Abbott Laboratories comments on the Appraisal Consultation Document of tocilizumab (RoActemra) for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198)

Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) prepared by the Committee for the rapid review of tocilizumab for the treatment of active moderate to severe rheumatoid arthritis (RA). Abbott's detailed comments following the executive summary are set out under section headings containing the questions NICE asks consultees to comment on for the ACD.

Executive Summary

- **Although the PAS reduces the cost of tocilizumab, the level of discount appears to be based on incorrect assumptions about the drug acquisition cost for tocilizumab in a UK RA population.**
- **The PAS is based on the incorrect assumption that the annual drug acquisition cost for tocilizumab is equal to that of etanercept. However, even using the manufacturer's assumption of a 70kg patient, the annual acquisition cost of tocilizumab is £9,318.40 and not £9,295**
- **The annual cost per patient of treating a 70kg patient with tocilizumab is not representative of the true cost of treating a cohort of RA patients in the UK. The weight distribution of patients enrolled in the BSRBR from the adalimumab cohort (N=4,364 patients) was examined to determine the most likely average annual drug acquisition cost of tocilizumab in the UK. An average cost of £10,460.78 per patient per annum is much more likely given the UK RA patient population demographics.**
- **The level of discount offered by the manufacturer is not only applied to an incorrect drug acquisition cost, but also appears to be based on a fixed cost of administering an infusion, around which there is much uncertainty. Furthermore, the cost on which this discount is based appears to be at the lower end of the plausible range.**
- **Despite the PAS, drug acquisition and administration costs are still greater for tocilizumab than for anti-TNF therapy.**

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

Abbott believes that the relevant evidence has been taken in to account, but that some incorrect assumptions have been made. Further details of these issues are outlined in the following sections.

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 considers it important to highlight some pertinent issues in the summary cost-effectiveness that may affect the interpretation of the evidence, and the preliminary views on the resource impact and implications for the NHS. These issues have been discussed in detail below.

2.1 Costs used in the manufacturer's economic analysis

Abbott understands that the recommendations outlined in the ACD are based on the availability of a patient access scheme (PAS) which takes the form of a discount applied to all invoices, but that the level of this discount is commercial-in-confidence.

However, information provided alongside the ACD indicates that the aim of the PAS is to equalise drug acquisition costs between etanercept and tocilizumab. Abbott is concerned that the PAS is based on incorrect assumptions about drug acquisition and administration cost of tocilizumab, and that tocilizumab remains a more expensive treatment option when compared to etanercept even when the PAS is taken into account.

Furthermore, Abbott would like to highlight the fact that with an annual cost of £9,295, etanercept itself is actually more expensive than adalimumab which costs £9,155.64 per annum.

2.1.1 Incorrect tocilizumab drug costs and administration costs

2.1.1.1 Tocilizumab drug acquisition costs

In paragraph 2.3 on page 5 of the ACD, it states that "*The cost for tocilizumab as reported by the manufacturer is £9295 per year for a patient weighing approximately 70 kg*." Furthermore, on pages 5 and 6 of the patient access scheme submission form, the manufacturer states that "*tocilizumab and etanercept have equivalent annual drug acquisition costs*". Abbott believes that this statement is incorrect.

The recommended dosage of tocilizumab is 8mg/kg, but no lower than 480mg. Therefore a 70kg patient would require 560mg of tocilizumab, which at £1.28/mg equates to £716.80 per infusion session, for which the recommended dose is once every 4 weeks (i.e. 13 infusions per annum). Therefore, the annual acquisition cost of tocilizumab for a 70kg patient with rheumatoid arthritis is **£9,318.40** and not £9,295 as the manufacturer claims (one 400mg vial and two 80mg vials).

Abbott accepts that not every RA patient in the UK weighs 70kg; instead there will be a distribution of differing weights about this 'average' patient weight. This has obvious implications on the average annual cost of tocilizumab. As such, Abbott has examined the weight distribution of patients enrolled in the BSRBR from the adalimumab cohort (N=4,364 patients) to determine the most likely average annual drug acquisition cost of tocilizumab in the UK. The weight distribution observed in the BSRBR is shown in Figure 1. Of note, the recommended dosage of tocilizumab should go no lower than 480mg and therefore the lower weight range has to be capped at 60kg.

Figure 1 BSRBR patient weight distribution

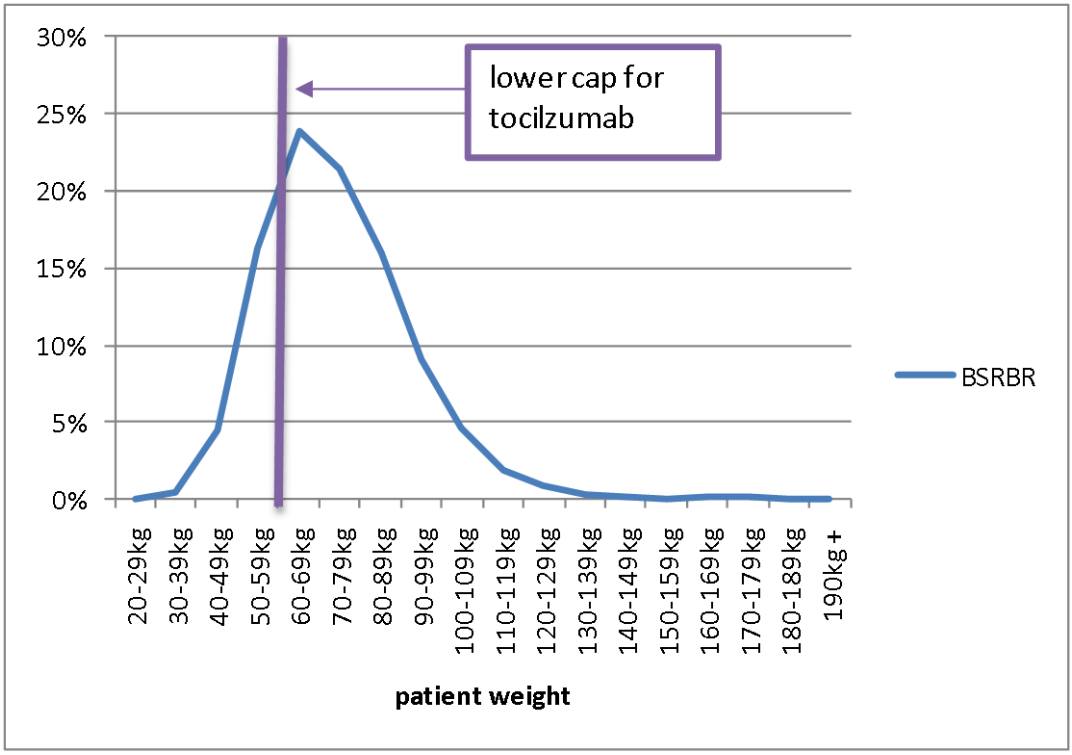

Table 1 shows the annual drug acquisition cost of tocilizumab over a range of weights, and subsequently the average annual cost per patient derived from the proportions of patients in the BSRBR at these different weights. Since the lower weight range has to be capped at 60kg, the cost of tocilizumab is also capped at the lower range. The additional cost of treating high weight patients with tocilizumab is therefore not offset by reduced costs for low weight patients.

Table 1: Average annual drug acquisition cost of tocilizumab derived from BSRBR patient weights

Possible combinations of tocilizumab vials	Total dose	Lower weight	Upper weight	Cost per dose	% patients in BSRBR	Annual drug acquisitioncost
400+80	480	-	60	£614.40	24.27%	£7,987.20
400+80+80	560	61	70	£716.80	23.97%	£9,318.40
400+200	600	71	75	£768.00	11.07%	£9,984.00
400+200+80	680	76	85	£870.40	17.42%	£11,315.20
400+200+80+80	760	86	95	£972.80	11.73%	£12,646.40
400+400	800	96	100	£1,024.00	4.12%	£13,312.00
400+400+80	880	101	110	£1,126.40	3.99%	£14,643.20
400+400+80+80	960	111	120	£1,228.80	1.72%	£15,974.40
400+400+200	1000	121	125	£1,280.00	0.66%	£16,640.00
400+400+200+80	1080	126	135	£1,382.40	0.30%	£17,971.20
400+400+200+80+80	1160	136	145	£1,484.80	0.34%	£19,302.40
400+400+400	1200	146	150	£1,536.00	0.07%	£19,968.00
400+400+400+80	1280	151	160	£1,638.40	0.14%	£21,299.20
400+400+400+80+80	1360	161	170	£1,740.80	0.07%	£22,630.40
400+400+400+200	1400	171	175	£1,792.00	0.07%	£23,296.00
400+400+400+200+80	1480	176	185	£1,894.40	0.05%	£24,627.20
400+400+400+200+80+80	1560	186	195	£1,996.80	0.02%	£25,958.40
Average cost per dose				£804.68		
Average cost per year (13 doses)						**£10,460.78**

Data from the BSRBR are representative of the patient population that tocilizumab is intended for use in, and importantly are UK specific. Therefore, the annual drug acquisition cost for tocilizumab that the manufacturer proposes is an underestimation of the actual drug acquisition cost that would be incurred in the UK. An average cost of **£10,460.78** per patient per annum is much more likely given the UK RA patient population demographics.

The average annual cost of £10,460.78 is based on the most convenient way to make up the tocilizumab dosage for a given patient weight; however, Abbott has also conducted another analysis minimising vial wastage to see the impact on the drug acquisition cost. In this scenario the average annual cost based on the weight distributions in the BSRBR cohort is £10,244.51 per person. However, in order to minimise vial wastage in some cases up to 8 vials of tocilizumab would be required for one patient's infusion. In clinical practice it is highly unlikely that the nurse preparing the infusion would decant 8 vials as it would be extremely time consuming and importantly increase the chance of administration error. Furthermore, the increased nurse time spent minimising vial wastage subsequently means that an administration cost of £142 per infusion is not plausible.

Therefore, Abbott asks that when the Committee prepares the final appraisal determination, the true cost of tocilizumab is considered. Using the average annual drug cost based on the weight distributions from the BSRBR (approximately £10,460), the drug acquisition cost of tocilizumab is in fact higher than the cost of etanercept (which in turn is more expensive than adalimumab).

2.1.1.2 Tocilizumab administration costs

The patient access scheme submission form also states that "*the value of the discount is linked to the assumed tocilizumab drug administration cost, as reported in the FAD and included in the final economic model of £154.30*" (p6)

The cost of administering tocilizumab therefore appears to be of central importance in determining the relative cost (and therefore the cost-effectiveness) of tocilizumab versus etanercept. Abbott is concerned that not only is the PAS based on an underestimate of the drug acquisition cost of tocilizumab, but that the cost of an infusion may also be underestimated.

Abbott have reviewed all of the documentation from the original NICE appraisal, and note that there was a significant amount of discussion around the most appropriate cost to apply for an infusion. This indicates a considerable amount of uncertainty around the cost of an infusion, and Abbott is unclear whether this has been taken into account when calculating the revised ICERs.

Although the final guidance for tocilizumab indicates that the Committee concluded that an administration cost of £154 is acceptable, in the third ACD for this appraisal, the Committee concluded that the cost of administering tocilizumab was "at least £154" indicating that this is in fact at the lower end of plausible values.

2.1.1.3 Etanercept administration costs

Abbott notes that the manufacturer's model includes an administration cost for subcutaneous therapies based on an assumption that 10% of injections would be performed by a district nurse. The rationale for this assumption is unclear however discussions with rheumatologists and rheumatology nurses indicate that this is likely to be a significant overestimate of the proportion of patients requiring assistance with a subcutaneous therapy. The inclusion of such a cost is likely to bias any cost-effectiveness analysis in favour of tocilizumab.

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?

The Committee's original decision not to recommend tocilizumab for the treatment of RA in patients whose disease has responded inadequately to disease-modifying anti-rheumatic drugs (DMARDs) was based on the conclusion that tocilizumab does not offer any clinical benefit over etanercept, and was found to be more costly.

It is Abbott's understanding that in order to warrant a change in the recommendations, tocilizumab must be considered to be equivalent or lower cost when compared with etanercept. Although the exact level of discount applied to the drug acquisition cost of tocilizumab is confidential, Abbott does not believe that the PAS offered by the manufacturer reduces the cost of tocilizumab sufficiently to warrant such a change in the recommendations. Furthermore, Abbott believes that tocilizumab is still a more expensive treatment option when compared with anti-TNF therapy.

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

Abbott is not aware of any equality related issues that may need special consideration in the preliminary recommendations.

References