National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)
Rituximab in combination with corticosteroids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Arthritis Research UK	Appropriate. ANCA vasculitis (AAV) has a high unmet need for newer therapies. Rituximab is an effective newer therapy addressing some of the unmet need.	Comment noted. No action needed.
	British Renal Society	Yes. In fact, there are various local commissioning policies exist already (Cambridgeshire, East Lancashire , Derbyshire etc)	Comment noted. No action needed.
	British Society for Rheumatology	Yes	Comment noted. No action needed.
	CSAS	The topic is appropriate for consideration.	Comment noted. No action needed.
	NHS Bournemouth and Poole and NHS Dorset Cluster	The topic is appropriate for consideration.	Comment noted. No action needed.
	Royal College of Nursing	Yes as individuals with these rare conditions are now surviving longer and we need access to alternative immunosuppressive agents.	Comment noted. No action needed.

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	The Lauren Currie Twilight Foundation	We think that this is an appropriate appraisal as there are clearly some severe cases where conventional therapies are insufficient.	Comment noted. No action needed.
	Vasculitis UK	Yes. There is a clear need for alternative drugs for treating Anca Associated Vasculitis (AAV) especially to avoid repeated use of cyclophosphamide and high dose steroids in relapsing cases.	Comment noted. No action needed.
	Roche Products Limited	AAV is a serious but rare condition. With limited treatment options available for AAV patients in the UK, we consider there to be a high need for effective alternative treatments.	Comment noted. No action needed.
Wording	Arthritis Research UK	The current unmet need is not clearly articulated. Especially relapsing/refractory disease, the high levels of permanent organ damage and drug related toxicity. Also, the absence of good quality of life or health economic data in this rare disease area.	Comment noted. No action needed.
	British Renal Society	Yes	Comment noted. No action needed.
	British Society for Rheumatology	Yes, although the wording states that the remit is "To appraise …within its licensed indication for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis. No guidance is given to commentators as to the intended licensed indication for the use of Rituximab in vasculitis, in particular dosage and frequency	Comment noted. Information on dose and frequency will be provided by the manufacturer at a later stage.
	CSAS	The wording of the draft scope is appropriate.	Comment noted. No action needed.
	NHS Bournemouth and Poole and NHS Dorset	The wording of the draft scope is appropriate.	Comment noted. No action needed.

Section	Consultees	Comments	Action
	Cluster		
	Royal College of Nursing	Yes	Comment noted. No action needed.
	The Lauren Currie Twilight Foundation	Yes, as the therapy may result in improved outcomes.	Comment noted. No action needed.
	Vasculitis UK	Yes	Comment noted. No action needed.
	Roche Products Limited	Yes	Comment noted. No action needed.
Timing Issues	Arthritis Research UK	Urgent. Rituximab is effective and life-saving.	Comment noted. No action needed.
	British Renal Society	Urgent as there are no other alternative to cyclophosphamide for induction treatment at the moment.	Comment noted. No action needed.
	British Society for Rheumatology	The 2 randomised clinical trials of Rituximab, the recent FDA licence, and the many positive case series have provided clinical support/evidence for UK clinicians who have needed to use off-licence Rituximab to treat their most difficult patients. However, NICE guidance is urgently needed to avoid the risk of inequality of access to this treatment, which potentially occurs both due to post-code access/funding according to PCT willingness to fund, and also according to clinician expertise/willingness to use an unlicensed, non-NICE approved, drug.	Comment noted. NICE will consider this issue through a technology appraisal if referred by the Department of Health.
	CSAS	The completion date for one relevant phase III randomised trial is June 2012. Only one phase III trial has published results so far. Rituximab does not currently have marketing authorisation for this indication.	Comment noted.If rituximab is referred to NICE for an appraisal, it will be timed to

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			coincide with the timing of the marketing authorisation for the indication.
	NHS Bournemouth and Poole and NHS Dorset Cluster	The completion date for one relevant phase III randomised trial is June 2012. Only one phase III trial has published results so far. Rituximab does not currently have marketing authorisation for this indication. As a PCT we have considered this through our Prescribing Forum due to a wish to use this drug for this indication locally and have agreed a local position.	Comment noted. If rituximab is referred to NICE for an appraisal, it will be timed to coincide with the timing of the marketing authorisation for the indication.
	The Lauren Currie Twilight Foundation	This is an urgent issue as the consequences of failed therapy in such severe disease are significant.	Comment noted. No action needed.
	Vasculitis UK	Urgent only insofar as difficulty in getting this drug prescribed for some patients (where it is indicated) causes distress and possible further organ damage	Comment noted. No action needed.
	Roche Products Limited	We are not aware of any specific timing issues aside from the general urgency conferred by the unmet medical need in AAV.	Comment noted. No action needed.
Additional comments on the draft remit	Arthritis Research UK	It is encouraging that NICE are looking at vasculitis which has received very little attention from DOH/NHS	Comment noted. No action needed.
	British Renal Society	Although rituximab is not currently licensed in the UK for treatment of AAV, on 19th April 2011, the US Food and Drug Administration (FDA) approved rituximab in combination with glucocorticosteroids for the treatment of Wegener's granulomatosis	Comment noted. No action needed.

Section	Consultees	Comments	Action
		and microscopic polyangiitis	

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Arthritis Research UK	Renal outcomes (20% end stage renal disease), and other outcomes are not reviewed.	Comment noted. Attendees at the scoping workshop agreed that other outcomes, including 'change in renal function' should be included in the draft scope.
	British Renal Society	Complete	Comment noted. No action needed.
	British Society for Rheumatology	There is a typing error - the correct term is Microscopic rather than Microscopical. It is complete but there will need to be a distinction between de novo presentation and relapsing/refractory disease. The draft scope might wish to consider in more detail the exact situation where RTX would be used.	Comment noted. Typographical errors were corrected. The scope has been updated to include, where evidence allows, people for whom cyclophosphamide is contraindicated.
	CSAS	For clarity in the draft scope, consider explaining MPA and GPA abbreviations in paragraph one (currently only provided in paragraph two).	Comment noted. The scope has been amended to provide a clearer description of MPA and GPA.
	NHS Bournemouth and Poole and NHS Dorset Cluster	For clarity in the draft scope, consider explaining MPA and GPA abbreviations in paragraph one (currently only provided in paragraph two).	Comment noted. The scope has been amended to provide a clearer description of MPA and GPA.
	Royal College of Nursing	In Norfolk the annual incidence of GPA was 11.3 per million and MPA 5.9 per million (Watts et al 2012).	Comment noted. The scope has been updated to include

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		Watts RA, Mooney J, Skinner J, Scott DGI, MacGregor AJ. The contrasting epidemiology of granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis. Rheumatology 2012; 51: 926-31	the UK incidence figures.
	The Lauren Currie Twilight Foundation	This appears accurate.	Comment noted. No action needed.
	Vasculitis UK	Although treatment outcomes for AAV have improved dramatically in the past 30-40 years, the one and five year survival rates for AAV compare unfavourably with those for both breast and prostate cancer. It is important to emphasise the very high rate of recurring relapse in this group of diseases which can only be controlled, not cured.	Comment noted. No action needed.
	Roche Products Limited	We do not believe that immunosuppressive agents such as methotrexate, mycophenolate, leflunomide and ciclosporin are regularly used in the UK as maintenance treatment. This statement may therefore be misleading as to what are the relevant comparators.	Comment noted. Attendees at the scoping workshop agreed that some immunosuppressive agents were used in UK clinical practice. However, there was an agreement that leflunomide and ciclosporin were not routinely used and they have been removed from the list of comparators in the draft scope.
The technology/ intervention	Arthritis Research UK	Yes	Comment noted. No action needed.
	British Renal Society	Accurate	Comment noted. No action needed.
	British Society for	Yes	Comment noted. No action

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	Rheumatology		needed.
	CSAS	The description of the intervention is accurate.	Comment noted. No action needed.
	NHS Bournemouth and Poole and NHS Dorset Cluster	The description of the intervention is accurate.	Comment noted. No action needed.
	Royal College of Nursing	Yes	Comment noted. No action needed.
	The Lauren Currie Twilight Foundation	unable to comment	Comment noted. No action needed.
	Vasculitis UK	Yes	Comment noted. No action needed.
	Roche Products Limited	Yes	Comment noted. No action needed.
Population	Arthritis Research UK	The indication for rituximab in GPA/MPA can be divided into three areas: (1) induction for new patients; (2) induction for relapsing/refractory patients; (3) remission maintenance. There is a paucity of data on Churg Strauss angiitis although this is included under the AAV category. Limited published, and more extensive unpublished data points to similar response rates in refractory disease to GPA.	Comment noted. The scope has been updated to include, where evidence allows, people for whom cyclophosphamide is contraindicated.
	British Renal Society	Yes. It would be more cost effective to target use of rituximab in whom leucopaenia is more common (e.g. elderly, patient with severe renal failure) and also in man and women in reproductive age who have not completed their	Comment noted. The scope has been updated to include, where evidence allows, people

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		family. Moreover, there is also evidence that rituximab should be used in refractory and cyclophosphamide resistant disease.	for whom cyclophosphamide is contraindicated.
	British Society for Rheumatology	The draft scope describes the treatment population as adults with "severe" forms of systemic vaculitis. This may not be entirely appropriate to restrict the treatment population to "severe" without further qualification of this term i.e. there will be individuals with very significant localised rather than systemic disease who may benefit from this intervention. Severe needs defining. Based on BVAS or alternative scoring system, life threatening, refractory, relapsing???	Comment noted. Attendees at the scoping workshop considered the definition of 'severe' to be unclear. Therefore the term 'severe' has been removed from the population.
	CSAS	The draft scope defines the population as: 'adults with severe forms of anti-neutrophil cytoplasmic antibody associated vasculitis'. However, severe disease has not been defined and it is unclear whether this is inclusive of aggressive disease (i.e. rapidly progressing disease). The National Horizon Scanning Centre states that for aggressive disease, plasmapherisis is recommended in addition to standard therapy. Consider clarifying the population definition to include those with aggressive disease. It is not clear if the therapy is to be considered for induction of remission, for maintenance therapy or for both.	Comment noted. Attendees at the scoping workshop considered the definition of 'severe' and 'aggressive' to be unclear. Therefore the term 'severe' has been removed from the population. The scope has been updated to include, where evidence allows, people for whom cyclophosphamide is contraindicated.
	NHS Bournemouth and Poole and NHS Dorset Cluster	The draft scope defines the population as: 'adults with severe forms of anti-neutrophil cytoplasmic antibody associated vasculitis'. However, severe disease has not been defined and it is unclear whether this is inclusive of aggressive disease (i.e. rapidly progressing disease). The National Horizon Scanning Centre states that for aggressive disease, plasmapherisis is recommended in addition to standard therapy. Consider clarifying the population definition to include those with aggressive disease. It is not clear if the therapy is to be considered for induction of remission, for maintenance therapy or for both.	Comment noted. Attendees at the scoping workshop considered the definition of 'severe' and 'aggressive' to be unclear. Therefore the term 'severe' has been removed from the population. The scope has been updated to include, where evidence

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		Locally we have agreed a policy to use this in patients with very severe vasculitis who have tried and failed on other treatment options where there is agreement by two consultants that this is the most appropriate option. We anticipate that the numbers of patients requiring this treatment will be very small, possibly one a year.	allows, people for whom cyclophosphamide is contraindicated.
	Royal College of Nursing	Yes	Comment noted. No action required.
	The Lauren Currie Twilight Foundation	Clarity as to the lower age range is required.	Comment noted. The population has been amended to specify 'people' rather than 'adults'. The age range of the indicated population will be informed by the marketing authorisation for rituximab.
	Vasculitis UK	AAV affects predominantly the 50+ age group, but can affect any from infancy onward. Children and females of reproductive age should be given special consideration.	Comment noted. The population has been amended to specify 'people' rather than 'adults'. The age range of the indicated population will be informed by the marketing authorisation for rituximab. The Committee will be expected to assess whether any of their decision restrict access to the technology for any people with the protected characteristics outlined in the current Equalities legislation. The fact has been noted for

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			the Committee to consider, but no changes to the scope are required.
	Roche Products Limited	The population outlined by NICE is consistent with the planned licence. We note there is considerable uncertainty within the clinical community on the definition of 'severely' active ANCA-associated vasculitis. The BSR guidelines attempt to stratify severity by whether disease is localised or systemic, but the expert opinion we have sought would suggest that this is inappropriate. We would encourage NICE to seek further expert opinion in developing its wording around the population. To our knowledge, there are no clinically relevant subgroups that can be identified.	Comment noted. Attendees at the scoping workshop considered the definition of 'severe' to be unclear. The reference to 'severe' has therefore been removed. The scope has been updated to include, where evidence allows, people for whom cyclophosphamide is contraindicated.
Comparators	Arthritis Research UK	Cyclophosphamide is the comparator for new and relapsing patients. there is no comparator for refractory patients.	Comment noted. The comparators section of the scope has been amended as follows: treatment strategies without rituximab including cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids).
	British Renal Society	The only real comparator would be oral or iv cyclophosphamide. All the other agents have not been established as induction agent for AAV (apart from MTX in mild vasculitis NORAM). Moreover, please note that in RITUXIVAS study, patients who received rituximab also received 2 doses of iv cyclophosphamide, as opposed to RAVE study where the rituximab group received no	Comment noted. The comparator section of the scope has been amended as follows: treatment strategies without rituximab including

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		cyclophosphamide	cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids).
	British Society for Rheumatology	It is important to assess the comparators according to their correct place in current treatment paradigms, as this varies according to stage of disease. There are likely to be several clinical situations where it would be appropriate for clinicians to consider using Rituximab. 1. As a remission induction agent. The current gold standard comparator is Cyclophosphamide given either orally or IV for 3-6 months. Methotrexate is an alternative comparator drug for remission induction for early systemic or localised disease, although it associated with a higher risk of relapse than Cyclophosphamide. Current evidence does not appear to provide evidence of superiority of Rituximab compared to Cyclophosphamide. However, Rituximab would be preferred in those situations where there is a relative contraindication to the use of Cyclophosphamide. These would include previous uroepithelial malignancy, previous Cyclophosphamide use, pre-menopausal females who have not completed family. At the moment RTX has not replaced CYC as the agent of choice for remission induction as no clear benefit over CYC has not been established and the long term optimal treatment strategy i.e. timing and duration of retreatment has yet to be determined. 2. As a remission induction agent for refractory disease i.e which has remained active despite an adequate trial of Cyclophosphamide and steroids. This is a clinical situation which comprises many of the individual case series of Rituximab use. The comparators in this situation are likely to include Plasma Exchange, continued higher dose Cyclophosphamide or progression to renal replacement therapy. 3. As a remission maintenance agent. Clinicians are likely to wish to use Rituximab has been needed to induce remission and the disease has been	Comment noted. The comparator section of the scope has been amended as follows: treatment strategies without rituximab including cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids). The scope has also been amended to include, where evidence allows, people for whom cyclophosphamide is contraindicated..

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		characterised by previous relapses on alternative maintenance agents, or where the risk of relapse also includes (known from previous relapses) a risk of threatened organ damage, or where alternative remission maintenance agents have not been tolerated due to toxicity. The most likely used comparators in this setting would be Azathioprine, Methotrexate (if no renal disease) and Mycophenolate Mofetil 4. As a remission induction agent at time of first relapse. There is evidence from the RAVE trial that Rituximab is more effective than Cyclophosphamide (the main comparator in this setting) and also avoids the cumulative risk of further Cyclophosphamide exposure.	
	CSAS	Consider adding plasmapherisis (in combination with cyclophosphamide and corticosteroids) as an additional comparator for aggressive forms of the disease. The National Horizon Scanning Centre state that immunosuppressive agents (listed as comparators in the draft scope: azathioprine, methotrexate, leflunomide, mycophenolate and ciclosporin) are all used primarily as maintenance therapy. If the population remains as 'all' adults with severe forms of anti-neutrophil cytoplasmic antibody associated vasculitis, consider splitting the comparators into those relevant for induction and those relevant for maintenance.	Comment noted. The comparator section of the scope has been amended as follows: treatment strategies without rituximab including cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids). Plasma exchange was not considered a relevant comparator by workshop attendees.
	NHS Bournemouth and Poole and NHS Dorset Cluster	Consider adding plasmapherisis (in combination with cyclophosphamide and corticosteroids) as an additional comparator for aggressive forms of the disease. The National Horizon Scanning Centre state that immunosuppressive agents (listed as comparators in the draft scope: azathioprine, methotrexate, leflunomide, mycophenolate and ciclosporin) are all used primarily as maintenance therapy. If the population remains as 'all' adults with severe forms	Comment noted. The comparator section of the scope has been amended as follows: treatment strategies without rituximab including cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in

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		of anti-neutrophil cytoplasmic antibody associated vasculitis, consider splitting the comparators into those relevant for induction and those relevant for maintenance.	combination with corticosteroids). Plasma exchange was not considered a relevant comparator by workshop attendees.
	Royal College of Nursing	Yes, but no mention of plasma exchange	Comment noted. The comparator section of the scope has been amended as follows: treatment strategies without rituximab including cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids). Plasma exchange was not considered a relevant comparator by workshop attendees.
	The Lauren Currie Twilight Foundation	unable to comment	Comment noted. No action required.
	Vasculitis UK	To my knowledge, the use of leflunomide and ciclosporin is not mainstream treatment.	Comment noted. Attendees at the scoping workshop did not consider leflunomide and ciclosporin to be in routine use and therefore they have been removed. The comparator section of the scope has been amended as follows: treatment strategies without rituximab

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			including cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids).
	Roche Products Limited	Comparator treatments should be stratified according to whether they are administered to: • induce remission or treat disease flares • maintain remission **Regarding induction of remission and treatment of disease flare:** we consider the most relevant comparator to be cyclophosphamide. We have observed that some centres may replace cyclophosphamide when it is considered inappropriate with methotrexate, mycophenolate mofetil or leflunomide, albeit relatively infrequently. **Regarding maintenance of remission**: we consider the most relevant maintenance treatment comparator to be azathioprine.	Comment noted. The comparator section of the scope has been amended as follows: treatment strategies without rituximab including cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids).
Outcomes	Arthritis Research UK	Yes	Comment noted. No action required.
	British Renal Society	Yes and should include mortality and renal survival (these are standard outcome in long term follow up studies).	Comment noted. The outcomes have been amended to include mortality, remission rate and duration of remission, number and severity of relapses, change in renal function, cumulative dose of immunosuppressants, adverse effects of treatment,

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			and health-related quality of life.
	British Society for Rheumatology	1. Remission rate: Yes, although it would be important to document remission according to a validated assessment tool e.g. BVAS. Time to remission is also important 2. Number and severity of relapses. Yes, but also important to include time to relapse i.e. disease-free interval. 3. Adverse effects of treatment: Yes, suggest also include surrogate measures if appropriate (e.g. leucopenia) and cumulative steroid dose. 4. Health-related quality of life. Yes	Comment noted. The outcomes have been amended to include mortality, remission rate and duration of remission, number and severity of relapses, change in renal function, cumulative dose of immunosuppressants , adverse effects of treatment, and health-related quality of life. Particular indices are not specified in the scope.
	CSAS	The outcomes are appropriate	Comment noted. No action required.
	NHS Bournemouth and Poole and NHS Dorset Cluster	The outcomes are appropriate	Comment noted. No action required.
	Royal College of Nursing	Consider using the BVAS as an outcome measure	Comment noted. Particular indices are not specified in the scope.
	The Lauren Currie Twilight Foundation	Survival rate on treatment should be included.	Comment noted. The outcomes have been amended to include mortality, remission rate and duration of remission, number and

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			severity of relapses, change in renal function, cumulative dose of immunosuppressants, adverse effects of treatment, and health-related quality of life.
	Vasculitis UK	Yes	Comment noted. No action required.
	Roche Products Limited	We agree with the outcome measures suggested by NICE.	Comment noted. No action required.
Economic analysis	Arthritis Research UK	3-5 years	Comment noted. No action required.
	British Society for Rheumatology	This is important - many clinicians use IV CYC and not oral (see CYCLOPS trial). Most IV courses will involve 6-12 day case admission with attendant costs. Depending on RTX regimen this may be reduced to 2-4/year. The precise RTX regimen will be key to an economic analysis i.e. 1gx2 or 375/m2 x4. Also repeat dosing strategy.	Comment noted. Information on dose and frequency will be provided by the manufacturer at a later stage.
	CSAS	The time horizon is appropriate.	Comment noted. No action required.
	NHS Bournemouth and Poole and NHS Dorset Cluster	The time horizon is appropriate.	Comment noted. No action required.
	Royal College of Nursing	Yes	Comment noted. No action required.
	The Lauren	Our expectation is that any successful treatment for severe vasculitis should be	Comment noted. No action

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	Currie Twilight Foundation	adequately funded.	required.
	Vasculitis UK	The usual accepted induction treatment for most cases of AAV is cyclophosphamide combined with high dose corticosteroids. These powerful drugs are very effective and invaluable in terms of saving life but carry a heavy burden of side effects, some of which are irreversible. This applies especially where induction treatment is repeated one or several times to control relapses. The long term financial cost of dealing with these side effects for the NHS and Social Services is very significant. I have personal experience of the cancer-inducing side effects of cyclophosphamide and am very conscious of the consequent long term personal cost and the substantial ongoing financial cost incurred by the NHS.	Comment noted. The Committee will consider the clinical effectiveness of treatments, including any potential differences in adverse effects of treatment.
	Roche Products Limited	A lifetime time horizon is considered appropriate for this disease indication.	Comment noted. No action required.
Equality	Arthritis Research UK	Paediatric vasculitis should be included, although excluded from the clinical trials	Comment noted. The population has been amended from 'adults' to 'people'. Should the topic be referred to NICE for appraisal, the eligible population will be limited to the population covered by the marketing authorisation.
	British Society for Rheumatology	No issues identified	Comment noted. No action required.
	CSAS	There were no equality issues identified.	Comment noted. No action required.

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	NHS Bournemouth and Poole and NHS Dorset Cluster	There were no equality issues identified.	Comment noted. No action required.
	The Lauren Currie Twilight Foundation	Our concern is that IV administration may disadvantage those within the target group who have transport issues due to financial issues or physical disability and may disadvantage those who live in rural areas.	Comment noted. The Committee will be expected to assess whether any of their decision restrict access to the technology for any people with the protected characteristics outlined in the current Equalities legislation. The fact has been noted for the Committee to consider, but no changes to the scope are required.
	Vasculitis UK	None that I can think of	Comment noted. No action required.
	Roche Products Limited	n/a	Comment noted. No action required.
Other considerations	Arthritis Research UK	Rituximab is already being widely used in vasculitis outside its market authorisation	Comment noted. No action required.
	British Society for Rheumatology	The assessment of ANCA- associated vasculitis is complex, both in determining disease extent, disease activity, and damage. Treatment is usually tailored to all these parameters. It would be important to include in the guidance recommendations for how these parameters should formally be assessed, particularly in terms of assessing eligibility for use of Rituximab and	Comment noted. The technology appraisal process is limited to assessing the clinical and cost effectiveness of the technology. Further

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		response to treatment. This could include recommendations for integration into routine practice the use of formal disease activity/damage tools and multidisciplinary working to reflect the diversity of potential organ involvement. BVAS would be the most appropriate to use - well validated and simply to use.	guidance on clinical practice is beyond the scope of this process.
	CSAS	No additional comments	Comment noted. No action required.
	NHS Bournemouth and Poole and NHS Dorset Cluster	No additional comments	Comment noted. No action required.
	Royal College of Nursing	Use of Rituximab in women of child bearing age	Comment noted. The Committee will be expected to assess whether any of their decision restrict access to the technology for any people with the protected characteristics outlined in the current Equalities legislation. The fact has been noted for the Committee to consider, but no changes to the scope are required
	The Lauren Currie Twilight Foundation	unable to comment	Comment noted. No action required.
	Roche Products Limited	n/a	Comment noted. No action required.

Section	Consultees	Comments	Action
Innovation	Arthritis Research UK	Rituximab should be used now for remission induction in patients with relapsing/refractory disease. Rituximab should be considered for remission induction for new patients with vasculitis where it is probably cost neutral when compared to cyclophosphamide. It should be used for this indication when cyclophosphamide use is contra-indicated. Rituximab is currently under evaluation in an RCT for remission maintenance although retrospective experience indicates a role. Churg-Strauss patients were excluded from the RCTs, but evidence suggests a similar role.	Comment noted. The scope has been amended to include, where evidence allows, people for whom cyclophosphamide is contraindicated. The manufacturer may submit evidence on the innovative nature of rituximab for ANCA-associated vasculitis.
	British Renal Society	Yes, most data would be from RAVE and RITUXIVAS trial. There are also plenty of anecdotal evidence for refractory and cyclophosphamide resistant disease.	Comment noted. No action required.
	British Society for Rheumatology	1. Yes. This is the first drug to demonstrate efficacy as a remission induction agent since Cyclophosphamide was introduced. There are potential major advantages in that it is a non-chemotherapy drug, and would be given much less frequently than a full course of IV CYC. Clinical experience of widespread use of Rituximab in Rheumatoid Disease indicates that the drug appears to have a good safety profile (although effects of very-long term treatment on immune function is unknown). 2. Potentially this technology would have benefits outside of any QALY calculation. The analogy for this is the significant health-related benefits that are likely to have accrued with the introduction of anti-TNF therapy for Rheumatoid Disease. The introduction of this particular technology mandated a requirement for regular formal assessment of disease activity according to standardised methods. This required clinicians to assess disease activity and response to treatment in a much more systematic way, which in itself is likely to have raised standards of care for patients. It is therefore likely that any appraisal of Rituximab, which in turn raises the	Comment noted. The manufacturer may submit evidence on the innovative nature of rituximab for ANCA-associated vasculitis.

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		raises the profile of the management of any aspect of Systemic Vasculitis is likely to also have a health benefit through better assessment of disease etc.	
	Royal College of Nursing	Yes	Comment noted. No action required.
	Vasculitis UK	Yes. Rituximab is an innovative targeted therapy which can be both cyclophos and steroid sparing and will almost certainly lead to the development of other similar MAB drugs for the treatment of AAV. As stated previously, the side effects of the standard drugs can be serious. Rituximab is especially effective in treating relapses, thereby avoiding exposure to repeated doses of cyclophos and high dose steroids. Cyclophosphamide is known to cause reduced fertility in both males and females and early menopause in females. As a consequence, some young females decline the use of cyclophos for induction treatment, thus leaving themselves dependant on induction treatment with less effective drugs normally reserved for use as maintenance therapy. This tends to result in early relapse or even continuing permanent damage to organs. Thus rituximab should be considered as an alternative induction therapy for women in this group as well as for those who are unable to tolerate cyclophos for one reason or another. There is a wealth of data available on the use of rituximab in treating lymphoma and leukaemia as well as rheumatoid arthritis and off-label use in the treatment of systemic lupus and MS. There is evidence of its use in controlling AAV and side effects from clinical trials undertaken in the UK. There is plentiful established clinical evidence of both the effectiveness and the damaging side effects of cyclophos and corticosteroids.	Comment noted. The scope has been amended to include, where evidence allows, people for whom cyclophosphamide is contraindicated. The manufacturer may submit evidence on the innovative nature of rituximab for ANCA-associated vasculitis.
Questions for consultation	Arthritis Research UK	The comparators are routinely used. Cyclophosphamide is used for induction. Azathioprine, methotrexate and mycophenolate mofetil for remission maintenance. Leflunomide and ciclosporin are rarely used alternatives.	Comment noted. Workshop attendees agreed that leflunomide and ciclosporin

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		Rituximab is relatively more effective and cost-effective as induction therapy for relapsing/refractory disease.	were not routinely used and they have been removed from the list of comparators. The comparator section of the scope has been amended as follows: treatment strategies without rituximab including cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids). The scope has also been amended to include, where evidence allows, people for whom cyclophosphamide is contraindicated.
	Roche Products Limited	The evidence available consists of two randomised control trials, one a non-inferiority study, the other a superiority trial. Both compared rituximab to standard of care in ANCA-associated vasculitis. We are also aware of a number of smaller supporting studies and case reports.	Comment noted. No action required.
Additional comments on the draft scope	Arthritis Research UK	Patient subgroups: It has been noted that there is an apparent increase in AAV in immigrants (first or second generation) from the Indian subcontinent. This subgroup may be more at risk from conventional SOC due to background tuberculosis and other infections, and higher risk of steroid induced complications. Rituximab is potentially safer in this setting both by avoiding cyclophosphamide and permitting steroid minimisation. Children, adolescents and younger adult females: SOC with cyclophosphamie	Comment noted. The Committee will be expected to assess whether any of their decision restrict access to the technology for any people with the protected characteristics outlined in the current Equalities legislation. The fact has been noted for

Section	Consultees	Comments	Action
		threatenes fertility, rituximab is the effective alternative. Rituximab will make a significant impact on health related benefits, this is a step change in management of AAV. Health-related benefits: working ability, prevention of infertility and health resource use will be modified by rituximab and may not be captured by QALYs. Simplicity of treatment should be captured, and includes treatment closer to home and less monitoring. Available data on rituximab includes two RCTs and a series of retrospective studies.	the Committee to consider, but no changes to the scope are required. The comparator section of the scope has been amended as follows: treatment strategies without rituximab including cyclophosphamide, azathioprine, methotrexate, and mycophenolate (in combination with corticosteroids). The scope has also been amended to include, where evidence allows, people for whom cyclophosphamide is contraindicated.
	The Lauren Currie Twilight Foundation	We would support the appraisal of new treatments for severe vasculitis.	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Pfizer Ltd
Royal College of Pathologists
Department of Health
MHRA

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Add British Association for Paediatric Nephrology	Arthritis Research UK		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. The British Association for Paediatric Nephrology has been included in the matrix of consultees and commentators under 'professional groups.'

2.	Add British Society for Paediatric and Adolescent Rheumatology	Arthritis Research UK		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. The British Society for Paediatric and Adolescent Rheumatology has been included in the matrix of consultees and commentators under 'professional groups.'
3.	Add Vasculitis Rare Disease Working Group of the UK and Ireland -UKVas	Arthritis Research UK		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Vasculitis Rare Disease Working Group of the UK and Ireland -UKVas has been added to the matrix of consultees and commentators under 'research groups'.

4.	Add European Vasculitis Society	Arthritis Research UK		Not included	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. European Vasculitis Society has not been included in the matrix of consultees and commentators under 'research groups'.
5.	Remove Dexcel Pharma	NICE Secretariat		Removed	This organisation's interests are not closely to the appraisal topic and as per our inclusion criteria. Dexcel Pharma has not been included in the matrix of consultees and commentators.
6.	Remove Sanofi	NICE Secretariat		Removed	This organisation's interests are not closely to the appraisal topic and as per our inclusion criteria. Sanofi has not been included in the matrix of consultees and commentators.