**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**Health Technology Appraisal**

# Tocilizumab for the treatment of rheumatoid arthritis (rapid review of TA198)

**Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

**Definitions:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

**Clinical specialists and patient experts** – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

**Commentators –** Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

**Public –** Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

**Comments received from consultees**

| Consultee | Comment | Response |
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| Roche | Has all the relevant evidence been taken into account - No comment. | Comment noted. |
| Roche | We would like to comment on sections 4.7 to 4.9 in the ACD. These three sections concern the Appraisal Committee's considerations of the relative efficacy of etanercept, tocilizumab and rituximab.<br><br>In Section 4.7 it is stated that the Appraisal Committee noted that "etanercept appeared at least equal to, and possibly had higher efficacy than, tocilizumab" once the Klareskog trial was removed from the indirect comparison analysis initially presented by Roche. Section 4.8 subsequently concludes that results from this indirect comparison should not be used as the basis for decision-making, because the adjustment method in the analysis appears to preferentially improve ACR responses associated with tocilizumab whilst reducing the ACR responses of rituximab and etanercept. Section 4.9 finally notes the Committee's conclusion, based on unadjusted trial estimates of ACR rate, that "the evidence was not conclusive of a benefit of any one drug over another".<br><br>Taken together, we believe the statements in 4.7 and 4.8 could be interpreted to mean that the Committee considered etanercept to be equally if not more efficacious than tocilizumab, a difference which they found was 'masked' by Roche's initially-submitted indirect comparison analysis. This interpretation runs contrary to the Committee's final approach to efficacy in section 4.9, which allowed use of unadjusted trial statistics in the final economic model but considered that there was little to distinguish the treatments with regard to ACR response.<br>The comments in 4.7 through 4.9 also do not acknowledge that by using unadjusted trial statistics, slight differences in the placebo response rate seen in the etanercept and tocilizumab trials are unchecked and allowed to influence the results. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication. |

| Consultee | Comment | Response |
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| | Furthermore, no description is provided of the direction or magnitude of any bias which could potentially arise through this approach.<br><br>To improve clarity, we would recommend that the wording in 4.7 about relative efficacy of etanercept and tocilizumab be changed to more closely reflect the conclusion in 4.9. | |
| Roche | We welcome the Appraisal Committee's preliminary recommendations on the use of tocilizumab in rheumatoid arthritis (RA).<br><br>However, we believe that the layout of the guidance, its conditions and wording could be simplified to avoid confusion and challenges in the NHS in implementing the guidance. Below, we highlight the key parts of the guidance which we feel could be improved for clarity. | Comment noted. The wording of the guidance section has been reviewed and amended; see section 1.1 of the FAD. |
| Roche | Description of disease severity<br><br>There is a lack of consistency in the description of disease severity. "Active disease" is referred to on pages 3 and 4 of this document, but on pages 44 and 45 of the document the term "severe active disease" is used. We would recommend using the same wording for both. For your information, tocilizumab is licensed for moderate to severe active RA. | Comment noted. The wording of the guidance section has been reviewed and amended; see section 1.1 of the FAD. |
| Roche | Conditionality and wording in main recommendations<br><br>We note that each of the Institute's three guidance points for tocilizumab contain conditions under which the product is recommended for use. | Comment noted. |
| Roche | Use of word "only"<br><br>We note that in section 1.2 the phrase 'only recommended' is used prior to a list of conditions under which tocilizumab may be used in people whose disease has responded inadequately to one or more tumour necrosis alpha (TNF-α) inhibitors. | Comment noted. The wording of the guidance section has been reviewed and amended; see section 1.1 of the FAD. |

| Consultee | Comment | Response |
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| | We cannot see a particular semantic need for using the word "only" ahead of the conditions listed in 1.2, when all recommendations include bullet-lists of conditions, preceded by the word "if:"<br><br>In case NICE considers it important to emphasise the conditionality of guidance in 1.2 through use of the word "only", we would suggest that this word be moved such that the bullet lists are each preceded by the words "only if:" | |
| Roche | Use of wording "other TNF-inhibitors" in 1.1 and 1.3.<br><br>In section 1.1, tocilizumab is recommended for use in the DMARD-IR population. The condition for use in this population is that tocilizumab is used as per guidance set out for TNF-α inhibitors in TA130. Since tocilizumab acts on the IL-6 pathway and does not directly inhibit TNF-α, we suggest that the word "other" be removed from the guidance point in order to be clinically accurate.<br><br>The same wording is used in section 1.3 to refer to the TA195 guidance for use of TNF-α inhibitors. Our suggestion would be to make a similar amendment in that section. | Comment noted. The wording of the guidance section has been reviewed and amended; see section 1.1 of the FAD. |
| Roche | Overall, we would comment that the current draft guidance wording may be confusing and difficult for clinicians to follow. To ensure we have correctly understood the preliminary recommendations, we would like to provide our interpretation of each of the guidance points in sections 1.1 through 1.3:<br><br>Tocilizumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults with active disease:<br><br>• Where their disease has responded inadequately to disease-modifying anti-rheumatic drugs (DMARDs), **providing that** tocilizumab is used as described for TNF- | Comment noted. The wording of the guidance section has been reviewed and amended; see section 1.1 of the FAD. |

| Consultee | Comment | Response |
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| | α inhibitor treatments in NICE TA130<br><br>**or**<br>• Where their disease has responded inadequately to one or more biologic treatments including a TNF-α inhibitor, **providing that** their rheumatoid arthritis has also responded inadequately to rituximab, or rituximab was contraindicated or withdrawn because of an adverse event<br><br>**or**<br>• As an alternative to rituximab, **providing that**<br>o Their disease has responded inadequately to DMARDs, including a TNF-α inhibitor **and**<br>o They cannot receive rituximab because they have a contraindication or rituximab was tried and withdrawn due to an adverse event **and**<br>o Tocilizumab is used as described for TNF-α inhibitor treatments in NICE TA195.<br><br>**These recommendations are only valid if the manufacturer provides the discount agreed as part of the patient access scheme.**<br><br>If at all possible, we would be grateful to receive the Institute's confirmation that this interpretation is correct. We would also encourage the Institute to consider simplifying the guidance wording, in order to ensure that tocilizumab is used correctly and in compliance with the recommendations made in the ACD. | |
| Roche | Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belier? | Comment noted. |

| Consultee | Comment | Response |
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| | No comment. | |
| Roche | Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?<br><br>No comment. | Comment noted. |
| Roche | If you wish to comment on the evaluation report, please do so under a separate heading from your comments on the ACD.<br><br>N/A (no new evaluation report created). | Comment noted.<br>The evaluation report for this appraisal can be found at: http://guidance.nice.org.uk/TA/Wave18/63/Consultation/EvaluationReport |
| The Royal College of Nursing | We welcome the review of the evidence of the use of tocilizumab in a number of treatment approaches on the pathway and have nothing further to add with regards to the evidence reviewed. | Comment noted. |
| The Royal College of Nursing | The clinical summaries bring together the results of a number of trials and although we have no specialist knowledge of economic modeling, the interpretation of the evidence would appear to be reasonable. The clinical summaries confirm the benefits of using tocilizumab that we have seen in our practice, including the ongoing benefits in patients who took part in the trial for DMARD-IR and were TNF- alpha inhibitor naive who remain in remission, both of whom have been able to return to full time work.<br><br>We also know of patients who have managed to return to heavy manual work when tocilizumab has been used after failure of a TNF- alpha inhibitor.<br><br>We have experience of an increasing number of patients who are on this medication in its current place in the pathway who by the nature of this position have had their RA for several years with a high level of chronicity who are also in remission.<br><br>Inclusion of the patient access scheme is also noted and welcomed. | Comment noted. |

| Consultee | Comment | Response |
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| | We understand that NICE, under its current remit, cannot take into account the societal costs of sub-optimal treatment of patients with RA but would like to state that these remain a significant cost to the economy as a whole. | |
| The Royal College of Nursing | We welcome the inclusion of toclizumab plus methotrexate as an option after inadequate response to one or more DMARDS as well as the continued recommendation of its place as a treatment choice after inadequate response to DMARD and TNF- alpha inhibitor and rituximab as well as in patients for whom rituximab is contra-indicated.<br><br>The patient access scheme recognises the cost of biologic treatments and is welcomed as a means to keep costs down and reduce some of the burden on the Health Service.<br><br>We do not have full details on the patient access scheme agreed with Roche and Department of Health. We are aware that with a previous patient access scheme (as seen with certolizumab and UCB) there has been instruction from some PCTs that Certolizumab must be used first line and know of at least three PCTs who have enforced this.<br><br>If the patient access scheme for tocilizumab makes the total acquisition cost of tocilizumab much cheaper than the other biologics, then we would hope that PCTs do not enforce that tocilizumab must be the preferred first line biologic as this would limit patient choice.<br><br>It would have been helpful if there are more details regarding the patient access scheme, (for example will the discount be on the infusion costs or the drug cost?), we however, understand that this could be subject to the confidential agreement with Roche & Department of Health. | Comment noted. See section 2.4 and 5.2 of the FAD, The Department of Health and the manufacturer have agreed that tocilizumab will be available to the NHS with a patient access scheme in which a discount from the list price is applied to original invoices. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. The manufacturer has agreed that the patient access scheme will remain in place until any review of this NICE technology appraisal guidance is published. It is the responsibility of the manufacturer to communicate the level of discount to the relevant NHS organisations.<br><br>See section 4.24 of the FAD which states; the Committee noted that, in clinical practice and as recommended in the guidance on adalimumab, etanercept and infliximab for rheumatoid arthritis (NICE technology appraisal guidance 130), treatment should normally be initiated with the least expensive drug; this would not necessarily be the same drug in individual cases because of differences in the mode of administration and treatment schedules. The Committee therefore concluded that it was appropriate to recommend tocilizumab as an option following the same considerations as for the drugs recommended as options in NICE technology appraisal guidance 130. |

| Consultee | Comment | Response |
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| The Royal College of Nursing | None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate. | Comment noted. |
| The British Society of Rheumatology | The decision by NICE to allow tocilizumab (the only interleukin-6 antagonist currently available) to be used earlier in the management sequence of rheumatoid arthritis (RA) is greatly welcomed. The evidence base for the use of this biologic agent in RA is extensive and tocilizumab is well placed to be started in patients who have failed traditional DMARDs, such as methotrexate (MTX), as well as those individuals no longer responding to anti-TNF agents.<br><br>One of the challenges rheumatologists face is to determine which medication is most appropriate for any particular person with RA. Due to the heterogeneic nature of the condition rheumatologists do not know who will respond optimally to any specific therapy. In spite of this, however, certain clinical features lend themselves to favouring tocilizumab over other biologic agents such as TNF antagonists. This includes patients with a high inflammatory response (eg. high CRP) and those with systemic features such as fatigue and anaemia, which are driven largely by interleukin-6. Furthermore tocilizumab is an excellent choice for those patients where compliance may be an issue as it is given intra-venously. | Comment noted. |
| The British Society of Rheumatology | The BSR would like clarification of the draft guidance due to the ambiguity of statements 1.1 and 1.2 which appear to be mutually exclusive. In statement 1.1 tocilizumab may be used in combination with methotrexate prior to anti-TNF therapy however statement 1.2 states that it is only recommended in patients who have failed on TNF antagonists. Furthermore bullet point 3 of statement 1.1 suggests that tocilizumab may be used as monotherapy as 3 of the anti-TNF biologics can be used as monotherapy (etanercept, adalimumab and certolizumab). | Comment noted. The wording of the guidance section has been reviewed and amended; see section 1.1 of the FAD. |

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| The British Society of Rheumatology | Overall the decision is a major step forward in combating the debilitating condition of RA and has given clinicians greater freedom to optimise patient outcomes. | Comment noted. |

**Comments received from clinical specialists and patient experts**

None received.

**Comments received from commentators**

| Commentator | Comment | Response |
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| Abbott Laboratories | 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. | Comment noted. |

| Commentator | Comment | Response |
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| Abbott Laboratories | Executive summary<br><br>• 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.<br><br>• 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<br><br>• 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.<br><br>• 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.<br><br>• Despite the PAS, drug acquisition and administration costs are still greater for tocilizumab than for anti-TNF therapy. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See responses below on pages 9 to 16.<br><br>Comment noted, see section 4.15 of the FAD. |

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| Abbott Laboratories | 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. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication. |
| Abbott Laboratories | 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. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication. |

| Commentator | Comment | Response |
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| Abbott Laboratories | 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.<br><br>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.<br><br>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. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.24 of the FAD which states; the Committee noted that, in clinical practice and as recommended in the guidance on adalimumab, etanercept and infliximab for rheumatoid arthritis (NICE technology appraisal guidance 130), treatment should normally be initiated with the least expensive drug; this would not necessarily be the same drug in individual cases because of differences in the mode of administration and treatment schedules. The Committee therefore concluded that it was appropriate to recommend tocilizumab as an option following the same considerations as for the drugs recommended as options in NICE technology appraisal guidance 130. |

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| Abbott Laboratories | **2.1.1 Incorrect tocilizumab drug costs and administration costs**<br><br>*2.1.1.1 Tocilizumab drug acquisition costs*<br><br>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.<br><br>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).<br><br>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. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.24 of the FAD which states; the Committee noted that, in clinical practice and as recommended in the guidance on adalimumab, etanercept and infliximab for rheumatoid arthritis (NICE technology appraisal guidance 130), treatment should normally be initiated with the least expensive drug; this would not necessarily be the same drug in individual cases because of differences in the mode of administration and treatment schedules. The Committee therefore concluded that it was appropriate to recommend tocilizumab as an option following the same considerations as for the drugs recommended as options in NICE technology appraisal guidance 130. |

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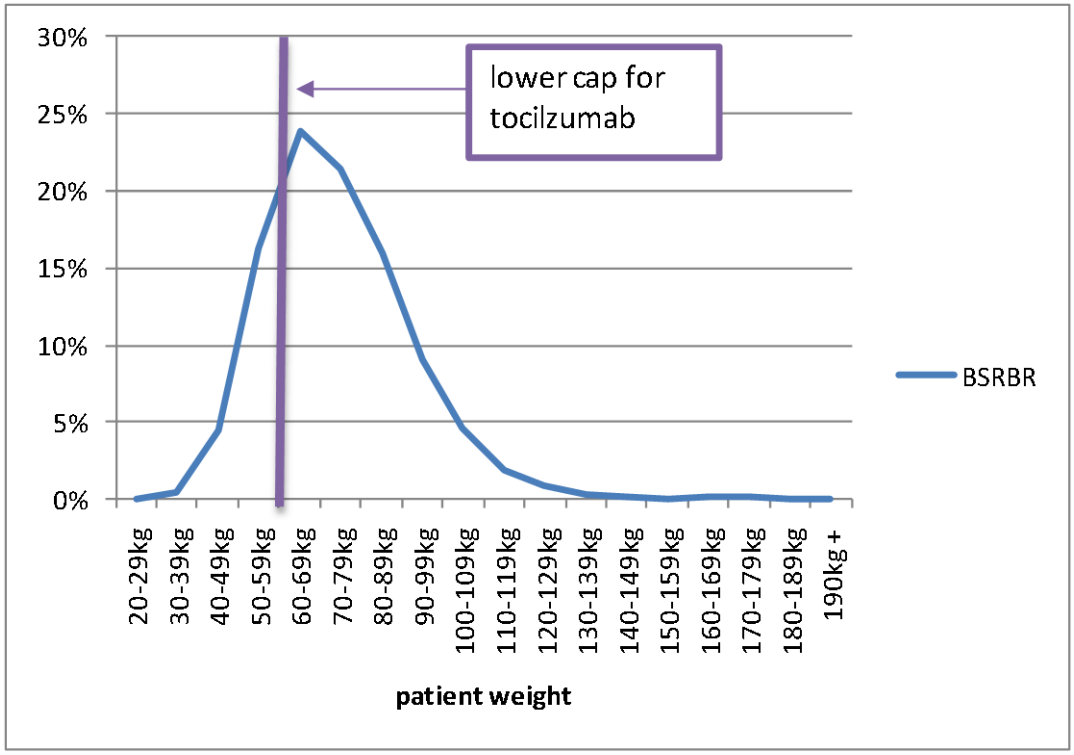
| Abbott Laboratories | **Figure 1 BSRBR patient weight distribution**<br>  <br><br>Table 1 shows the annual drug acquisition cost of tocilizumab over a range of weights, and subsequently the average annual cost per patient derived from the proportions of patients in the BSRBR at these different weights. 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. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.24 of the FAD which states; the Committee noted that, in clinical practice and as recommended in the guidance on adalimumab, etanercept and infliximab for rheumatoid arthritis (NICE technology appraisal guidance 130), treatment should normally be initiated with the least expensive drug; this would not necessarily be the same drug in individual cases because of differences in the mode of administration and treatment schedules. The Committee therefore concluded that it was appropriate to recommend tocilizumab as an option following the same considerations as for the drugs recommended as options in NICE technology appraisal guidance 130. |

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<tr><th>Commentator</th><th>Comment</th><th>Response</th></tr>
<tr><td>Abbott Laboratories</td><td>

**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** |

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Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.

See section 4.24 of the FAD which states; the Committee noted that, in clinical practice and as recommended in the guidance on adalimumab, etanercept and infliximab for rheumatoid arthritis (NICE technology appraisal guidance 130), treatment should normally be initiated with the least expensive drug; this would not necessarily be the same drug in individual cases because of differences in the mode of administration and treatment schedules. The Committee therefore concluded that it was appropriate to recommend tocilizumab as an option following the same considerations as for the drugs recommended as options in NICE technology appraisal guidance 130.

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| Commentator | Comment | Response |
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| Abbott Laboratories | 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.<br><br>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.<br><br>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). | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.24 of the FAD which states; the Committee noted that, in clinical practice and as recommended in the guidance on adalimumab, etanercept and infliximab for rheumatoid arthritis (NICE technology appraisal guidance 130), treatment should normally be initiated with the least expensive drug; this would not necessarily be the same drug in individual cases because of differences in the mode of administration and treatment schedules. The Committee therefore concluded that it was appropriate to recommend tocilizumab as an option following the same considerations as for the drugs recommended as options in NICE technology appraisal guidance 130. |

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| Abbott Laboratories | *2.1.1.2 Tocilizumab administration costs*<br><br>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)<br><br>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.<br><br>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.<br><br>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. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.15 of the FAD; Although the Committee agreed that a cost based on an administration time of 1 hour represented the minimum cost to the NHS, it did not agree that the true cost would be as much as double. The Committee therefore considered that it was not appropriate to double the administration cost of tocilizumab and concluded that the manufacturer's revised estimate of £154 was acceptable. |
| Abbott Laboratories | *2.1.1.3 Etanercept administration costs*<br><br>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. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication. |

| Commentator | Comment | Response |
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| Abbott Laboratories | 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.<br><br>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. | Comment noted, see sections 4.11 and 4.17 to 4.24 of the FAD. |
| Abbott Laboratories | Abbott is not aware of any equality related issues that may need special consideration in the preliminary recommendations. | Comment noted. |
| MSD | MSD welcomes the opportunity to comment on the ACD for tocilizumab for the treatment of RA. Our comments are outlined below. | Comment noted. |
| MSD | **MSD is concerned that the wording and layout of the advice in the ACD could result in inappropriate use of tocilizumab.**<br><br>The ACD states that: "Tocilizumab in combination with methotrexate (MTX) is recommended as an option for the treatment of RA…if:<br>…it is used as described for other tumour necrosis factor (TNF) inhibitor treatments"<br><br>This statement can easily be misinterpreted and may lead the reader to believe that tocilizumab is a tumour necrosis factor (TNF) inhibitor which of course it is not. Tocilizumab is a humanised monoclonal antibody against the interleukin-6 receptor (IL-6R). It is not a TNF inhibitor treatment and thus should not be grouped together with this class. | Comment noted. The wording of the guidance section has been reviewed and amended; see section 1.1 of the FAD. |

| Commentator | Comment | Response |
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| MSD | **<u>Advice for tocilizumab should align clearly to licensed indications.</u>**<br><br>Tocilizumab is licensed for use in combination with methotrexate (MTX) for the treatment of RA in patients who have responded inadequately to or were intolerant to previous therapy with one or more DMARD OR tumour necrosis factor (TNF) inhibitor treatments.<br><br>Tocilizumab can be given as monotherapy in patients who are intolerant to MTX, or where continued treatment with MTX is inappropriate.<br><br>By separating the advice for tocilizumab across sections 1.1, 1.2 and 1.3 of the ACD, MSD believe that the licensed indications for tocilizumab may, inadvertently, be misrepresented. We would suggest that sections 1.1 and 1.2 should be combined so that advice is given for patients who responded inadequately to one or more DMARDs or TNF inhibitor treatments. It should be made clear that tocilizumab is not a TNF inhibitor treatment, and thus should be prescribed after inadequate response to one or more DMARD or TNF inhibitor treatments. This is in line with licence. | Comment noted. The wording of the guidance section has been reviewed and amended; see section 1.1 of the FAD.<br><br>No recommendation has been made regarding using tocilizumab as a monotherapy. See section 4.6 of the FAD which states " the Committee concluded that no evidence for tocilizumab monotherapy within its licensed indication was available, and therefore no recommendations for tocilizumab as a monotherapy could be made"' |

| Commentator | Comment | Response |
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| MSD | **<u>Treatment pathway and sequential use.</u>**<br><br>Currently there is clear NICE guidance on the options available for patients who have experienced an inadequate response to a TNF inhibitor as a first line biologic. TA195 states that:<br><br>*"Rituximab in combination with methotrexate is still recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs,* ***including at least one TNF inhibitor.*** *Additional treatment options are now recommended for these adults if rituximab therapy is contraindicated or withdrawn because of an adverse event, specifically:*<br>• *If rituximab is contraindicated or withdrawn, adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are now recommended as treatment options.*<br>• *If rituximab therapy cannot be given because methotrexate is contraindicated or withdrawn because of an adverse event, adalimumab and etanercept, each as monotherapy, are now recommended as treatment options"*<br><br>This wording has also been incorporated into TA225 (appraisal of golimumab) and TA186 (appraisal of certolizumab).<br><br>However, there is no guidance on the treatment pathway if a non-TNF inhibitor is used as the first line biologic, nor are there any trials where efficacy of biologics used second line after an IL-6 inhibitor currently available.<br><br>It is currently unclear what impact a recommendation for tocilizumab as a first line biologic therapy would have on the treatment pathway. By recommending tocilizumab as a first line biologic the committee are requiring rheumatologists to take a prescribing decision with no evidence base and to assume that if patients fail tocilizumab, an alternative biologic will be effective and safe. | Comment noted. The wording of the guidance section has been reviewed and amended; see section 1.1 of the FAD.<br><br>Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication. |

| Commentator | Comment | Response |
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| MSD | **Consideration of all costs and relevant cost data within the submission and Patient Access Scheme (PAS).**<br><br>Central to the PAS supplied by Roche is the idea that the discount of 21.3% "*aims to equalize drug acquisition costs between etanercept and tocilizumab".*<br><br>This statement leads to a number of questions regarding the applicability of the discount in its proposed form and the validity of the figures used by Roche to achieve price parity with etanercept. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication. |

| Commentator | Comment | Response |
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| MSD | **Derivation of the annual cost of tocilizumab.**<br><br>There is inconsistency and a lack of clarity around how tocilizumab is costed within the PAS. Figure 1 from the PAS shows an annual cost of £7,250 for tocilizumab and an annual administration cost of £2,006. However, from table 1 below, it can be seen that for a 70 kg patient the annual drug cost based on MIMS October prices, and assuming the least possible wastage (best case for tocilizumab) less 21.3% discount, would be £7,314.94.<br><br>Adding a £2,005.90 administration cost results in an annual cost (including discount) of £9,320.84 per patient. As stated in the PAS, etanercept has an annual cost of £9,295 and thus this discount does not provide price parity with etanercept as is claimed. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.24 of the FAD which states; the Committee noted that, in clinical practice and as recommended in the guidance on adalimumab, etanercept and infliximab for rheumatoid arthritis (NICE technology appraisal guidance 130), treatment should normally be initiated with the least expensive drug; this would not necessarily be the same drug in individual cases because of differences in the mode of administration and treatment schedules. The Committee therefore concluded that it was appropriate to recommend tocilizumab as an option following the same considerations as for the drugs recommended as options in NICE technology appraisal guidance 130. |

| Commentator | Comment | Response |
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| MSD | **Applicability of a defined discount for weight based pricing**<br><br>As stated above, the PAS and economic modelling for the tocilizumab submission relies on a single patient weight of 70 kg. Whilst we acknowledge that NICE has taken this approach in previous assessments of infliximab within Rheumatoid Arthritis (TA130 and TA195), MSD would suggest that aggregated costs are a more suitable method for costing technologies where price is dependant on weight.<br><br>By assuming a patient weight of 70 kg and applying the 21.3% discount, price parity with etanercept is almost achieved (see above) for tocilizumab. However, by fixing the discount irrespective of the weight of the patient the NHS could stand to face a much larger budget impact than expected. Referring to Table 1 below, it can be seen that for any patient who weighs over 70 kg, even when the discount is applied, price parity with etanercept (the most expensive of the subcutaneous TNF inhibitor treatments) is not achieved.<br><br>**Table 2 – Calculation of weight based costing of Tocilizumab (TOCI) – SEE APPENDIX 1**<br><br>From the BSRBR registry data on infliximab it can be seen that of all monitored patients treated with infliximab, 53.83% weigh over 70 kg.<br><br>From Table 1 it can be demonstrated that the NHS could face costs of up to £12,455.82 per patient per year. In the DMARD experienced population (where tocilizumab is currently not recommended) the NICE costing statement for TA225 (appraisal of golimumab for the treatment of RA) states that approximately 34,600 patients are eligible for treatment with a biologic agent. The use of tocilizumab in such a large population where an estimated 54% weigh over 70 kg could create a large budgetary impact for the NHS.<br><br>Taking the weight distributions for infliximab from the BSRBR database and applying the discount to the cost of tocilizumab it can be seen that the aggregated cost per patient per year would be likely to be £11,276. This is much greater than the cost of the TNF inhibitor treatments and suggests that the proposed discount does not work as described. For the calculations used to derive this figure please see table 2 below.<br><br>**Table 3 – Calculation of aggregated cost per patient per year of tocilizumab – SEE APPENDIX 2** | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.24 of the FAD which states; the Committee noted that, in clinical practice and as recommended in the guidance on adalimumab, etanercept and infliximab for rheumatoid arthritis (NICE technology appraisal guidance 130), treatment should normally be initiated with the least expensive drug; this would not necessarily be the same drug in individual cases because of differences in the mode of administration and treatment schedules. The Committee therefore concluded that it was appropriate to recommend tocilizumab as an option following the same considerations as for the drugs recommended as options in NICE technology appraisal guidance 130. |

| Commentator | Comment | Response |
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| MSD | **The opportunity cost to the NHS**<br><br>MSD consulted with a number of clinical and specialist rheumatology nurses to advise on the potential impact of providing infusion services every 4 weeks. The consensus was that infusion services are currently operating either at or near to capacity, so if the NHS is required to provide infusion services every 4 weeks the resource required will need to be deployed from elsewhere. If these resources are moved from providing more cost-effective services, the NHS will not be maximizing possible QALY gains and will have the opportunity cost of the lost alternative services imposed upon it. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication. |

| Commentator | Comment | Response |
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| MSD | **<u>Additional costs of treatment with tocilizumab</u>**<br><br>Prior to initiating treatment with tocilizumab, blood tests are required to check for liver enzyme abnormalities and absolute neutrophil count in all indicated populations.<br><br>Section 4.4 of the tocilizumab SmPC also states that liver enzymes should be monitored every four to eight weeks for the first six months of treatment, followed by every twelve weeks thereafter. In JIA they should be measured after the second infusion and then thereafter according to good clinical practice. These tests are not required for infliximab (Remicade) or golimumab (Simponi). MSD would ask whether the associated costs of these tests and subsequent workup for abnormal values have been taken into account.<br><br>The SmPC for tocilizumab states that:<br><br>*" …assessment of lipid parameters should be performed four to eight weeks following initiation of therapy with tocilizumab…*<br><br>*During the six month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoActemra in clinical trials experienced sustained elevations in total cholesterol 6.2 mmol/ l, with 15% experiencing a sustained increase in LDL to 4.1 mmol/ l. Elevations in lipid parameters responded to treatment with lipid-lowering agents.*<br><br>*During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled trials".*<br><br>These elevations in lipid parameters are likely to mean significant additional treatment costs for patients prescribed tocilizumab, especially as the SmPC suggests that these patients should all be treated with lipid lowering drugs. MSD would query whether the associated costs have been taken into account. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.2 of the FAD, the Committee noted the safety data presented by the manufacturer, which reported 27 deaths and a serious adverse event of 5.8%. The Committee considered this adverse event rate was high, but heard that it was comparable with other biological treatments. |

| Commentator | Comment | Response |
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| MSD | Although this population isn't within any NICE guidelines, patients with RA are at increased risk of CVD. In light of the lack of clear data, any increases in lipids need to be considered or carefully monitored.[I II]. *([1] D H Solomon, N J Goodson, J N Katz, M E Weinblatt, J Avorn, S Setoguchi, C Canning, S Schneeweiss Patterns of cardiovascular risk in rheumatoid arthritisAnn Rheum Dis (2006) 65:1608–1612*<br><br>*[1] Christophe Meunea, Emmanuel Touzéb, Ludovic Trinquartc, Yannick Allanored High risk of clinical cardiovascular events inrheumatoid arthritis: Levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis Archives of Cardiovascular Disease (2010) 103: 253—261)* | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.2 of the FAD, the Committee noted the safety data presented by the manufacturer, which reported 27 deaths and a serious adverse event of 5.8%. The Committee considered this adverse event rate was high, but heard that it was comparable with other biological treatments. |
| MSD | In addition, section 3.14 of the ACD states that:<br><br>*" The manufacturer reported that…adverse events reported more frequently with tocilizumab 8 mg/kg monotherapy than in the methotrexate group were abdominal pain and discomfort, headache, dizziness, rash, pruritis and elevated blood pressure, neutropenia, leukopenia and hyperlipidaemia. Most of these events were mild and transient."*<br><br>MSD would challenge the use of the phrase "mild and transient" with respect to lipid elevations as this is in direct contradiction to the SmPC. The SmPC for tocilizumab states that:<br><br>*"With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoActemra in clinical trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/ l, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ l"*<br><br>The committee should also note that complications of diverticulitis and GI perforation are specifically mentioned in the SmPC for tocilizumab (sections 4.4 and 4.8). | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.2 of the FAD, the Committee noted the safety data presented by the manufacturer, which reported 27 deaths and a serious adverse event of 5.8%. The Committee considered this adverse event rate was high, but heard that it was comparable with other biological treatments. |

| Commentator | Comment | Response |
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| MSD | **Medium term safety data for the TNF inhibitor treatments.**<br><br>Since TA198, the established TNF inhibitor treatments, infliximab, etanercept, and adalimumab have accumulated a significant amount of medium term safety data which has been collected and published by the BSRBR. In addition, there is considerable long-term clinical trial safety data for the established TNF inhibitors. At this time no medium term safety data is available for tocilizumab. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.2 of the FAD, the Committee noted the safety data presented by the manufacturer, which reported 27 deaths and a serious adverse event of 5.8%. The Committee considered this adverse event rate was high, but heard that it was comparable with other biological treatments. |
| MSD | In conclusion MSD has concerns around the content, wording and layout of the advice in the ACD. This could potentially result in inappropriate use of tocilizumab for the treatment of patients with RA. | Comment noted. The wording of the guidance section has been reviewed and amended; see section 1.1 of the FAD. |

| Commentator | Comment | Response |
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| Pfizer | Pfizer welcomes the opportunity to comment on the ACD and the evaluation report for tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198). Whilst we understand the rationale for the recommendation, we are surprised that the decision was made on an unadjusted measure of efficacy as noted in point 4.8 of the ACD, page 34.<br><br>Instead, we believe that it would have been more appropriate to use an adjusted indirect comparison method. One such method is the Bucher method[1]. Another approach would have been to amend the original manufacturer's MTC whereby all biologic therapies are split out and compared against each other. From other MTCs already performed in this therapeutic area, there appears to be some differences in efficacy between the therapies.<br><br>As a result, we feel that the use of the unadjusted measure of efficacy has led to a lot of uncertainty in the clinical effectiveness and the cost effectiveness estimates used to make this decision.<br><br>1 Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997; **50:** 683–691. | Comment noted. This appraisal is a rapid review of technology appraisal guidance 198 (see sections 5.11 to 5.15 of the 'Guide to the single technology appraisal process' ) and considers the patient access scheme submitted after guidance publication.<br><br>See section 4.9: The Committee considered that the mixed treatment comparison included a set of heterogeneous trials, which meant that the results were subject to considerable uncertainty, and that limited confidence could be placed in the adjusted ACR response rates in the manufacturer's revised base case. |

**No comment received from commentators**

GlaxoSmith Kline

**Comments received from members of the public**

None received.

**Appendix 1 – MSD Table 4 – Calculation of weight based costing of Tocilizumab (TOCI)**

| Weight | Number of Vials per infusion (assuming least wastage) | Cost of TOCI per infusion | Cost of TOCI per year | Cost of TOCI per year less discount | Admin cost per year | Total cost | Total cost less discount |
|---|---|---|---|---|---|---|---|
| 135 | 2x 400mg | £1,024.00 | £13,312.00 | £10,449.92 | £2,005.90 | £15,317.90 | £12,455.82 |
| 130 | 2x 400mg | £1,024.00 | £13,312.00 | £10,449.92 | £2,005.90 | £15,317.90 | £12,455.82 |
| 125 | 2x 400mg | £1,024.00 | £13,312.00 | £10,449.92 | £2,005.90 | £15,317.90 | £12,455.82 |
| 120 | 2x 400mg | £1,024.00 | £13,312.00 | £10,449.92 | £2,005.90 | £15,317.90 | £12,455.82 |
| 115 | 2x 400mg | £1,024.00 | £13,312.00 | £10,449.92 | £2,005.90 | £15,317.90 | £12,455.82 |
| 110 | 2x 400mg | £1,024.00 | £13,312.00 | £10,449.92 | £2,005.90 | £15,317.90 | £12,455.82 |
| 105 | 2x 400mg | £1,024.00 | £13,312.00 | £10,449.92 | £2,005.90 | £15,317.90 | £12,455.82 |
| 100 | 2x 400mg | £1,024.00 | £13,312.00 | £10,449.92 | £2,005.90 | £15,317.90 | £12,455.82 |
| 95 | 400mg+200mg+80mg+80mg | £972.80 | £12,646.40 | £9,927.42 | £2,005.90 | £14,652.30 | £11,933.32 |
| 90 | 400mg+200mg+80mg+80mg | £972.80 | £12,646.40 | £9,927.42 | £2,005.90 | £14,652.30 | £11,933.32 |
| 85 | 400mg+200mg+80mg | £870.40 | £11,315.20 | £8,882.43 | £2,005.90 | £13,321.10 | £10,888.33 |
| 80 | 400mg+80mg+801mg+80mg | £819.20 | £10,649.60 | £8,359.94 | £2,005.90 | £12,655.50 | £10,365.84 |
| 75 | 400mg+200mg | £768.00 | £9,984.00 | £7,837.44 | £2,005.90 | £11,989.90 | £9,843.34 |
| **70** | **400mg+80mg+80mg** | **£716.80** | **£9,318.40** | **£7,314.94** | **£2,005.90** | **£11,324.30** | **£9,320.84** |
| 65 | 400mg+80mg+80mg | £716.80 | £9,318.40 | £7,314.94 | £2,005.90 | £11,324.30 | £9,320.84 |
| 60 | 400mg+80mg | £614.40 | £7,987.20 | £6,269.95 | £2,005.90 | £9,993.10 | £8,275.85 |
| 55 | 200mg+80mg+80mg+80mg | £563.20 | £7,321.60 | £5,747.46 | £2,005.90 | £9,327.50 | £7,753.36 |
| 50 | 400mg | £512.00 | £6,656.00 | £5,224.96 | £2,005.90 | £8,661.90 | £7,230.86 |

**Appendix 2 – MSD Table 5 – Calculation of aggregated cost per patient per year of tocilizumab**

| | Weight group (Kg) | | | | |
|---|---|---|---|---|---|
| | **0-33** | **34-66** | **67-100** | **101-133** | **>133** |
| infliximab patients per BSRB weight group | 2 | 1039 | 1546 | 176 | 12 |
| **Percentage of patients in each weight category** | **0.07%** | **37.44%** | **55.71%** | **6.34%** | **0.43%** |
| Cost per tocilizumab infusion | £358 | £717 | £1,024 | £1,024 | £1,024 |
| Cost per tocilizumab infusion less discount | £281 | £563 | £804 | £804 | £804 |
| tocilizumab infusions per annum | 13 | 13 | 13 | 13 | 13 |
| tocilizumab cost per patient per weight group | £3,657 | £7,315 | £10,450 | £10,450 | £10,450 |
| **Total cost per weight group** | **£7,315** | **£7,600,227** | **£16,155,576** | **£1,839,186** | **£125,399** |
| tocilizumab Administration cost per patient per year | £2,006 | £2,006 | £2,006 | £2,006 | £2,006 |
| **Total tocilizumab admin cost per weight group** | **£4,012** | **£2,084,130** | **£3,101,121** | **£353,038** | **£24,071** |
| Total tocilizumab cost per weight group | £11,327 | £9,684,357 | £19,256,698 | £2,192,224 | £149,470 |
| **Total tocilizumab cost per patient per weight group** | **£5,663** | **£9,321** | **£12,456** | **£12,456** | **£12,456** |
| | | | | | |
| Therefore expected tocilizumab cost per patient per year is equal to: | (number of patients*total cost 0-33 kg group*percentage of patients in 0-33 kg group)+(number of patients*total cost 34-66 kg group*percentage of patients in 34-66 kg group)+(number of patients*total cost 67-100 kg group*percentage of patients in 67-100 kg group)+(number of patients*total cost 101-133 kg group*percentage of patients in 101-133 kg group)+(number of patients*total cost >133 kg group*percentage of patients in >133 kg group) | | | | |
| Which equates to: | (1*£5,663*0.07%)+(1*£9,321*37.44%)+(1*£12,456*55.71%)+(1*£12,456*6.34%)+(1*£12,456*0.43%) **= £11,276.26** | | | | |