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Single Technology Appraisal (STA)

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

Dear Dave,

The Evidence Review Group, ScHARR, and the technical team at NICE have now had an opportunity to take a look at the submission received on 20 March by Roche Products. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on 25 April. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Linda Landells, Technical Lead (linda.landells@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (kate.moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Because of the high number of clarification questions, this letter is split into two sections – Section 1 lists high priority questions where a response is very important. Section 2 lists questions that are of lower priority – although these questions are also important, it is recognised that the timescales involved in the STA process are relatively short so we suggest focusing on the questions listed in Section 1 first.

Section 1: High Priority Questions and Requests

Literature searching

1) **Priority question:** Please clarify why only "RTX" is used as a search term for the intervention, rather than synonyms such as rituximab, Rituxan or Mabthera.

2) **Priority question:** With reference to Appendix 1, please state whether searches for ongoing or completed and unpublished trials were undertaken and considered in the submission, using sources such as ClinicalTrials.gov, the metaRegister of controlled clinical trials, or the WHO ICTRP portal.

3) **Priority request:** The ERG believes that not all safety data have been retrieved from the direct evidence searches and that using the data presented in the Summary of Clinical Safety provided to the EMA is not sufficient. The ERG has provided search strategies for adverse events that could have been used in Appendix 1 of this letter. Please clarify whether there are any other relevant adverse event data that are not considered in the submission.

4) **Priority request:** The ERG believes that relevant comparators have been excluded from the manufacturer's submission due to the absence of direct evidence comparing them to rituximab. However, valuable evidence comparing these interventions to cyclophosphamide (CYC) is likely to be available. Please clarify why searches that could have been used to inform indirect comparisons were not conducted. The ERG has provided a search strategy that could have been used in Appendix 2 of this letter.

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Section A – Description of the technology, context, equality, innovation and the decision problem

5) **Priority request:** Please clarify why the oral regimen of CYC was used within the RAVE trial, and why that regimen has been used as the primary comparator in the submission. Some evidence suggests that 15mg/kg IV pulses have fewer adverse effects than oral 2mg/kg, while providing similar remission rates (de Groot, *Ann Intern Med*, 2009). This is particularly important given the cumulative lifetime dose limit associated with CYC – the IV regimen is very likely to lead to a lower dose of CYC received per cycle, which may enable a larger number of cycles to be administered over time for an individual patient.

6) **Priority request:** With respect to Section 5, statements made and supported with the rationale that they are "*in line with the proposed licence*" are inadequate given later, possibly equivocal statements such as 6.9.2: "*The RTX licence is likely to cover the induction of remission*".

- Please clarify by specifying and defining each element of the proposed licence. The ERG notes that the EMA CHMP positive opinion does not specify whether rituximab should only be used in newly diagnosed patients.
- Please include clarification on whether the population is limited to those contraindicated for, or refractory to CYC.
- Also please clarify whether the only possible intervention regimen is 375mg/m² x4, for induction for *de novo* disease only (1st line) for the stated populations, or for induction after first relapse (2nd line) after CYC only.

7) **Priority question:** Given that the RAVE trial looked at the use of RTX to treat flares, why will this not be included in the licence?

8) **Priority question:** Given that maintenance therapy with RTX appears to be used in practice, and has been included in various studies, why will this not be included in the licence?

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Section B – Clinical Effectiveness

9) **Priority request:** With respect to Section 6.2.7, please clarify the justification for including each of the non-RCT studies as supporting evidence. In Section 6.7.1 it is stated that the non-RCTs were "*found not to have sufficient data to be useful to the decision problem*". Please clarify this statement providing justifications. Currently, it is not clear how or why these trials could not contribute to the decision problem, especially as some are cited later in 6.8.1 as having relevant safety data. A clear justification also needs to be given for not appraising these trials critically.

10) **Priority request:** In Table 9 it is stated that patients with a serum creatinine level of >4.0 mg/dL were excluded from the RAVE trial. Please clarify that the RAVE population therefore does not include patients with severe renal disease.

11) **Priority question:** With regard to Section 6.3.6, please clarify and justify more fully the choice of the 70% rate of 6-month remission in this population (treated with CYC) based on WGET trial 2005 (n=180), given that de Groot, *Ann Intern Med*, 2009 (n=149) = 87% at 9 months; Jayne, *NEJM*, 2003 (n=155) = 93% at 6 months, and RITUXVAS = 82%, sustained, at 12 months; all report higher rates for CYC in *de novo* AAV populations.

12) **Priority request:** The choice of subgroup analyses presented in Section 6.3.7 needs to be clarified, justified and described, as required: "*specify the rationale and whether they were pre-planned or post-hoc*". The RAVE trial describes a series of analyses as "*predefined*", but the ERG cannot see these described in the article itself, the freely-available clinicaltrials.gov protocol (NCT00104299) or the NEJM accessible, supplementary file protocol. Please clarify where these subgroup analyses were pre-specified. This is important as *post hoc* sub-group analysis was a stated exclusion criterion in Section 6.2.

13) **Priority question:** No indirect comparisons were drawn in the manufacturer's submission. However, several comparator interventions included in the scope for this appraisal have been excluded. Also, the RAVE trial includes oral CYC as the comparator, whereas the ERG's clinical advisors suggest that IV CYC may provide a better safety profile, and results in a lower cumulative dose of CYC per cycle. While

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there may not be direct evidence on all potential comparator treatments, there is likely to be indirect evidence (comparisons to CYC / IV CYC) in a number of cases. The ERG's clinical advisors suggest that other treatments are likely to have an important role to play in the treatment of ANCA-associated vasculitis, as part of treatment sequences. Please clarify why indirect comparisons were not undertaken for both efficacy and adverse events.

14) **Priority request:** Please clarify exactly how the safety studies in Table 33 were sourced and the inclusion criteria that were applied; please clarify the reason for the omission of potentially relevant non-RCT evidence from this list (e.g. the non-RCT studies by Holle, *Ann Rheum Dis*, 2012, Roll, *J Rheumatol*, 2012 and Cartin-Ceba, *Arth Rheum*, 2012; all use a 375mg/m² dose of RTX and report safety outcomes).

15) **Priority request:** In Section 6.8.2, only safety data from RAVE and RITUXVAS are actually considered. Please clarify why this is and why data from the other studies cited in Table 33 are omitted.

16) **Priority request:** Please provide tables presenting adverse event data for each grade 3 or above event observed in each treatment arm in RAVE and RITUXVAS. For RAVE please present data for 6 month and 18 month timepoints. Data may be provided in a similar form to Table 40 (but with the inclusion of the number of patients with the event, the number in the group, and the percentage with the event).

Section C – Economic evaluation

17) **Priority question:** It is stated in Section 2.5 that only major relapses lead to treatment with CYC. In the model do the relapses represent major relapses based upon the RAVE trial, or are mild / moderate relapses also included? Or are all relapses included and assumed to be major?

18) **Priority question:** Please clarify why relapses of different severity were not modelled.

19) **Priority question:** Stone *et al* 2010 is given as the source for the relapse rates presented in Table 44, however the ERG cannot find these figures in the paper. The ERG understands that these rates were calculated by fitting exponential models to time-to-relapse data from

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RAVE. Measures of explained variation such as R^2 are not recommended for use with time-to-event data (Collett, 2003).

- Please provide relevant data on the fit of the exponential models (such as AIC and BIC statistics) compared with alternative parametric models.
- Please clarify whether proportional hazards were assumed and justify the use of exponential models rather than other parametric models.
- In graphs such as that presented in Figure 14 please include values for numbers at risk.

20) **Priority question:** Please explain the relapse rates presented in Table 38.

- Were these calculated using exponential models fitted to the subgroup data from RAVE?
- It seems surprising that “newly diagnosed” and “relapsing patients” relapse rates of 0.07 and 0.17 respectively for CYC combine to give a relapse rate of 0.15 for all patients; whereas rates of 0.12 and 0.31 respectively combine to 0.16 for RTX. Is this due to the fit of the exponential models?
- Please provide the information specified in question 20 for these subgroup analyses.

21) **Priority question:** The economic model looks at a situation whereby RTX may be used as a remission induction agent in newly diagnosed patients and in previously relapsing patients. However, the model does not consider a sequence whereby newly diagnosed patients initially receive CYC and following relapse they receive RTX. Please clarify why this sequence is not considered.

22) **Priority question:** Please clarify why a wider range of possible treatment sequences were not considered in the economic analysis. The ERG’s clinical advisors suggest that treatments other than rituximab and CYC may play an important part in the treatment

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pathway for ANCA-associated vasculitis. This is linked to question 22, as regards the positioning of rituximab within the pathway, but also involves the consideration of additional treatments within the pathway.

23) **Priority question:** Please clarify why the base case version of the economic model allows newly diagnosed patients to only receive 2 courses of CYC once they enter the model, whereas previously treated patients are also allowed to receive 2 courses of CYC once they enter the model.

24) **Priority question:** Please clarify the rationale for assuming that all patients that initially do not respond to rituximab treatment are immediately retreated with rituximab. Clinical experts consulted by the ERG suggest that this assumption is questionable.

25) **Priority question:** Please provide further clarity and justification around the assumption that following relapse after initial treatment with rituximab, one course of CYC will be given.

26) **Priority question:** Please justify why it is reasonable to assume that the probability of obtaining remission with CYC is the same (that is, it is equal to that observed for “all patients” in the RAVE trial, rather than that observed for “relapsing patients”) regardless of prior RTX therapy.

27) **Priority request:** Please clarify why sensitivity analysis was not undertaken around the assumption that the diminishing effectiveness associated with a second rituximab course is the same as the diminishing effectiveness observed between the CYC newly diagnosed and relapsing patient groups

28) **Priority question:** Please clarify the implications for the economic model of basing the CYC efficacy and adverse event data on the RAVE trial, in which CYC was administered orally. The ERG’s clinical advisors suggest that IV CYC is likely to result in fewer AEs, and also a lower dose of CYC per cycle, which may allow more than 2 cycles of CYC to be given.

29) **Priority question:** Please clarify why different degrees of response were not modelled – for example responses where BVAS/WG=0 but prednisone had not reduced to zero? The ERG’s clinical advisors suggest that patients who achieve this type of “partial” response may

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be clinically significantly different from patients who do not achieve a BVAS/WG score of 0. For instance, such patients may be in remission, but may remain on steroids to control a certain aspect of their disease. However, in the economic model these patients are classified as not being in remission.

30) **Priority request:** Please comment on the face validity of the results of the economic evaluation: For the new patient subgroup (approximately half of all patients) the ICER is approximately £60,000 per QALY gained, for previously treated patients (the remainder of patients) the ICER is approximately £47,000 per QALY gained, yet for all patients combined the ICER is approximately £11,000 per QALY gained. Why is the ICER for all patients not between the ICERs for the two individual subgroups?

31) **Priority question:** Please clarify why different relapse rates were not used in the economic model after first and second relapses (as differential rates are used in the new and previously treated patient subgroup analyses).

32) **Priority request:** Please clarify why the utility score for the "uncontrolled" health state was not varied in probabilistic sensitivity analysis (its value is hard-coded in cell D102 of worksheet "PSAInputs" in the model).

33) **Priority request:** Please check the numbers in Table 51, and the corresponding numbers in the model: The BNF March 2013 lists the price of 56 *50*mg tablets of azathioprine to be £5.04, not 56 *25*mg tablets. Also, the cost/mg for RTX and AZA appear to be incorrect. Also, clarify why methotrexate and mycophenolate mofetil are included in this table but not in the model.

34) **Priority request:** Please clarify why the cost of a pack of 30 1mg prednisone tablets is used in the model and in Tables 51 and 52, rather than the cost of 2mg or 5mg 30 tablet or 100 tablet packs (which have much reduced costs per mg). This is particularly relevant considering the initial dose of prednisone given in RAVE was 1mg/kg/day and the average dose per cycle is stated to be 3506mg.

35) **Priority request**: Please justify why NHS reference cost SD04A was used to reflect best supportive care in the "uncontrolled disease" health

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state. Are any other cost sources available? Please confirm that where the frequency "*1.5 times weekly*" has been stated for this cost and those presented in Table 55, you actually mean "1 appointment every 1.5 weeks".

36) **Priority request:** Please provide further justification for the existence of an "uncontrolled disease" health state, in which patients do not receive any specific treatment for relapses, and which patients currently transit to after two courses of CYC. In Section 7.3.1 it is stated that details on this health state were informed by clinical expert opinion. Does any supporting evidence exist?

37) **Priority request:** Please clarify the justification for assuming that RTX and IV CYC monitoring occurs during the administration appointment – given that clinicians may wish to see the results of monitoring tests before proceeding with the administration. Clinical advice received by the ERG suggests that monitoring of patients treated with rituximab may be required in the long-term, after treatment discontinuation, due to limited evidence on long-term side effects. Please clarify why this has not been included in the economic model.

38) **Priority request:** Table 52 suggests that the same average dose of methylprednisolone and prednisolone is assumed for RTX and CYC, taken from the RAVE trial. Please clarify whether the average doses of these drugs received in the two treatment groups were the same in the trial.

39) **Priority request:** Please clarify how many patients had died in each arm of the RAVE trial at the longest data cut.

40) **Priority request:** Please clarify why the base case analysis (and seemingly all subgroup analyses) presents cost-effectiveness results based on point estimates of parameters rather than expectations of the mean (from the probabilistic model).

41) **Priority request:** Please justify why the standard error is assumed to be 30% of the mean in rows 11-16 of the "PSAInputs" worksheet in the economic model. Also please clarify whether these values are assumed to be standard errors or standard deviations. This impacts upon the formulas used to estimate the alpha and beta values for the beta distributions. Finally please explain why standard errors were not

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estimated based upon the exponential model fits for relapse rates. The ERG suggests that these beta distributions have a very important impact upon the probabilistic analysis.

42) **Priority request:** Please clarify and justify why a Markov model (with underlying assumptions of exponential sojourn time) was used, particularly given the seemingly poor fit of the exponential models used to estimate relapse rates.

Section 2: Lower Priority Questions and Requests

Literature searching

1) Section 10.2 Appendix. The search appears inconsistent and thus inadequate. Some databases are limited to searching for the population only, e.g. Cochrane, whereas others are interrogated for population and intervention. Please clarify why this is the case.

2) Please state the total number of records identified through database searching prior to the removal of duplicate titles in the PRISMA flow diagram presented in Section 2.2.2. Also please explain which sources were used in addition to database searching as shown by "*additional records identified through other sources*".

3) The subject heading ("ANCA associated vasculitis") usage described in Tables 73 and 74 of Appendix 1 is somewhat restrictive. Please state the entry date used for this heading in the searches. This is important because the thesauri year of entry for the subject heading of "ANCA vasculitis" is 2010 (Medline, Ovid) and 2005 (Embase, Ovid), respectively (previously records were indexed under "Vasculitis").

4) The intervention term usage described in Table 74 of Appendix 1 is not comprehensive – alternative terms for rituximab were lacking. Please update the search using the full range of terms that may be used to describe rituximab and clarify whether any additional evidence is found.

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Section A – Description of the technology, context, equality, innovation and the decision problem

5) In Section 2.5 it is stated that "*Patients may continue maintenance therapy/immunosuppression for up to 5 years*". Clinical advice received by the ERG suggests that in fact maintenance therapy may last much longer than 5 years. Please clarify this, and also comment upon how this is captured in your economic analysis.

Section B – Clinical Effectiveness

6) With regard to the exclusion criteria presented in Table 6, please provide a justification for each to ensure that the rationale for exclusion is transparent.

7) Figure 1 appears to only present the results of the Embase/Medline search from Appendix 10.2. Please present results that include the Cochrane and PubMed searches (270 more citations), or clarify why these results do not seem to be included in Figure 1.

8) Figure 1 states that 45 full-text articles were excluded. Please provide a full list of these studies with reasons to explain their exclusion.

9) Please comment upon the ability to make statements upon the effectiveness of rituximab in patients with life-threatening disease (for example, those with pulmonary haemorrhage or active central nervous system vasculitis), given available evidence.

10) In Table 9, it is stated that patients intolerant to CYC were excluded from the RAVE trial. The ERG suggest that this makes any analysis of CYC intolerant patients based upon the RAVE trial inappropriate. Please comment upon this point – is any data available on patients intolerant to CYC who have been treated with RTX?

11) Please clarify whether data are available on how many courses of CYC treatment (or what lifetime dose of CYC treatment had so far been received) had been received by patients who had previously used CYC that were recruited into the RAVE trial. Related to this, how many relapses had these patients had prior to trial entry? Please comment upon whether these patients fit within the proposed rituximab licence.

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12) Please clarify the justification for the use of the BVAS/WG outcome measure, considering that it has only been validated in WG patients. Please comment upon the implications of using this measure in MPA patients. Please clarify why the BVAS/WG measure was used instead of the validated BVAS measure and provide citations on the validation of the BVAS scale.

13) In Section 6.3.6 it is stated that a "*worst case*" analysis was undertaken whereby data for patients who switched treatments were imputed as treatment failures. Clarify why this is a "*worst case*" analysis, considering that it was previously stated that early treatment failure triggered treatment switch.

14) Please provide more information on the "*anomalies*" identified in the clinical data referred to in Section 6.3.6.

15) With respect to Section 6.4, the non-inferiority extension to the CONSORT statement should have been applied and used as a critical appraisal tool (Piaggio, *JAMA*, 2006). Please clarify why this checklist was not used.

16) Tables 15, 16 and 21 refer to the "*ITT Population*", but exclude patients with "*missing*" data. In addition, patients who failed treatment prior to 6 months were excluded from the "*primary efficacy analysis*". Please comment on the susceptibility of these analyses to selection bias.

17) Please clarify the flare rates presented in Table 21 (that are also presented in Table 15). A footnote to Table 21 states that flare assessments for patients during crossover were excluded from the analysis. In Section 6.3.2, it is stated that patients who experienced severe disease flares or treatment failure between Visit V5 and Visit V8 (month 6) were crossed over to the opposite treatment arm. Please confirm the timing of Visit V5, and clarify whether disease flares that triggered treatment switch are included in the figures presented in Tables 21 and 15.

18) The majority of the additional analyses described in Section 6.5.1 (for example, Tables 25-30, Figs.7 and 8), were neither clearly pre-specified nor address the decision problem (decision problem subgroups were only *de novo* patients; CYC-relapse patients; and CYC

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contraindicated patients). Please clarify and justify the inclusion of these analyses.

19) In Table 32, please clarify what Group C refers to in the description of the Smith *et al* 2012 study.

Section C – Economic evaluation

20) Please clarify whether all relevant co-medication and pre-treatment costs are included in the model – for example, premedication with analgesic/anti-pyretic/anti-sickness drugs, anti-histaminic drugs, and PCP prophylaxis.

21) Please clarify whether all relevant adverse events have been included in the economic model, and explain why a number of serious AEs mentioned in Section 2.3 do not appear to be in the economic model.

22) Please provide justification for choosing a lifetime horizon for the analysis – please describe how and why the treatment sequence impacts upon survival, with supporting evidence.

23) Please provide justification for the use of the Lane *et al* (2005) study to model mortality risks over time. The Lane *et al* (2005) study identified 99 patients with AAV between 1988 and 2000, and therefore the data are dated.

- Please comment on the impact that the age of this cohort data may have on its validity to be used to model present-day and future survival of patients with AAV, taking into account issues such as treatment and dosing regimens and any trends in survival over time.
- In addition, only 31 deaths were observed and patients were not classified as regards whether they were in remission or not – please comment upon the uncertainty associated with these data and their importance in the economic model.

24) Please clarify whether any other data exist to support the mortality assumptions used in the economic model. Please justify the

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assumption that patients in complete remission have a lower risk of mortality.

25) Please clarify whether the use of the arbitrary ±10% applied to the estimated SMR taken from the Lane *et al* (2005) study for the uncontrolled and remission health states will lead to the average SMR implied by the model being different from the 4.8 estimated by Lane *et al* (2005) (due to the different proportions of time spent in these states in the model).

26) Please clarify why the Barton *et al* (2004) reference has been used for the cost of RTX administration – a cost estimated for the administration of infliximab with a price year of 2000. Are more relevant and recent estimates available?

27) Please clarify how the data that suggest that 72% of CYC given is by IV were obtained. How many clinicians/centres were surveyed?

28) Please clarify what the comparator treatment was in the subgroup analysis for patients intolerant to CYC. In Tables 4 and 70 the comparator is labelled as “CYC”, yet this is for patients who are intolerant to CYC.

- Do patients in the “CYC” arm transit immediately to the “uncontrolled disease” health state?
- Please clarify why alternative comparator treatments were not considered for this subgroup.

29) Please justify why only the events included in Tables 40 and 41 are relevant for the economic model. Please justify why adverse event rates at 6 months were used instead of adverse event rates at 18 months. Since AZA treatment is given during the remission phase please justify why the data presented in Table 42 refer to the 6 month time-point.

30) Please clarify and justify the duration assumed for the AEs included in the model.

31) Please comment on the face validity of allocating lower adverse event costs to rituximab in the economic model, given that it is noted in

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Section 6.8.2 that hospitalisations associated with study drug were more frequent in the rituximab group. Is this adequately reflected in the economic model?

32) The ERG notes that the economic model includes inputs for malignancies, but these are not actually part of the functional economic model. Please clarify why this is the case.

33) Please clarify why 2009-10 reference costs were used, rather than more recent data, e.g. 2011-2012 costs.

34) Please provide justification for the statement made in the second paragraph of Section 7.2.5 that "*These limitations we believe may lead to an underestimation of the true benefit of successful induction therapy*".

35) Please clarify whether the numbers presented in Table 37 are correct – for rituximab they do not appear to match the figures in the economic model.

36) Please clarify whether the * is in the wrong place in Table 40.

37) Please clarify why a standard error is given for Imaging in Table 43, but not in the economic model.

38) In Section 7.3.8, it is stated that an average body surface area of $1.79m^2$ was assumed based upon an estimate for UK cancer patients, rather than the body surface area observed in the RAVE trial. Please justify why UK cancer patients are thought to provide a good proxy for AAV patients. Are any other sources of data available?

39) In Section 7.4.5, it is stated that papers were included if utilities were derived directly or indirectly, yet in Figure 15 the inclusion criteria says only directly derived utilities. Please clarify which is correct?

40) Please provide justification for the assumption that the difference in utility between the uncontrolled disease health state and the non-remission health state is the same as that between the complete remission health state and the non-remission health state. Why is there likely to be such a substantial difference between patients who are not in remission and patients who are "uncontrolled"?

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41) Please clarify why the numbers do not add up in paragraph 4 of Section 7.5.3 (i.e. 86 – 10 ≠ 78).

42) Please clarify why the price for the 1g vial of methylprednisolone was used in the economic model, and in the numbers presented in Tables 51 and 52, rather than the price for the 2g vial (which has a lower cost per mg).

43) Please check the numbers in Table 52: the average cost per cycle for AZA does not match what is in the model and needs to be corrected given the cost attributed to 25mg rather than 50mg azathioprine tablets in the model. Again clarify why methotrexate and mycophenolate mofetil are included in this table but not in the model. Also the * appears to be in the wrong place.

44) Please clarify your statement underneath Table 53 that: "*Since the cost of administering methylprednisone in the comparator arm is already included in the cost of infusing RTX, the model conservatively assumes zero cost for the administration of methylprednisone*". Is this because methylprednisolone is given at the same time as RTX?

45) Please check the numbers in Table 55: some of these values are different from those in the economic model.

46) Please clarify what the "*Probabilistic*" column of values in Table 60 represents.

47) Please clarify the statement made in Section 7.9.5 – that an analysis of the relapsing disease subgroup was not undertaken. Analyses for patients who have previously relapsed prior to entry to RAVE *have* been presented in Table 69.

48) Do the numbers reported in Section 8.2 refer to only severe ANCA-associated vasculitis patients, or all patients?

49) Please justify why the standard error is assumed to be 20% of the mean in rows 19-22 and row 33 of the "PSAInputs" worksheet in the economic model. Also please clarify whether these values are assumed to be standard errors or standard deviations. This impacts

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upon the formulas used to estimate the alpha and beta values for the beta distributions.

50) Please clarify how the standard errors were calculated in rows 100-101 and 105-107 of the “PSAInputs” worksheet in the economic model. Also please clarify whether these values are assumed to be standard errors or standard deviations. This impacts upon the formulas used to estimate the alpha and beta values for the beta distributions.

51) Please clarify why lognormal distributions rather than normal distributions were used for the reference cost data included in the model.

52) Please clarify why the probability of death associated with the uncontrolled disease health state becomes 1 in cell O208 instead of cell O210 in the “Mortality” worksheet of the economic model.

53) Please clarify why rows 5 and 6 of the “PSAOutput” worksheet of the economic model only look at the first 100 samples, rather than all 1000.

54) Please describe how the analysis that included wastage was carried out, and provide costs for each drug. Did it assume that there was wastage associated with each administration, or with each course of treatment? The figure presented in cell H18 of the ”TreatmentCost” worksheet in the economic model appears to have been calculated on the basis that all four treatments with rituximab would be made up in one go, thus the potential wastage associated with each administration is not taken into account.

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Appendix 1: ERG Medline and Embase search strategies for adverse events

Rituximab

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

1. rituximab.mp.
2. mabthera.mp.
3. rtx.mp.
4. rituxan.mp.
5. rituxin.mp.
6. or/1-5
7. ((side or adverse or undesirable) adj2 (event$ or effect$ or reaction$ or outcome$)).ti.
8. (safe or safety).ti.
9. (harm$ or complication$).ti.
10. risk$.ti.
11. (treatment adj emergen$).ti.
12. tolerability.ti.
13. mortality.ti.
14. or/7-13
15. 6 and 14
16. Death/
17. Leukopenia/ci [Chemically Induced]
18. Thrombocytopenia/ci [Chemically Induced]
19. Neoplasms/ci [Chemically Induced]
20. Infection/ci [Chemically Induced]
21. Hemorrhage/ci [Chemically Induced]
22. Venous Thrombosis/ci [Chemically Induced]
23. Stroke/ci [Chemically Induced]
24. hospitalisation.ab,ti.
25. or/16-24
26. 6 and 25
27. 15 or 26

Embase 1974 to 2013 April 05

1. rituximab.mp.
2. mabthera.mp.
3. rtx.mp.
4. rituxan.mp.
5. rituxin.mp.
6. or/1-5

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7. ((side or adverse or undesirable) adj2 (event$ or effect$ or reaction$ or outcome$)).ti.
8. (safe or safety).ti.
9. (harm$ or complication$).ti.
10. risk$.ti.
11. (treatment adj emergen$).ti.
12. tolerability.ti.
13. mortality.ti.
14. or/7-13
15. 6 and 14
16. rituximab/ae, to [Adverse Drug Reaction, Drug Toxicity]
17. vasculitis/
18. vasculiti$.mp.
19. 17 or 18
20. neutrophil cytoplasmic antibody/
21. anti neutrophil cytoplasmic antibody associated.mp.
22. anca.mp.
23. or/20-22
24. 19 and 23
25. ANCA associated vasculitis/
26. 16 and (24 or 25)
27. 15 or 26
15. 6 and 14

Cyclophosphamide

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

1. cyclophosphamide.mp.
2. cytoxan.mp.
3. cyc.mp.
4. 50-18-0.rn.
5. or/1-4
6. ((side or adverse or undesirable) adj2 (event$ or effect$ or reaction$ or outcome$)).ti.
7. (safe or safety).ti.
8. (harm$ or complication$).ti.
9. risk$.ti.
10. (treatment adj emergen$).ti.
11. tolerability.ti.
12. mortality.ti.
13. or/6-12
14. 5 and 13

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15. Death/
16. Leukopenia/ci [Chemically Induced]
17. Thrombocytopenia/ci [Chemically Induced]
18. Neoplasms/ci [Chemically Induced]
19. Infection/ci [Chemically Induced]
20. Hemorrhage/ci [Chemically Induced]
21. Venous Thrombosis/ci [Chemically Induced]
22. Stroke/ci [Chemically Induced]
23. hospitalisation.ab,ti.
24. or/15-23
25. 5 and 24
26. 14 or 25

Embase 1974 to 2013 April 05

1. cyclophosphamide.mp.
2. cytoxan.mp.
3. cyc.mp.
4. 50-18-0.rn.
5. or/1-4
6. ((side or adverse or undesirable) adj2 (event$ or effect$ or reaction$ or outcome$)).ti.
7. (safe or safety).ti.
8. (harm$ or complication$).ti.
9. risk$.ti.
10. (treatment adj emergen$).ti.
11. tolerability.ti.
12. mortality.ti.
13. or/6-12
14. 5 and 13
15. cyclophosphamide/ae, to [Adverse Drug Reaction, Drug Toxicity]
16. vasculitis/
17. vasculiti$.mp.
18. 16 or 17
19. neutrophil cytoplasmic antibody/
20. anti neutrophil cytoplasmic antibody associated.mp.
21. anca.mp.
22. or/19-21
23. 18 and 22
24. ANCA associated vasculitis/
25. 15 and (23 or 24)
26. 14 or 25

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Appendix 2: Example of ERG Medline search strategy for indirect comparison searches for cyclophosphamide, azathioprine, methotrexate and mycophenolate

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

1. cyclophosphamide.mp.
2. cytoxan.mp.
3. cyc.mp.
4. 50-18-0.rn.
5. azathioprine.mp.
6. aza.mp.
7. (azasan or imuran).mp.
8. 446-86-6.rn.
9. methotrexate.mp.
10. mtx.mp.
11. mycophenol$.mp.
12. cellcept.mp.
13. or/1-12
14. Vasculitis/
15. vasculiti$.mp.
16. 14 or 15
17. Antibodies, Antineutrophil Cytoplasmic/
18. anti neutrophil cytoplasmic antibody associated.mp.
19. anca.mp.
20. or/17-19
21. 16 and 20
22. exp Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/
23. 21 or 22
24. 13 and 23