ABBOTT LABORATORIES LTD

NOTICE OF APPEAL AGAINST

FINAL APPRAISAL DETERMINATION FOR ADALIMUMAB, ETANERCEPT AND INFLIXIMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS AFTER FAILURE OF A PREVIOUS TNF-α INHIBITOR (JULY 2008)

1 AUGUST 2008

1. NOTICE OF APPEAL

Abbott Laboratories Limited wishes to give formal notice of its intention to appeal against the Final Appraisal Determination (the "FAD") for adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis ("RA") after failure of a previous TNF-α inhibitor prepared by the National Institute for Health and Clinical Excellence ("NICE").

Details of the appeal are presented below in accordance with NICE's process for appeal.

2. GROUNDS OF APPEAL

2.1 The aspect(s) of the guidance to the NHS or appraisal process being appealed against:

Section 1.1 of the FAD:

"Adalimumab, etanercept and infliximab are not recommended for the treatment of rheumatoid arthritis after the failure of a previous tumour necrosis factor alpha (TNF-α) inhibitor, except in the context of research. Such research should be designed to evaluate the clinical effectiveness of adalimumab, etanercept and infliximab when used sequentially after the failure of a previous TNF-α inhibitor, in comparison with management strategies that do not include the use of TNF-α inhibitors."

2.2 The grounds of the appeal:

a) The Institute has failed to act fairly and in accordance with the appraisal procedure set out in the Institute's Guide to the Technology Appraisal Process. The submissions on this ground are set out in paragraph 3.

b) The Institute has prepared guidance which is perverse in the light of the evidence submitted. The submissions on this ground are set out in paragraph 4.

3. FIRST GROUND OF APPEAL – PROCEDURAL UNFAIRNESS

The Institute has failed to act fairly and in accordance with the appraisal procedure set out in the Institute's Guide to the Technology Appraisal Process

Exclusion of cost offsets from the economic modelling

3.1 Abbott contends that NICE has failed to act fairly by not giving due consideration to the impact of joint replacement costs, costs of outpatient visits and inpatient stays on the estimates of the cost effectiveness of sequential TNF inhibitor use in this appraisal. Section 1.2.5 of the Guide to the Technology Appraisal Process[1] and Section 3.3.1 of the Guide to the Methods of Technology Appraisal[2] both highlight the importance of quantifying costs to the NHS and Personal Social Services. Therefore, by not including an estimation of these cost offsets, Abbott contends that NICE has failed to act fairly and in accordance with its Guide to the Technology Appraisal Process and its Guide to the Methods of Technology Appraisal.

3.2 Abbott and other consultees have highlighted that these important costs have not been included in the analyses of the cost effectiveness of sequential use. It is unfair to exclude

these given that these costs were included in both the appraisal of rituximab and the appraisal of abatacept. The appraisal committee noted the exclusion of these costs in section 4.3.11 of the FAD[3], and justified their exclusion on the following grounds:

"The Committee noted that sensitivity analyses including offset costs had been explored in the first-use analyses of TNF-α inhibitors (TA130) and that these had not demonstrated a significant impact on the incremental cost-effectiveness ratios (ICERs). The committee concluded that consideration of offset costs was important, but that this had been explored by the Assessment Group in their original analyses and had been shown not to be a key driver of cost effectiveness." FAD Page 28 of 44.

3.3 In the BRAM, as in the model submitted by Abbott, cost offsets due to hospitalisation/ surgery are modelled as a function of the HAQ improvement i.e. each HAQ point improvement was associated with a £860 reduction in medical costs. Sensitivity analyses indicated that the cost offsets have a negligible impact on the BRAM model results[4]. However, these analyses were run on the base-case model where TNF inhibitors were considered to be broadly similar in effectiveness to conventional DMARDs in terms of the HAQ multipliers used for short-term improvement.

3.4 Abbott considers that it is inappropriate and unfair for the Committee to speculate on the importance of these cost offsets when these could easily have been incorporated in the base case analyses. Abbott considers that this is an important consideration given that the lower end of the ICER estimates for sequential TNF inhibitor use were £31K per QALY versus conventional DMARDs and £32K per QALY versus rituximab. Furthermore, it is unfair in that the ICER estimates calculated in the appraisals of rituximab and abatacept for the same patient population both incorporated these cost offsets.

3.5 In its written comments on the Appraisal Consultation Document, Abbott requested that sequential use analyses incorporating cost offsets be conducted. It would appear from the decision that such analyses were not conducted, so that the impact of these offsets was never fully evaluated and potentially significant data ignored. Abbott considers it is procedurally unfair for the appraisal committee not to have had the analyses conducted given the acknowledgement that they are an important consideration.

Refusal to supply economic model in fully executable form

3.6 In accordance with the recent Court of Appeal decision in the case of Regina (Eisai Limited) vs. National Institute for Health and Clinical Excellence dated 7th May 2008, procedural fairness required the National Institute for Health and Clinical Excellence to release a fully executable version of an economic model to those consulted in the course of an appraisal process and not simply a read-only version. To do otherwise would place drug companies at a significant disadvantage in challenging the reliability of such models.

3.7 A fully executable copy of the BRAM model was requested as part of Abbott's comments on the ACD. Abbott was informed by email correspondence from NICE on 2nd July 2008 that "*the Institute is currently considering the implications of the Court of Appeal judgement in R ota Eisai v NICE, and whether to appeal that decision to the House of Lords. Until that consideration is complete the Institute is not releasing copies of economic models in fully executable form*."

3.8 NICE's current position not to release fully executable economic models significantly restricts the ability of consultees to formally analyse what impact any proposed changes would have on the cost effectiveness estimates thereby undermining any ability to legitimately challenge any findings based on the use of such models and creating an unfair procedure.

4. SECOND GROUND OF APPEAL – PERVERSITY

The Institute has prepared guidance which is perverse in the light of the evidence submitted

Data used in the modelling of the effectiveness of conventional DMARDs do not reflect the effectiveness of conventional DMARDs in clinical practice for established RA

4.1 The data inputs for HAQ multipliers for conventional DMARDs used in the BRAM model are perverse in the light of the evidence submitted on the effectiveness of conventional DMARD therapy. This results in the distortion of the cost effectiveness of TNF inhibitors used sequentially compared to conventional DMARDs in established RA.

4.2 Estimates on the effectiveness of conventional DMARD in established RA indicate that conventional DMARDs have a minimal impact in terms of HAQ improvement when patients have failed prior conventional DMARDs. At 6-12 months the mean HAQ improvement ranges from 0 in the US National Databank of rheumatic diseases, 0 in the BSRBR patients not switching to a 2nd TNF inhibitor, and 0.11 in the placebo arm for the abatacept trial.

4.3 HAQ changes in the BRAM model are made up from two components, firstly the HAQ improvement on starting a new treatment and underlying HAQ progression over time. Abbott considers that the abatacept trial HAQ multipliers applied for conventional DMARDs in the BRAM model are perverse in the light of evidence submitted on the change in HAQ available on conventional DMARDs. The application of mean HAQ multipliers based on the 0.11 HAQ improvement from the abatacept trial placebo arm means that an average patient with a starting HAQ of 1.82 will have an initial HAQ improvement of 0.11. The underlying HAQ progression of 0.045 per year then leads to a HAQ worsening, which returns the patient to their initial HAQ level after 2.5 years. This is a simplification of what actually occurs in the modelling as patients fail treatments at different times and move on to their next conventional DMARD. However, each time a new conventional DMARD is started there will be a HAQ improvement in line with that observed for the abatacept trial placebo arm. Therefore, patients could have their HAQ score maintained for several years using a sequence of conventional DMARDs in the BRAM model.

4.4 Abbott considers that the HAQ multipliers applied for conventional DMARDs are perverse in the light of the evidence submitted on the effectiveness of conventional DMARDs from the BSRBR, BROSG and the US National Databank for Rheumatic Diseases. These data sources indicate that either the mean HAQ improvements observed in the abatacept trial placebo arms are not achievable in clinical practice for conventional DMARDs or that the mean HAQ progression is greater than 0.045 whilst on conventional DMARDs. Abbott considers that the use of a lower HAQ multiplier for conventional DMARDs than applied using the abatacept trial placebo data would result in improved cost effectiveness for sequential use of TNF inhibitors versus conventional DMARDs. Abbott is unable to predict what the cost per QALY estimates would be without seeing further sensitivity analyses on this point using the BRAM model.

References

[1] National Institute for Health and Clinical Excellence. Guide to the Technology Appraisal Process, May 2004.
[2] National Institute for Health and Clinical Excellence. Guide to the Methods of Technology Appraisal, April 2004.
[3] National Institute for Health and Clinical Excellence. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after failure of a previous TNF-α inhibitor. Final Appraisal Determination, July 2008.
[4] "Revisions to the BRAM model following the NICE Appraisal Committee meeting", August 2006.