[redacted]

Tuesday 20th May 2008

Natalie Bemrose
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

BY E-MAIL

Dear Natalie,

MULTIPLE TECHNOLOGY APPRAISAL –
Sequential use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (RA)

Thank you for sending us the Appraisal Consultation Document (ACD) for the above technology appraisal. Our response is provided below, under the 3 standard headings of response.

1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT

Roche believe that the majority of relevant evidence has been taken into account in this appraisal. Roche feel that further evidence could have been considered regarding:

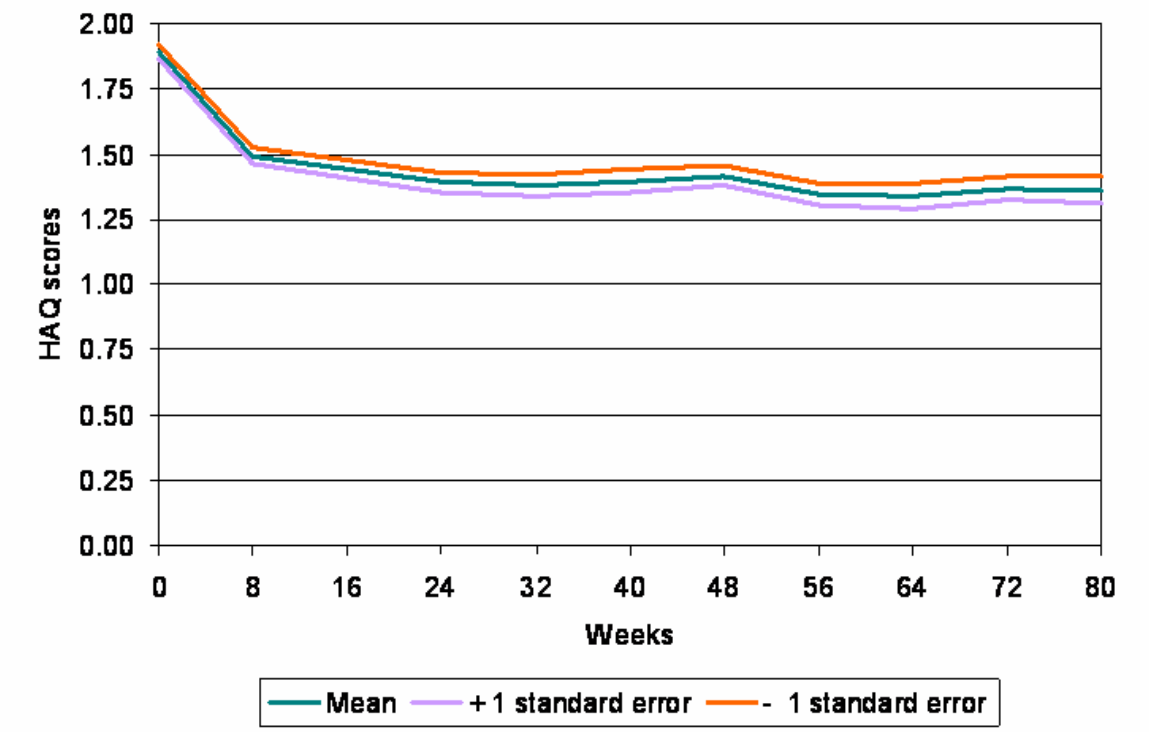
- **Long term HAQ progression while on rituximab treatment**
  Roche believe that assuming zero HAQ progression for TNF inhibitors and 0.03 for rituximab may be unfair. Evidence suggests that rituximab is associated with an on treatment zero HAQ progression in the post TNF inhibitor patient population, whereas the evidence supporting zero HAQ progression for TNF inhibitors is likely to be from a first-line TNF inhibitor patient population. Given the additional effectiveness of rituximab compared to TNF inhibitors in the patient population of interest for this appraisal (Finckh et al (2007)) it seems unreasonable to assume a worse HAQ progression rate for rituximab than for the TNF inhibitors. The Finckh paper (discussed by the Decision Support Unit report) illustrated a greater DAS28 score decrease with rituximab therapy (-1.61) compared with TNF inhibitor therapy (0.98), p=0.01, when comparing patients who had already been treated with one or more

TNF inhibitors, showing the additional benefit of rituximab compared to a second or third TNF inhibitor for these patients.

Analysis of the REFLEX study which evaluates HAQ changes up to and including week 80 confirms it may be reasonable to propose a zero HAQ progression over time in patients treated with rituximab (previously submitted to NICE in response to the ACD for the STA of rituximab for the treatment of rheumatoid arthritis, 23/04/07). Over the time-horizon of the REFLEX study, Figure 1 below illustrates a flat to negative slope to the HAQ progression curve. The number of patients analysed at each timepoint (N), mean HAQ scores and means plus and minus one standard error for each time point are presented. Also, an estimate for the change in HAQ over 6 months has been calculated by fitting a regression model to patient HAQ scores over time using HAQ score raw data and time relative to the first treatment with rituximab + MTX as independent variables. This led to an estimate that in the long term HAQ scores are actually expected to fall while on treatment with rituximab + MTX.

Given this evidence Roche believes that if a zero HAQ progression rate is assumed for TNF inhibitors in a sequencing scenario a similar assumption should be made for rituximab.

Figure 1: 80 week data from REFLEX. HAQ scores over time for patients who received 1 or more courses of rituximab 1g+MTX



Time (weeks)	N	Mean	+ 1 standard error	- 1 standard error
0	479	1.8905	1.8636	1.9175
9	406	1.4927	1.4600	1.5254
16	455	1.4406	1.4068	1.4743
24	416	1.3908	1.3543	1.4272
32	292	1.3782	1.3347	1.4217
40	279	1.3938	1.3491	1.4386
48	315	1.4162	1.3764	1.4560
56	256	1.3451	1.3021	1.3880
64	254	1.3396	1.2925	1.3868
72	233	1.3688	1.3223	1.4153
80	206	1.3605	1.3100	1.4109
Change over 6 months (95% CI)		**-0.0458**	**-0.0779**	**-0.0136**

Mean of patients with a valid HAQ assessment / Missing assessments are ignored

- **Long term safety profile of rituximab**

  Roche note that this topic was mentioned by one of the manufacturer's in their response to the further analysis undertaken. The publication by Keystone et al (Arth Rheum 2007; 56:3896-3908) showing safety after 2 courses and the abstract by van Vollenhoven et al (ARD 2007; 66 (suppl II): 88 demonstrating safety after 4 courses of rituximab should reassure the Committee of the long term safety profile of rituximab.

  Safety analyses were performed on 1053 RA pts exposed to RTX as of September 15, 2006 in the clinical trial program. Data on patients receiving up to 4 treatment courses have been reported (Keystone et al Arth Rheum 2007; 56:3896-3908, van Vollenhoven et al (ARD 2007; 66 [suppl II]: 88) :

  - Acute infusion reactions decrease with repeat courses: acute infusion reactions (first infusion, each course) decreased from 26% during Course 1 to 10-15% during Courses 2 to 4. Also, fewer acute infusion-related events occurred during or within 24 hours of the second infusion for all courses than the first infusion

  - After 4 courses, a slight upward trend was observed in the rate of infections; however, the rate of serious infections remained stable with repeated treatment. No opportunistic infections, viral reactivations or tuberculosis were seen.

  - 25% of patients had low IgM and 6% of patients had low IgG at some point post rituximab, however, there was no increase in rate of serious infection in these patients; the rates of serious infections were all consistent with those expected with biologic RA therapy.

  - Conclusions: This further update on the long-term follow-up (2438 pt-yrs) of RA pts receiving rituximab showed a safety profile consistent with that reported previously.

- **Evidence on radiographic progression**

  Roche wish to highlight that rituximab is the only biologic to have demonstrated inhibition of progressive joint destruction in a TNF inhibitor-inadequate responder population.

  The REFLEX trial provided strong evidence that rituximab inhibits radiographic progression in RA as measured by the total Genant-modified Sharp score, joint space narrowing and erosion scores (Keystone et al, 2008 ARD online: doi:10.1136/ard.2007.085787).

  Furthermore, additional analyses have shown that patients who do not exhibit a clinical response to rituximab are still able to experience the benefit of reduced radiographic progression relative to placebo-treated patients (Keystone et al. Arthritis Rheum 2006;54 (Abstract 1307)).

- **Cost effectiveness after treatment with more than one TNF inhibitor**
  Roche note that in their response, one of the manufacturer's questioned the logic of NICE's previous recommendation for rituximab which did not differ depending on the number of prior TNF inhibitors a patient had been treated with, given that response rates for all treatments fall when they are given at a later stage. It is unclear how the Appraisal Committee took this comment into account and Roche would like to point out that the evidence included in the rituximab technology appraisal illustrated the cost effectiveness of rituximab both after one prior TNF inhibitor and after 2 or more TNF inhibitors (Manufacturers Submission, Rituximab for the treatment of rheumatoid arthritis, November 2006)

2 WHETHER 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

Roche considers the range of the clinical and cost effectiveness analysis undertaken by the Decision Support Unit and WMHTAC to be appropriate based on the evidence considered however as noted above Roche does not endorse all of the assumptions made in the economic modeling.

3 WHETHER 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

Based on the broad range of scenario analysis undertaken in order to tackle the uncertainty surrounding this appraisal, Roche believe that the provisional recommendations of the Appraisal Committee are sound.

We hope that our feedback is helpful to the Appraisal Committee in its subsequent deliberations.

Yours sincerely,

[redacted]