rituximab could be recommended for people who cannot have cyclophosphamide (see FAD sections 1.1, 4.8, and 4.20–4.22).

Consultee	Comment	Response
Joint response	**The technology** *The committee have concluded that there was limited evidence showing rituximab did not affect fertility and that it did not consider rituximab to be a step change in managing AAV (2.1, 4.22, 4.9).* Clinical experts disagree with this conclusion. The introduction of rituximab has been scene changing in the management of AAV and the most significant advance in patient care since the introduction of cyclophosphamide in the 1970s. It has proved a reliable treatment for those failing standard of care, an alternative to those in whom cyclophosphamide avoidance is desirable and is reshaping approaches to disease management. There is data on long-term safety and efficacy of RTX from several studies in a wide range of patients with connective tissue disease, idiopathic thrombocytopenia and lymphoma. The malignancy risk has been examined in rheumatoid arthritis, an inflammatory autoimmune disease with similarities to AAV, and is low[6, 7]. There is emerging data on rituximab use in and before pregnancy from rheumatoid arthritis, SLE and AAV[8, 9]. The rituximab global drug safety database reports 231 pregnancies associated with maternal rituximab exposure, of those pregnancies with known outcomes no safety signal was identified[8]. The long-term infective risk of rituximab appears low in rheumatoid arthritis, and it has been preferred to cyclophosphamide in AAV in the presence of severe infection[6, 10, 11].	Comment noted. Section 4.21 of the FAD has been amended to: '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.'

Consultee	Comment	Response
Joint response	**Evidence for clinical effectiveness** Evidence from the RAVE trial suggests that at 6 months patients who have a relapsing course are more likely to benefit from rituximab as induction therapy compared with cyclophosphamide. RAVE is an induction remission trial and its aim was to investigate short-term outcomes not long term maintenance of remission. None of the patients in the rituximab limb received maintenance therapy. The analysis at 18 months was a secondary end-point and should be viewed as hypothesis generating (4.7). Routine practice within the UK currently utilises rituximab for patients who relapse their disease and where cyclophosphamide avoidance is preferred. Clinical experts agree there are substantial uncertainties within the economic modelling. The model used to generate the ICER is questioned by clinical experts. There is concern about the plausibility of the utility values placed on the remission and non-remission health states. The costs for the long-term toxicities of cyclophosphamide are not included. Short-term costs acquired from University Hospitals Birmingham and Addenbrookes Hospital have estimated that a cycle of 2g rituximab compared with a course of cyclophosphamide (10 pulses) is equivalent. The ICER quote a cycle of cyclophosphamide, which includes 10 infusions, as £1802. This significantly underestimates NHS treatment costs.	Comment noted. The FAD recommends rituximab for people who cannot have cyclophosphamide, including those with disease that has remained active or progressed despite a course of cyclophosphamide lasting 3–6 months. See sections 1.1, 4.8, and 4.20–4.22. The summary of product characteristics for rituximab states that the recommended dosage for treating granulomatosis with polyangiitis and microscopic polyangiitis is 375 mg/m^2 body surface area, administered intravenously once weekly for 4 weeks (4 infusions in total). The NICE Guide to the methods of technology appraisal (2013) states, 'The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer's summary of product characteristics' (section 6.1.12). Therefore, consideration of a 2 g dose of rituximab is outside the scope of the appraisal. No action required.
Royal College of Physicians	The RCP has had sight of the [*joint response*] submitted from a consortium of professional organisations and vasculitis experts. We wish to endorse the comments made.	Comment noted. No action required.

Consultee	Comment	Response
Vasculitis UK	1) Vasculitis UK is the only UK national patient support charity which supports and represents those suffering from **all** types of vasculitis. 2) As a patient group, we do understand that NICE has an obligation to ensure that the treatment regimes which it approves are both effective and cost effective, representing Best Value for Money. In this context, it is inappropriate for a more costly regime to replace a cheaper one without there being significant demonstrable additional benefit. We consider that the relative benefits of the use of rituximab in treating AAV, as an alternative to cyclophosphamide, can be very well demonstrated, especially when **all** the socio-economic factors are taken into consideration and that in most cases the additional cost is easily justified.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, the views of patient experts and clinical specialists, the manufacturers' submissions, and the ERG's reports. It also carefully considered the comments received from consultees and commentators in response to consultation. No action required.
Vasculitis UK	3) We welcome the fact that in this second ACD, NICE are now minded to approve the use of rituximab in treating major relapse after exposure to a second course of cyclophosphamide. However we consider that this reconsidered conclusion does not go far enough and will leave certain groups of patients seriously disadvantaged.	Comment noted. The Committee considered the consultation comments and concluded that rituximab could be recommended for people who cannot have cyclophosphamide (see FAD sections 1.1, 4.8, and 4.20–4.22).
Vasculitis UK	4) We are also mindful that earlier this year, Vasculitis UK made a similar submission to the Scottish Medicines Consortium to assist their deliberations on the use of rituximab for treating ANCA vasculitis. The SMC final decision was more pragmatic than the current position adopted by NICE – we would consider more realistic – and it addresses the issues described below. If this divergence between NICE and SMC persists, there will be a cross-border tension reminiscent of the "postcode lottery".	Comment noted. The Committee considered the consultation comments and concluded that rituximab could be recommended for people who cannot have cyclophosphamide (see FAD sections 1.1, 4.8, and 4.20–4.22).
Vasculitis UK	5) We consider that, following the development of rituximab, its off-label use for treating ANCA (and other types) of vasculitis has convincingly demonstrated it to be at least as effective as the only other proven reliable induction medication, cyclophosphamide, albeit without most of the serious side effects associated with such a potent cytotoxic drug.	Comment noted. No action required.

Consultee	Comment	Response
Vasculitis UK	6) We consider it to be a step change as this is a targeted drug with a very different pharmacological action to cyclophosphamide and other less potent immune suppressing drugs (mycophenolate, methotrexate, azathioprine).	Comment noted. Section 4.21 of the FAD has been amended to: '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.'

Consultee	Comment	Response
Vasculitis UK	7) We consider that as rituximab is now licensed for the treatment of ANCA vasculitis, failure to make it available for certain categories of patients listed below, who are in the care of the NHS and who suffer disability due to their ANCA vasculitis will represent an **inequality** and constitute **discrimination** against them. 8) The categories of patients are listed below:- a) Patients who have been given a full maximum cycle of 10-12 pulses without evidence of remission. In these cases there is no reason to expect a further cycle of cyclophosphamide would improve the outcome, whereas rituximab is shown to be highly effective in these cases. b) Patients with pre-existing endothelial conditions where exposure to the toxic excretory metabolites of cyclophosphamide will increase the probability of developing carcinoma of the endothelial lining of ureter, bladder or urethra.. c) Patients with infections where the use of cyclophosphamide is contra-indicated. d) Patients who are intolerant to, or show adverse reaction to cyclophosphamide or to mesna (used to reduce endothelial toxicity). e) Young adult females who may be unnecessarily rendered infertile or brought into a state of premature menopause through exposure to cyclophosphamide. f) Young adult males whose fertility and potency may similarly be affected. g) ANCA vasculitis does affect children as young as five, occasionally younger. This group have a lifetime risk of recurrent relapse, involving retreatment and of the long term effects associated with cyclophosphamide exposure. h) Pubertal and post-pubertal adolescents are believed to be at particularly high risk of infertility due to cyclophosphamide exposure. For this group, cyclophosphamide should certainly be the exception rather than the rule. i) For a very small refractory group who suffer recurrent relapse despite conventional maintenance therapy, rituximab administered as a single dose at fixed intervals has proved to be a highly effective maintenance regime.	Comment noted. The Committee did not agree that the groups specified in this response to consultation were people with the protected characteristics covered by the equality legislation. However, the Committee considered the consultation comments and concluded that rituximab could be recommended for people who cannot have cyclophosphamide (see FAD sections 1.1, 4.8, and 4.20–4.22). Consultees suggested that children and adolescents should be included in the population. The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the summary of product characteristics. Therefore, this is not an equality issue that falls within the remit of a NICE technology appraisal (see FAD section 4.26).
Vasculitis UK	9) <u>As ANCA vasculitis is a rare disease affecting **mainly** those aged 40+ and these categories listed above are exceptions, the total numbers of individuals in these categories is relatively small, consequently the total increased cost to the NHS of treating them with rituximab is correspondingly relatively small.</u>	Comment noted. The NICE guide to the methods of technology appraisal (2013) states, “The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision” (section 6.2.14). No action required.

Consultee	Comment	Response
Vasculitis UK	10) We most certainly consider that failure to include these categories of patients in any restricted list of applications that NICE might be minded to approve for initial induction, in new cases or relapsing cases , would be an unconscionable and grave omission. At the very least, at the point where informed patient consent is being sought, there should be **an informed c**hoice between cyclophosphamide and rituximab for those whose fertility is at risk.	Comment noted. No action required.
Vasculitis UK	11) We understand that the deterministic concept of a "safe" limit of 25gms for exposure to cyclophosphamide is not firmly evidence based and that the stochastic effect of exposure to the metabolites of cytotoxic drugs can induce somatic mutation leading to cancer. This increases with the level of exposure, but no level can be considered "safe".	Comment noted. The views of patient experts were considered by the Appraisal Committee when formulating its recommendations. Sections 4.2 and 4.19 of the FAD describe the Committee's discussion of the maximum cumulative dose of cyclophosphamide. No action required.
Vasculitis UK	12) Despite the published AAV treatment guidelines , which advocate induction using pulsed intravenous infusions, many patients have been and continue to be treated with oral cyclophosphamide which results in exposure to very much higher cumulative doses of cyclophoshamide. This does not seem to have been addressed in the context of "2 full cycles of cyclophosphamide" stated in the current ACD.	Comment noted. The views of patient experts were considered by the Appraisal Committee when formulating its recommendations. Section 1.1 recommends rituximab only if further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose. Sections 4.2 and 4.19 explain that draft guidelines from the British Society for Rheumatology state the maximum cumulative cyclophosphamide dose is 25 g. If a person has received oral cyclophosphamide and further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose, then treatment with rituximab is recommended in section 1.1 of the FAD. No action required.
Vasculitis UK	13) The committee does not appear to have taken note of the strong evidence that when used for a second round of induction, cyclophosphamide is significantly less effective for inducing remission.	Comment noted. The economic models submitted by the manufacturer, which were used for the ERG's exploratory analyses, used remission rates from the RAVE trial. The models used a lower remission rate for the second course of cyclophosphamide than the first course of cyclophosphamide (see page 55 of the ERG's original report). No action required.

Consultee	Comment	Response
Vasculitis UK	14) We accept that, for most patients other than those in the categories listed above, pulsed IV cyclophosphamide is an effective and slightly cheaper agent than rituximab for initial induction remission in new cases.	Comment noted. No action required.
Vasculitis UK	15) However we noted at the first appraisal that the treatment regime for rituximab which was quoted in the manufacturer's submission was at odds with that which we know to be practised in the UK. We understand that when this is taken into account, the additional cost of administering a full course of rituximab (usually 2-4 infusions) relative to a full course of cyclophosphamide (7-10 infusions) is significantly reduced from those figures used in the health economic studies, thus distorting the ICER result. Thus, inclusive of drug and administration costs, the true difference between the overall cost of rituximab and cyclophosphamide is not as great as has been represented.	Comment noted. The NICE guide to the methods of technology appraisal (2013) states, "The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer's summary of product characteristics" (section 6.1.12). No action required.
Vasculitis UK	16) With all rare diseases, it is very difficult to produce evidence based on adequate sizes of cohort to be statistically significant. Unlike more common diseases, such as cancer or vascular disease, there is little in the way of coherent collection of data and statistics, making it impossible to produce some of the evidence demanded by NICE.	Comment noted. The NICE guide to the methods of technology appraisal (2013) states, "the Committee is aware that the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases" (section 6.2.16). No action required.
Vasculitis UK	17) With the inception of the new NHS Commissioning process involving Specialised Clinical Reference Groups and the development of new rare disease registries,such as that for vasculitis (which is funded by this charity), these data will soon be increasingly available, so the true value of expensive new biological drugs will be more readily assessed.	Comment noted. No action required.

Consultee	Comment	Response
Vasculitis UK	18) As a fundamental issue, we consider the concept and use of QUALYS to be inappropriate, simplistic, narrowly focussed and a flawed measurement in diseases such as AAV which may not be curable but can usually be effectively controlled with appropriate treatment and brought into full long-term remission. As we understand, QUALYS fail to take into account the full socio-economic impact of induction failure or relapse. Patients with AAV may be in early or middle stages of life and effective treatment routinely enables them to continue with a normal working and personal life. Conversely, repeated relapse with associated cumulative organ damage renders them unable to work, dependant on social welfare, requiring ongoing medical and community care, with a consequent substantial cost to the both the NHS and national economy. When all this is taken into account, the case for the use of rituximab as the treatment of choice for all cases of relapse and for maintenance in selected cases is very strong.	Comment noted. The NICE Guide to the methods of technology appraisal stipulates that, in the reference case, the health effects of treatments should be expressed in terms of quality-adjusted life years (QALYs). If the assumptions that underlie the QALY are inappropriate in a particular case, then evidence to this effect should be produced and analyses using alternative measures may be presented as an additional non-reference-case analysis. During this appraisal, the manufacturer did not present non-reference-case analyses using alternative measures of health effects. See sections 5.1.11 and 5.1.12 of the Guide to the methods of technology appraisal. The reference case stipulates that the perspective on costs should be that of the NHS and personal and social services. If the inclusion of a wider set of costs is expected to influence the results significantly, such an analysis should be presented in addition to the reference case analysis. Productivity costs are not included in either the reference-case or non-reference-case analyses. During this appraisal, the manufacturer did not present non-reference-case analyses using a wider set of costs. See sections 5.1.7 to 5.1.10 of the Guide to the methods of technology appraisal. No action required.
Vasculitis UK	19) As a further fundamental consideration, we consider it unfortunate that the NICE STA process for a new drug is largely driven by an application made by the manufacturer of that drug, rather than by the clinicians who have gained experience in use of the drug. This tends to make the NICE appraisal process into an adversarial process rather than an inquisitorial one, which one might consider more appropriate for healthcare considerations. In the case of this appraisal, the motivation for the manufacturer is not great as the potential market for treating AAV is not large, especially in comparison to that for other applications for this drug.	Comment noted. No action required.

Consultee	Comment	Response
Vasculitis UK	20) **In conclusion:** we consider the introduction of rituximab to be a step change in the treatment of ANCA vasculitis. As a targeted, "biological", manufactured, monoclonal antibody it is a fore-runner of a rising generation of similar tailored antibodies. Failure to give adequate market access for innovative use of existing drugs or of new drugs for treating rare diseases such as AAV provides a strong disincentive for manufacturers to develop other such drugs, or to support new uses for existing drugs, in the future.	Comment noted. Section 4.21 of the FAD has been amended to: '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.'
Vasculitis UK	21) Rituximab has now been used in the treatment of ANCA vasculitis for over 8 years, with great success. Its use has been enshrined in recommendations by NHS England and its use is core to the newly revised British Society of Rheumatologists' "Guidelines for the Treatment of Adult ANCA Vasculitis". Severely restricting access to this new drug will most certainly be viewed by those with vasculitis as a retrograde step.	Comment noted. No action required.
Vasculitis UK	*[A list of trustees was received but is not reproduced here.]* *[A list of approximately 850 signatories was received but is not reproduced here.]*	Comment noted. No action required.

The joint response was submitted by: Arthritis Research UK, British Association for Paediatric Nephrology, British Society for Paediatric and Adolescent Rheumatology, British Society for Rheumatology, NHS England, Vasculitis Rare Disease Working Group of the UK and Ireland (UKVas), Renal Association, Royal College of Nursing, Professor Lorraine Harper - clinical expert nominated by Renal Association, Dr Peter Lanyon - clinical expert nominated by the British Society for Rheumatology, Dr Richard Watts - clinical expert nominated by Vasculitis Rare Disease Working Group of the UK and Ireland (UKVas).

A "no comment" response was received from the Department of Health and the British Association of Dermatologists.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
	The clinical specialists were signatories of the joint response.	
	The patient experts were signatories of the response from Vasculitis UK.	

Comments received from commentators

Commentator	Comment	Response
	Some commentators were signatories of the joint response.	

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professionals 1	Not applicable	On behalf of the consultants in the multidisciplinary vasculitis clinic at [redacted], I am writing to add our unanimous support to the case for the use of Rituximab as primary therapy in patients with ANCA-associated vasculitis. Without doubt, Rituximab has been a step change in the management of AAV, and we are incredulous that the NICE panel might suggest otherwise. We have a large clinic and see approximately 20 new cases of active AAV per year, with over 250 patients under active follow up. We frequently use Rituximab as first line management of AAV (new diagnoses and relapses), and have given 153 courses of treatment to 110 patients between December 2004 and January 2013. Rituximab has been demonstrated to be more effective than cyclophosphamide for inducing remission in relapsing patients. We have extensive experience of the complications of cyclophosphamide including the long term risks of malignancy (especially bladder and haematological), which are well documented but may not always be captured by clinical trial results where follow up is short. We do not believe that there is a 'safe' dose of cyclophosphamide and seek to minimize its use wherever possible. In addition, ANCA vasculitis affects patients of all ages including patients of childbearing age, and the impact of infertility and the costs of management of infertility in patients should not be underestimated. For these reasons, we have been using Rituximab first line to manage our patients with ANCA vasculitis, and any change to this would adversely affect our ability to give optimum treatment to our patients, which we strongly oppose. Yours sincerely Vasculitis specialists working in the [redacted] clinic: *[Names received but not reproduced here.]*	Section 4.21 of the FAD has been amended to: '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.' The FAD recommends rituximab for people who cannot have cyclophosphamide (see FAD sections 1.1).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional 2	Section 1 (preliminary recommendations)	Clinical experts disagree with this conclusion. The introduction of rituximab has proved a reliable treatment for those failing standard of care, an alternative to those in whom cyclophosphamide avoidance is desirable and is reshaping approaches to disease management. Â There is data on long-term safety and efficacy of RTX from several studies in a wide range of patients with connective tissue disease, idiopathic thrombocytopenia and lymphoma. The malignancy risk has been examined in rheumatoid arthritis, an inflammatory autoimmune disease with similarities to AAV, and is low[6, 7]. There is emerging data on rituximab use in and before pregnancy from rheumatoid arthritis, SLE and AAV[8, 9]. The rituximab global drug safety database reports 231 pregnancies associated with maternal rituximab exposure, of those pregnancies with known outcomes no safety signal was identified[8]. The long-term infective risk of rituximab appears low in rheumatoid arthritis, and it has been preferred to cyclophosphamide in AAV in the presence of severe infection	Comment noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document. 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. See final appraisal determination (FAD) section 1.1, 4.8 and 4.20–4.22.

Role*	Section	Comment	Response
NHS Professional 2	Section 5 (Implementation)	Clinical experts agree there are substantial uncertainties within the economic modelling. The model used to generate the ICER is questioned by clinical experts. There is concern about the plausibility of the utility values placed on the remission and non-remission health states. The costs for the long-term toxicities of cyclophosphamide are not included.	Comment noted. Sections 4.12–4.22 of the FAD discuss the Committee's interpretation of the sources of uncertainty within the economic model. No action required.
		Short-term costs acquired from University Hospitals Birmingham and Addenbrookes Hospital have estimated that a cycle of 2g rituximab compared with a course of cyclophosphamide (10 pulses) is equivalent. The ICER quote a cycle of cyclophosphamide, which includes 10 infusions, as Â£1802. This significantly underestimates NHS treatment costs.	Comment noted. The summary of product characteristics for rituximab states that the recommended dosage for treating granulomatosis with polyangiitis and microscopic polyangiitis is 375 mg/m^2 body surface area, administered intravenously once weekly for 4 weeks (4 infusions in total). The NICE Guide to the methods of technology appraisal (2013) states, 'The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer's summary of product characteristics' (section 6.1.12). Therefore, consideration of a 2 g dose of rituximab is outside the scope of the appraisal. No action required.