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BY EMAIL

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RE: Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis [ID567]

Dear Helen,

Thank you for giving us the opportunity to comment on the second ACD for the above appraisal. We have provided our comments under the standard four headings. The positive decision to recommend rituximab (RTX) in Granulomatosis with polyangiitis (GPA) and Microscopic polyangiitis (MPA) is strongly supported across the United Kingdom. We are pleased that the positive recommendation will provide patients with an alternative therapy in the management of severe GPA and MPA.

In our consultation response we have provided a weighted average ICER based on a threshold analysis. This has been completed to address the concerns of the Committee that they could not recommend the subgroup of patients who cannot receive cyclophosphamide (CYC). Factual inaccuracies and misinterpretations of the evidence have also been documented within Are the **summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?** Table 2. Please do not hesitate to contact us should you require any further clarification.

Yours Sincerely,

[redacted]

[redacted]

I. Has all of the relevant evidence been taken into account?

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.

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 1: Threshold Analysis Weighted Average ICER

Base Case ICER	Subgroup ICER	Weighted Average
£12,100	£80,000	£18,890
	£95,000	£20,390
	£110,000	£21,890
	£125,000	£23,390
	£140,000	£24,890
	£155,000	£26,390
	£170,000	£27,890
	£185,000	£29,390
	£200,000	£30,890

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.

II. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

Table 2: Factual inaccuracies and clinical misinterpretations

Description of problem (section in ACD)	Description of proposed amendment	Justification for amendment
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.	Add: and 15 of 16 patients (94%) achieved remission (BVAS/WG=0).	This gives a complete representation of the evidence provided by the manufacturer.
3.22 The manufacturer provided information on the long-term safety of rituximab when used as a treatment for rheumatoid arthritis.	Change to: The manufacturer provided published data on the long-term safety of rituximab when used as a treatment for rheumatoid arthritis.	Data have been published in a peer-reviewed abstract. This is a higher grade of evidence than “the manufacturer provided information”.
3.23 The manufacturer provided evidence that women can conceive after treatment with rituximab.	Add: there is no evidence to show that RTX has an adverse effect on fertility.	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.
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.	Change to clarify that there is clinical consensus on the max lifetime dose of CYC.	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.
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.	Consider adding: “superior to cyclophosphamide followed by azathioprine”	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.

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.	Consider removing this statement as no data are available.	Data are not available, so this is speculation and not an evidence based consensus.
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.	Consider adding: Additional QALYs remain unaccounted for within the analyses.	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.
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.	Re-write: data have not shown there to be any apparent fertility issues in women after treatment with RTX.	The sentence is misleading as it implies that most women lose fertility after treatment with RTX.
4.22 The Committee noted that there was only limited evidence showing rituximab does not affect fertility.	Change: "there is no evidence to show that RTX has an adverse effect on fertility".	It is important to note that there are no data to suggest that RTX has an adverse effect on fertility.

III. 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.

IV. 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.

References

Omalizumab for severe asthma [TA278, 2013]
http://publications.nice.org.uk/omalizumab-for-treating-severe-persistent-allergic-asthma-review-of-technology-appraisal-guidance-ta278

Mukhtyar, Hellmich, Jayne, Flossmann, Luqmani. Remission in antineutrophil cytoplasmic antibody-associated systemic vasculitis. Clin Exp Rheumatol 2006; 24 (Suppl. 43): S93-S99.