Abbott Laboratories comments on the Appraisal Consultation Document of tocilizumab (RoActemra) for the treatment of systemic juvenile idiopathic arthritis

Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the appraisal of tocilizumab for the treatment of systemic juvenile idiopathic arthritis (JIA). Abbott's comments are set out under section headings containing the questions NICE asks stakeholders to comment on for the ACD.

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

Abbott would like to highlight some relevant evidence which has not been taken into account in the ACD.

1.1 Adalimumab licence

The manufacturer submission states that:

"*Adalimumab, given its indication in polyarticular JIA, can be used as an alternative to etanercept. However, due to the age of patients adalimumab is indicated for (13 to 17 years old) it can be assumed it is placed on later line in the treatment sequence*".

In March 2011, the EMEA approved an extension to the existing adalimumab JIA indication, and adalimumab is now licensed to treat patients aged 4 to 12 years as well as those aged 13 to 17[1]. The paediatric vial presentation has been available in the UK since June 2011. Abbott therefore believes that the assumption that adalimumab would be used later in the treatment sequence is no longer valid.

1.2 Adalimumab price

The list price of adalimumab used in the manufacturer's submission is incorrect. The current list price (as of 1 January 2011) is £352.14 per 40mg[2], not £357.50 as reported in table 56 of the manufacturer's submission.

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?

Abbott believes that there are some issues that the Committee may want to consider when assessing the evidence the manufacturer provides in response to the ACD.

2.1 Use of infliximab in patients with juvenile idiopathic arthritis

Although Abbott understands that infliximab may be used in clinical practice, it is not currently licensed for any form of juvenile arthritis. Therefore, unlike tocilizumab, and the other anti-TNF therapies (adalimumab and etanercept) which currently have a licence for polyarticular JIA, the risk benefit profile of this drug has not been assessed by the regulatory authorities in patients with juvenile arthritis.

Infliximab does have a licence for use in patients aged 6-17 with Crohn's Disease. However, section 4.2 of the licence states that:

"*Due to insufficient data on safety and efficacy, Remicade is not recommended for use in any other paediatric indication*[3]"

The licence then refers the reader to section 4.8 (undesirable effects) – in particular the section on juvenile rheumatoid arthritis which reports data on infusion reactions, immunogenicity, and infections from the phase III trial of infliximab in patients with active juvenile rheumatoid arthritis. These data are summarised in Table 1 below.

Table 1 Safety findings from infliximab juvenile rheumatoid arthritis phase III trial

	Infliximab 3mg/kg	**Infliximab 6mg/kg**
Infusion reactions	35%	17.5%
Serious infusion reaction	4/60	2/57
Possible anaphylactic reaction	3/60	1/57
Antibodies developed	38%	12%
Infections*	68%	65%

*Infection rates for the 3mg/kg dose are over a 52 week period, and over a 38 week period for the 6mg/kg dose. Infections were also observed in 47% children receiving placebo for 14 weeks.

Further information on the safety findings from this trial are provided by Ruperto et al.(2007), who report that serious adverse events occurred in 31.7% patients receiving 3mg/kg over a 52 week period compared with 8.8% in patients receiving 6mg/kg over a 38 week period and 5% in patients receiving placebo over a 14 week period[4].

Abbott is concerned that the Committee may choose to not recommend a licensed treatment option in favour of an unlicensed comparator which is specifically not recommended by the regulatory authorities on the grounds of insufficient safety and efficacy data.

2.2 Uncertainty over the infliximab dose

Although the Committee request that the manufacturer conduct a cost-effectiveness analysis comparing tocilizumab to infliximab, it is unclear what dose of infliximab should be used in this comparison.

In the pivotal trial for infliximab in the treatment of patients with juvenile rheumatoid arthritis, patients were randomised to receive either 6 weeks placebo followed by infliximab 6mg/kg plus methotrexate, or infliximab 3mg/kg plus methotrexate. When presenting their findings from the open-label extension (OLE) of this trial, Ruperto et al. reported that:

"Results from the pivotal study suggested that paediatric patients might require higher infliximab doses than adults on a mg/kg basis to maintain adequate serum concentrations and minimise the development of antibodies to infliximab and related infusion reactions[4]."

Further details of these safety findings are reported in the 2007 publication of the pivotal trial results "*the safety profile of infliximab 3 mg/kg appeared less favorable than that of infliximab 6 mg/kg, with more frequent occurrences of serious adverse events, infusion reactions, antibodies to infliximab, and newly induced antinuclear antibodies and antibodies to double-stranded DNA observed with the 3 mg/kg dose."*[5]

Following these safety findings, study investigators were offered several options including an increase in the dose of infliximab, or discontinuation of infliximab therapy.

It therefore appears that the 6mg/kg dose may be the most appropriate infliximab dose to use in the cost-effectiveness analysis, and those are the costs that should be applied. However, it is worth noting that the effectiveness data used in the manufacturer's mixed treatment comparison were from the 3mg/kg arm of the pivotal trial. Furthermore, since the highest licensed dose for infliximab in any indication (including adult indications) is 5mg/kg, the long-term safety of using a 6mg/kg dose is unknown.

2.2 Treatment of patients who are intolerant of methotrexate

In the pivotal trial for infliximab in the treatment of patients with juvenile rheumatoid arthritis, all patients were required to receive concomitant methotrexate[4]. The licence for adult rheumatoid arthritis

also requires that infliximab be given concomitantly with methotrexate[3]. Although infliximab is not licensed for use in a juvenile arthritis population, based on the design of the clinical trial it is likely that the requirement for concomitant methotrexate also applies to its use in this population. If this were the case, infliximab would not be an appropriate treatment option for patients who are intolerant, or contraindicated to methotrexate.

In comparison, tocilizumab, adalimumab and etanercept are all licensed as monotherapies for use in a juvenile arthritis population and are therefore suitable for use in patients who are intolerant, or contraindicated to methotrexate.

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?

Abbott understands the Appraisal Committee's conclusion that there was not enough evidence to allow for a comparison of tocilizumab with methotrexate and their consequent decision not to recommend tocilizumab for patients who are methotrexate naïve.

For the methotrexate failure population, the Appraisal Committee have requested a substantial amount of additional information and analyses from the manufacturer and are therefore "minded not to recommend" tocilizumab for this population. The ACD therefore contains no firm recommendations for this population. However, Abbott does have some concerns about some of the analyses requested (these are outlined above).

4 Are there any equality related issues that may need special consideration?

None that Abbott is aware of.

References

[1] Humira (adalimumab) Summary of Product Characteristics, June 2011. Available at: www.medicines.org.uk
[2] MIMS, August 2011.
[3] Remicade (infiximab) Summary of Product Characteristics, June 2011. Available at www.medicines.org.uk
[4] Ruperto N, Lovell DJ, Cuttica R, Woo P, Meiorin S, Wouters C, Silverman ED, Balogh Z, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Ann Rheum Dis. 2010 Apr;69(4):718-22.
[5] Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, Wouters C, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2007 Sep;56(9):3096-106.