[redacted]

12th November 2010

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BY E-MAIL

Re: Single Technology Appraisal – Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs

Dear Kate,

Thank you for sending us the Appraisal Consultation Document (ACD) for the golimumab technology appraisal.

Roche has several comments to make on the ACD outlined below under the 4 standard headings.

Please do not hesitate to contact us should you require any further information or clarifications.

Yours Sincerely,

[redacted]

1. **Do you consider that all of the relevant evidence has been taken into account?**

The Final Scope for this appraisal (March 2009) listed tocilizumab as one of the comparators for this appraisal. Citing the lack of positive NICE recommendation golimumab's manufacturer has omitted the majority of data for tocilizumab. Tocilizumab has now been appraised by NICE (TA 198) and recommended in TNF-IR where rituximab and/or methotrexate is contraindicated and for patients that have responded inadequately to rituximab.

Four well designed phase III RCTs provide a wealth of relevant, to this submission, data in both DMARD-IR and TNF-IR. It is therefore appropriate that any indirect comparisons of golimumab with other biologics in the DMARD-IR setting, should include tocilizumab to increase the precision of the MTC estimates. Trials that should be taken into account include LITHE, OPTION and TOWARD (summary results of which are found in the tocilizumab Summary of Product Characteristics and Full Guidance). In the TNF-IR setting the RADIATE trial should be included in the MTC that will provide an appropriate assessment of the relative effectiveness of golimumab in this setting.

2. **Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?**

Golimumab's licence in the treatment post aTNF treatment

Roche believe that the ACD should reflect the fact that golimumab is not licensed for use after the failure of a TNF inhibitor, that is to say, not recommended in sequential use, in RA.

Roche understand that the manufacturers applied to the EMEA for the following indication for RA: "Simponi can be used in patients previously treated with one or more TNF inhibitor(s)."

However, this part of the indication was rejected by the EMEA, so there is no licence for use of golimumab in TNF-experienced patients and therefore no justification for considering golimumab in this part of the RA treatment pathway.

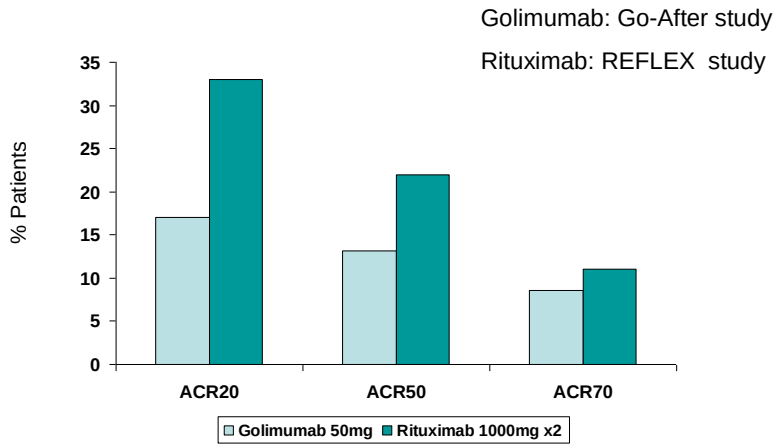
Rituximab efficacy in TNF-IR:

ACD section 3.35
"*rituximab was dominated by golimumab because golimumab was both less costly and more effective than rituximab*".

However, on the contrary, and in agreement with the ERG comments in the ACD, Roche believe that rituximab is clearly more effective and less costly than golimumab in the TNF-experienced population.

ACR responses at 24 weeks (the standard primary end-point in RA trials) clearly show that rituximab is more effective than golimumab in a TNF-experienced RA population. The chart and table below demonstrate the data from the REFLEX and GO-AFTER trials, showing the difference in ACR responses (active minus placebo) at 24 weeks in a TNF-experienced population:

Golimumab and Rituximab in TNF-IR Patients:
Δ ACR Scores at week 24 (active – placebo)



For clarity, the original ACR responses are also shown in the table below:

	Golimumab 50mg n=153	Golimumab PBO n=155	Δ Gol Active – PBO	Rituximab n=298	Rituximab PBO n=201	Δ RTX Active - PBO
ACR20 (%patients)	34	17	17	51	18	33
ACR50 (%patients)	18.3	5.2	13.1	27	5	22
ACR70 (%patients)	11.8	3.2	8.6	12	1	11

Cost of rituximab

The costs of rituximab quoted in the MS were also commented on in sections 3.35 and 3.36 of the ACD:

ACD section 3.35:
"The results for the deterministic base-case analysis of golimumab in a TNF inhibitor-experienced population show that rituximab is dominated by golimumab because

golimumab is less costly and more effective (£31 fewer costs and 0.189 additional QALYs)."

ACD section 3.36:
"The results from the probabilistic sensitivity analysis show that in the TNF inhibitor-experienced population, rituximab is extendedly dominated by golimumab based on the mean costs and QALYs"

Roche believe that this is an unsound conclusion, and believe that the MS has used incorrect assumptions around the time to re-treatment of rituximab in both the 1st and subsequent courses of treatment , thus increasing the cost of rituximab (section 3.40). Roche's belief is further validated by the ERG comments in the ACD (section 3.40):

ACD Section 3.40:
"The ERG also commented that the model assumes that rituximab is re-administered every 6 months but it considered that 9 months would be more reflective of current clinical practice."

Roche has demonstrated previously (TA195) that the frequency of administration of rituximab is consistently around 9 months (Rituximab SmPC). Several sources were utilised to determine the cost of rituximab. The latest market research data suggested that rituximab was given every 8.7 months on average (GfK HealthCare, a sample of 80 rheumatology clinicians in the UK). A further analysis of extension trial re-treatment data indicated that the time between treatments may be even greater; the mean time to re-treatment, taken from an extension study was 11.6 months (Roche analysis provided in original submission for TA195).

Two resource use studies also provided data in "real-life" settings, to substantiate these figures. The initial study, a single Centre study at the Norfolk and Norwich University Hospital NHS Trust, showed, in a retrospective analysis, that the mean time between the first and second rituximab cycles for patients initiated on rituximab was 10.5 months (range 4.7–17.3 months), (Somerville et al., BSR 2008).

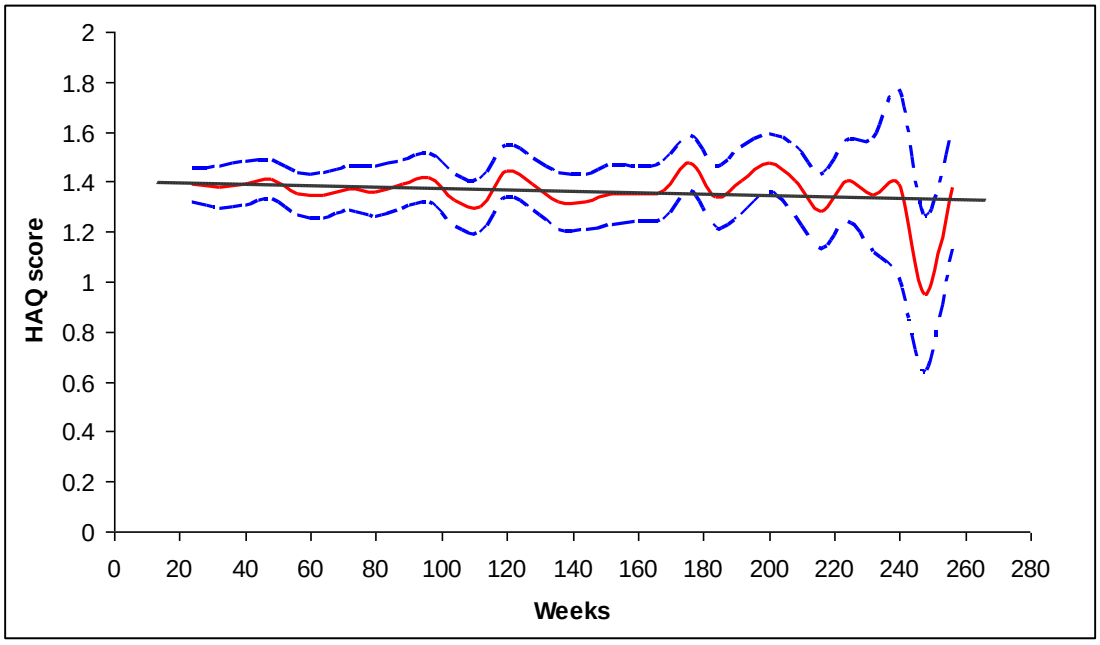
A repeat of this study in 3 centres showed a similar magnitude of response, with the time to repeat treatment being 43 weeks (range 15-84 weeks), Data on file.

Based on all the above evidence submitted as part of the Roche submission for the MTA of treatments after the failure of one aTNF, Roche has estimated the annual cost of rituximab to be £4,817 per patients (average over 4 years).

Rituximab HAQ progression whilst on treatment

Roche is unclear on the evidence base used by the manufacturer of golimumab to support the long term HAQ progression of the various treatments. With respect to rituximab Roche has provided long-term data of HAQ progression while on treatment as part of the MTA (TA 195). These data (figure below) clearly demonstrate that patients show no progression while on rituximab therapy. The assumption used in the model is biasing the overall treatment efficacy comparison in favour of golimumab.

Long term HAQ change for rituximab patients remaining on therapy (REFLEX extension population)



3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

Roche echo the Committee's concerns with respect to the evidence base and cost effectiveness analysis of golimumab in both DMARD-IR and TNF-IR.

4. Are there any equality related issues that need special consideration that are not covered in the ACD?

None