National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from School of Health and related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Monday 10 June 2013** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Comparative effectiveness in relapsing patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 122. The ERG state in relapsing patients, RTX 'appears to be of similar effectiveness' to CYC.	Reference should be made to the subgroup analysis results from RAVE where RTX was significantly more effective than CYC in relapsing patients.	Results from the RAVE publication [Stone et al, 2010]	This is not a factual error but is a matter of interpretation. The sentence referred to is not specific to relapsing patients, but is a general statement.

Issue 2 Multiple courses of therapy with RTX

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 122. ERG infers manufacturer did not consider scenarios where multiple courses of RTX are not given.	Remove the following sentence in the paragraph; '*This is in contrast to the manufacturer's submission.'*	We evaluated the effect of restricting RTX to one course only in the economic model sensitivity analysis. This was presented in our submission.	This is a minor issue. We have amended the sentence to read: "This is in contrast to the manufacturer's base case analysis"

Issue 3 Licence restriction for relapsing patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 125. The ERG notes that the RTX licence for AAV does not cover patients who have relapsed on treatments other than CYC. This is incorrect.	Remove '*or for relapse other than post-CYC'* from the sentence on page 125.	The licence for RTX states that it can be used as an induction therapy in patients with severe GPA and MPA. The licence does not make reference to a restriction based on prior treatments.	This is a minor issue. We have amended the sentence as requested.

Issue 4 RITUXVAS within the scope of the appraisal

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 3. The ERG suggests that both RAVE and RITUXVAS should be given equal consideration based on the NICE scope and decision problem. This is incorrect as the regimen in RITUXVAS falls outside the current licence and therefore should only be considered as supporting evidence within the context of the submission.	Although the ERG may have received clinical advice which considers RITUXVAS to be of equal importance, the NICE scope and decision problem do not support this view. Therefore the following sentence should be amended '*However, clinical advice received by the ERG~~, the NICE scope and decision problem criteria~~, suggests that both trials are relevant and that the two trials should be given equal consideration'*	RITUXVAS used a regimen (RTX+CYC) that falls outside the current licence. While clinical opinion may value the results of the study, the results fall outside the scope of the appraisal and should only be considered as supporting evidence and not given equal consideration with the evidence from RAVE.	This is not a factual error. In the NICE scope it is stated that the remit of the appraisal is: "To appraise the clinical and cost effectiveness of rituximab in combination with corticosteroids within its licensed indication for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis". However when the scope was written the licence for rituximab was not known, and the specific intervention to be considered (i.e. rituximab with or without cyclophosphamide) was not specified. Hence the scope and decision problem were open to a consideration of rituximab combined with cyclophosphamide, as studied in the RITUXVAS trial.

Issue 5 Manufacturer subgroup results

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 4/70/101. ERG has incorrectly presented sensitivity analysis results as 'most plausible	The most plausible ICER for treatment naïve patients is £1,274, and for recurrent patients it	The most plausible results for the subgroup analysis are provided in	This is not a factual error. For both subgroups we have reported the ICER reported for

estimates' for subgroup populations (treatment naïve and recurrent disease). The "base case" results given in our submission for the subgroup sensitivity analysis are not the values stated by the ERG.	is £12,556 as outlined in the submission.	our submission.	the "Base case # of CYC cycles" in the top row (for each subgroup) of Table 7 from the manufacturer's clarification response. Hence it is appropriate to label these as the manufacturer's base case subgroup analyses. The ICERs listed by the manufacturer are included in Table 14 of the ERG report. In the manufacturer's submission these are described as "More plausible # of CYC cycles for this subgroup" – they are not stated to be the base case.

Issue 6 Clinical effectiveness issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 125. The ERG states that a principal concern with the clinical evidence in our submission is the use of a RTX dose that does not represent the (off-label) dose most commonly given in the UK. We acknowledged within our submission that the dose currently used in the UK is not part of the current licence. This dose therefore falls outside the scope of the appraisal and has not been included within the submission.	We recommend the following points on page 125 be recognised as limitations relating to the NICE appraisal (where only the licensed dose can be evaluated) and not issues relating to the submission. • An indication heavily limited by the licence • An RTX dose that is not currently the common off-label dose in the UK. • A single trial offering evidence on an alternative dose or regimen	All three points are outside the scope of the appraisal and are therefore not limitations within the context of the submission.	This is not a factual error. In the NICE scope it is stated that the remit of the appraisal is: "To appraise the clinical and cost effectiveness of rituximab in combination with corticosteroids within its licensed indication for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis". However when the scope was written the licence for rituximab was not known, and the specific dose to be considered was not specified. Hence the scope and decision problem were open to a consideration of the 1g rituximab dose. The manufacturer has chosen to submit evidence based upon the anticipated licence, but in this case it is the licence that is limiting, rather than the NICE scope.

Issue 7 Modelled Population

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 74. The ERG indicates that	The population modelled in our economic	The final scope was '*To appraise*	This is not a factual error. The

the population modelled deviated from the NICE scope. This is incorrect, the final scope was '*To appraise the clinical and cost effectiveness of rituximab in combination with corticosteroids <u>within its licensed indication</u> for the treatment of antineutrophil cytoplasmic antibody-associated vasculitis'* As the licence restricts RTX treatment to those patients with <u>severe</u> GPA and MPA, we have not deviated from the NICE scope. We agree with the ERG there is considerable uncertainty around how 'severe' should be defined in the context of GPA and MPA.	analysis is in line with the scope of the appraisal. This should be reflected in section 5.3.1.	*the clinical and cost effectiveness of rituximab in combination with corticosteroids <u>within its licensed indication</u> for the treatment of antineutrophil cytoplasmic antibody-associated vasculitis'* The population modelled in the economic analysis was reflective of the population outlined in the NICE scope.	manufacturer has confused the "remit" of the appraisal with the scope and decision problem. In the NICE scope it is stated that the remit of the appraisal is: "To appraise the clinical and cost effectiveness of rituximab in combination with corticosteroids within its licensed indication for the treatment of anti-neutrophil cytoplasmic antibody-associated vasculitis". However when the scope was written the licence for rituximab was not known, and the specific population to be considered was not specified. Hence the scope and decision problem were open to a consideration of all people with anti-neutrophil cytoplasmic antibody-associated vasculitis. The manufacturer has chosen to submit evidence based upon the anticipated licence, but in this case it is the licence that is limiting, rather than the NICE scope.

Issue 8 Indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 77. The NICE scope was	*The specific indication described in the MS is in*	The NICE scope was to appraise	This is not a factual error.

drafted prior to the EMA decision on the licence. Consequently the wording in the scope stated the appraisal was to be 'within its licensed indication'. The ERG report can be read as inferring that we have deviated from the scope by restricting our economic analysis to induction therapy only. However, as the license has now been confirmed to include only induction, we do not consider that our submission deviates from the NICE scope on this matter. The ERG is correct in noting that there is strong clinical support for RTX maintenance therapy, including the recommendation from NHS Commissioning Board. However, as this is not part of the licence we have not included it in our economic analysis.	*line with that described in the final scope developed by NICE [page 77].*	RTX within its licensed indication. Our economic analysis was designed to achieve this.	When the scope was written the licence for rituximab was not known, and scope and decision problem were not specific with regards to the population and intervention. It is factual to say that the manufacturer's submission does not cover everything that was covered by the scope. The ERG agree that – given the licence – this is reasonable, and on page 1 of the ERG report it is stated that "The decision problem is appropriate given the anticipated licensed indication".

Issue 9 Modelling severity of flare

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 80/105. While we agree that not all patients may go on to receive CYC or RTX following a minor flare, we note the ERG has not outlined the limitations associated with modelling major flares only. We note that both clinical experts consulted by	Acknowledge the limitations associated with modelling major flares only.	Both clinical experts consulted by Roche and the ERG note that some patients who experience a minor flare will progress to a major flare even with appropriate treatment. There is no evidence about the expected frequency of such progression; this evidence gap has	This is a minor point. On page 90 of the ERG report we have added an acknowledgement of the limitations associated with modelling major flares only, as requested.

Roche and the ERG considered that some patients who experience a minor flare will progress to a major flare even with treatment. We are not aware of any evidence to inform the transition probabilities from a minor to a major flare. This is why we adopted a more simplistic approach to modelling treatment flares.		not been recognised as a limitation in the ERG report.	

Issue 10 UK body surface area (BSA) estimates

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 94. The ERG states that when the average BSA taken from RAVE study is used in the economic analysis it 'leads to an appreciable increase in the ICER'. In the sensitivity analysis presented in the MS, the ICER increased to £12,556 up from the base case estimate of £8,544. While this is a notable relative increase the absolute value appears to be overstated with the current wording.	Replace the 'appreciable increase in the ICER' with the actual ICER values.	The ERG description of this analysis could be made more objective to ensure it is correctly interpreted..	This is not a factual error. The value in question is stated on page 72 of the ERG report.

Issue 11 Results of Comparator studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 25 (and p. 19). The ERG states that "the manufacturer acknowledged the MYCYC trials, comparing MMF to CYC, but stated that the results of this study were not yet published. However, the ERG searched and found one published conference abstract reporting early results from this trial." We agree that this study has now been published (April 2013), but it had not been published by the time of the MS deadline and therefore could not have been included or used in an indirect comparison.	Acknowledge that this evidence could not have been used in the submission.	The abstract was published after the deadline of the submission.	This is not a factual error. The ERG report simply states that the manufacturer stated that results of this study were not published, but that when the ERG undertook a search a published conference abstract was found. This is factually accurate.