National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Assessment Group response to comments on the Assessment Report provided by companies

Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (including review of TA35)

Due to the limited time available to the Assessment Group, written responses have been provided for some but not all of the consultee comments received.

Comments relating to factual accuracy

Page	Text	Comment from consultee	Response from assessment group
12	Time to disease flare for participants receiving biologic DMARDs was statistically significantly longer (reported for abatacept and etanercept only).	AbbVie wishes to point out that the information relating to time to disease flare was provided in the AbbVie submission for study DE038 (p26): DB phase primary efficacy outcomes …In the MTX stratum, adalimumab was superior to placebo for delayed the time to onset of disease flare (>32 weeks for the adalimumab arm; ~20 weeks for the placebo arm) (p=0.03).	The AG agrees that these data, which were presented in the CS but not in the published papers, were overlooked and do not appear in the AG report. (see Erratum)
50	In all four studies, there were statistically significantly fewer arthritis flares in patients being treated with biologic DMARDs compared to those receiving placebo and in the two studies that reported time to disease flare this was statistically significantly longer in patients being treated with biologic DMARDs compared to those receiving placebo (Table 14)		
73	Patients who continued to receive biologic DMARDs during the randomised withdrawal phase of the studies had statistically significantly fewer arthritis flares compared to those receiving placebo in all four studies, while time to disease flare reported in two studies (abatacept and etanercept) was statistically significantly longer in those treated with biologic DMARDs		
148	Biologic DMARD-treated patients had fewer arthritis flares, longer time to disease flare (applicable to abatacept and etanercept), were more likely to achieve a treatment response as defined by the ACR		
12	A greater proportion of those treated with	AbbVie wishes to point out that the information relating	A signpost to these post-

	biologic DMARDs achieved ACR Pedi responses of ≥30 and had inactive disease (reported for abatacept and tocilizumab only)	to minimal disease in the DE028 study is available in a post-hoc analysis: Ruperto N et al. Treating to target of minimal disease activity and normal function in polyarticular juvenile idiopathic arthritis with adalimumab: analysis from a phase 3 clinical trial. Pediatr Rheumatol Online J. 2014; 12(Suppl 1): P9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4184352/ [Accessed August 2015]	hoc data, which have not yet been published in full, is presented in the AG report section 4.1.2, page 61. "***Results - Open-label extensions (OLE)*** All four studies included OLEs with some differences in which participants were eligible to enter, and how data were presented. ACR Pedi results are presented below and with additional outcomes presented either in the study data extraction forms (Appendix 5) or published papers (Adalimumab: minimal disease activity; Abatacept: ACR Pedi component items, analysis according to prior exposure to biologic agents, ACR Pedi data for those in the OLE who had not taken part in the double-blind phase and information on anti-
16	Continued DMARD treatment also led to a greater response level measured by the American College of Rheumatology Pediatric (ACR Pedi) criteria with the abatacept and tocilizumab trials reporting more participants with inactive disease		
52	The abatacept and tocilizumab studies[57;68] additionally report inactive disease, which was defined similarly in the two studies [no joints with active arthritis, normal erythrocyte sedimentation rate (ESR) of 20 mm per hour or less, physician's global assessment (PGA) <10 on a 100mm on a VAS (VAS)57 or PGA also <10 on a 100mm on a VAS, indicating no disease activity with the tocilizumab study68 also including an absence of uveitis (patients with uveitis were excluded from the abatacept study).		
53	Table 15 Inactive disease reported only for abatacept and tocilizumab		
62	Table 22 Inactive disease reported only for abatacept and tocilizumab		
73	The proportion of biologic DMARD-treated patients with inactive disease was more than twice that of placebo-treated patients in the two		

	studies (abatacept and tocilizumab) reporting this outcome		abatacept and ani-CTLA-4 antibody production; Etanercept: ACR Pedi component items, minimal disease activity; Tocilizumab: ACR Pedi component items, minimal disease activity).”
148	Biologic DMARD-treated patients had fewer arthritis flares, longer time to disease flare (applicable to abatacept and etanercept), were more likely to achieve a treatment response as defined by the ACR Pedi criteria, and to have inactive disease (only measured in the abatacept and tocilizumab trials).		
20 and 22	Psoriatic arthritis (PA), enthesitis-related arthritis (ERA), and undifferentiated arthritis (Table 1) and some forms of the disease are associated with extra-articular features such as uveitis (inflammation of the middle layer of the eye).	While rare in systemic arthritis, uveitis can occur in any subtype of JIA. The type of arthritis and age at onset dictates the risk of developing uveitis. Only the highest risk groups are included in the regular screening recommendations below.	Not a factual error but the AG will amend the wording for publication to indicate that some forms of JIA are more likely to be associated with extra-articular features.
30	Table 5 Summary of licensed indications of the biologic DMARDs under consideration in this assessment	The current table indicates that adalimumab is not licensed in psoriatic arthritis (PsA), however, AbbVie wishes to point out that adalimumab is licensed for PsA in adults. Presumably the table refers to paediatric indications, in which case the table would be correct. As such, AbbVie would request the text in the table be amended to indicate that it is licensed in adults, but not paediatric patients. Alternatively, the table title could be amended to indicate it relates only to paediatric populations.	Not a factual error. The Table heading indicates that only the licensed indications under consideration in this assessment are summarised.
32	Adalimumab (Humira®, AbbVie) in combination with methotrexate is indicated for the treatment of active polyarticular JIA in patients from the age of two years who have had an inadequate	As noted above, adalimumab has a license for adult PsA, but not paediatric patients. To avoid confusion that adalimumab does not have a license in PsA, we would request amendment to the text to include that	Not a factual error.

	response to one or more DMARDs. Adalimumab can be given as monotherapy in the case of intolerance to methotrexate, or when continued methotrexate treatment is inappropriate. Adalimumab is also indicated for the treatment of active ERA in patients six years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.	wording for PsA, with clarification that this is only for children	
37	Interventions: Etanercept, abatacept (with or without methotrexate), adalimumab (with or without methotrexate) and tocilizumab (with or without methotrexate). Each drug was evaluated within their licensed indication.	The text on these pages implies that etanercept is licensed as monotherapy only. Whilst it is true that the pivotal trial for etanercept in this population excluded the use of methotrexate, the SPC does not explicitly exclude the use methotrexate in this indication and AbbVie is aware that this does happen in clinical practice. To this point, the SPC refers to the registry data that evaluated the long-term safety of etanercept monotherapy (n=103), etanercept plus methotrexate (n=294) or methotrexate monotherapy (n=197). This would imply that the use of etanercept with methotrexate is not excluded from the licence and also does occur in clinical practice – more so than monotherapy use. AbbVie therefore requests correction to the wording in the report as well the assumptions made in the model	Not a factual error.
126	Patients receiving etanercept in the model do not also receive methotrexate, according to etanercept's marketing authorisation.		
42	Table 10 Indicates that the intervention was adalimumab / methotrexate and that the comparator was placebo / methotrexate	To the reader this table implies that methotrexate was used with adalimumab or placebo, but not with the others treatments. As noted in the report, patients on abatacept and tocilizumab were also permitted to receive methotrexate, only the etanercept trial	This distinction arose because the adalimumab trial also included trial arms without methotrexate. The AG

	For the other interventions and comparators the use of methotrexate is not indicated	excluded the use of methotrexate. AbbVie would suggest that the concomitant use of methotrexate in the active and placebo arms are reported consistently between the treatments in these two tables and in the other tables with abatacept and tocilizumab	has amended the tables. (see Erratum)
59	Table 20 Indicates that the intervention was adalimumab / methotrexate and that the comparator was placebo / methotrexate For the other interventions and comparators the use of methotrexate is not indicated		
45	Patients who had previously been treated with other biologic agents at any time or who had received recent treatment with intravenous immune globulin, cytotoxic agents, investigational agents, DMARDs (other than methotrexate) or corticosteroids were also excluded from participation.	The underlined text should read "corticosteroids administered by intra articular, intra muscular or intravenous route"	The AG has amended this text. (see Erratum)
47	None of the trials included patients with PA or ERA (based on the eligibility criteria given).	This is not necessarily true for adalimumab – inclusion criteria from Lovell et al 2008 state: Patients 4 to 17 years of age with polyarticular course juvenile rheumatoid arthritis (with any type of onset)	Table 12 already indicates that patients with ERA or PA could potentially have been included. The sentence on page 47 has been deleted. (see Erratum)
51	Table 14 –0.21 (–0.35, 0.08);	These results do not correspond to the text on p52, where it states "… (adjusted difference in flare rate: −0.21; 95% CI −0.35 to −0.08; p=0.0024)…" Presumably the text in the table is incorrect and should be amended.	Table 14 (page 50) has been corrected. (see Erratum)

<table>
<tr><td>58</td><td>There were 155 AEs in the adalimumab group (10.3 per patient-year) and 234 in the placebo group (12.8 per patient-year) during the eight-month double-blind period</td><td>The text should read:
“There were 155 AEs in the placebo group (10.3 per patient-year) and 234 in the adalimumab group (12.8 per patient-year) during the eight-month double-blind period”</td><td rowspan="2">These data had inadvertently been extracted incorrectly (also noted below for item on p.186). This has now been corrected. (see Erratum)</td></tr>
<tr><td>59</td><td>Table 20
<table><tr><td>Adalimumab[61] (during 8-month DB period)</td><td>ADA (+MTX) (n=37; 15 Pt-yrs)</td><td>PBO (+MTX) (n=38; 18.3 Pt-yrs)</td></tr><tr><td>Any AE, n of events (n of events per patient-year)</td><td>155 (10.3)</td><td>234 (12.8)</td></tr><tr><td>Serious AEs, possibly related to study drug,2 n of events (n of events per patient-year)</td><td>1 (0.1)</td><td>0</td></tr></table></td><td>The text should read:
<table><tr><td>Adalimumab[61] (during 8-month DB period)</td><td>ADA (+MTX) (n=37; 15 Pt-yrs)</td><td>PBO (+MTX) (n=38; 18.3 Pt-yrs)</td></tr><tr><td>Any AE, n of events (n of events per patient-year)</td><td>234 (12.8)</td><td>155 (10.3)</td></tr><tr><td>Serious AEs, possibly related to study drug,2 n of events (n of events per patient-year)</td><td>0</td><td>1 (0.1)</td></tr></table></td></tr>
<tr><td>74</td><td>Adalimumab appeared to be less effective than abatacept and tocilizumab in terms of preventing disease flare, but appeared to be more effective than these two comparators in terms of ACR Pedi 50 response.</td><td>Adalimumab was also more effective for ACR Pedi 70 response (See Figure 5 and Table 28)</td><td>Page 72
The text has been amended. (see Erratum)</td></tr>
<tr><td>81</td><td>At baseline, children had a mean age of 12.9 years, with 2.6 mean years of ERA symptoms, a mean enthesitis count and active joint count of 8.1 and 7.8 respectively.</td><td>The mean active joint count was 8.3 in the adalimumab group, 8.1 overall</td><td>Not a factual error. The mean active joint count for the adalimumab group is not presented in</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td>the conference abstracts that were available to the AG at the time of the assessment.</td></tr>
<tr><td>125-4</td><td>Assuming patients recovered HRQoL at a constant rate over the model cycle, then the average HRQoL for these patients during that cycle would be 0.655, and converting this to an annual disutility would be equivalent to 0.03 per flare</td><td>The text should read:

…and converting this to an annual disutility would be equivalent to 0.13 per flare

This also applies to the corresponding text in Table 51</td><td>This is an incorrect interpretation. The annual disutility is in fact equivalent to 0.03 as stated in the report.</td></tr>
<tr><td>135</td><td>Table 65 Deterministic sensitivity analysis for abatacept versus methotrexate only.

Column heading: Tocilizumab vs methotrexate</td><td>In line with the preceeding text and table heading, the column heading should read:

Abatacept vs methotrexate</td><td>Agreed. Column heading updated. (see Erratum)</td></tr>
<tr><td>154</td><td>Current guidance is to treat JIA patients with uveitis that has not responded to steroids or methotrexate with anti-TNF drugs (of which etanercept and adalimumab are the two anti-TNF drugs within the scope of this assessment).[29]</td><td>The reference for this statement is the draft NHS England Clinical Commissioning Policy on adalimumab and infliximab draft policy. The statement in the report is therefore misleading as it implies that the policy also covers etanercept.

AbbVie suggests that the text be amended appropriately to avoid confusion.</td><td>The AG agrees that the wording used in the AG report could be misinterpreted. This text has been reworded. (see Erratum)</td></tr>
<tr><td>186</td><td>Data extraction – Adalimumab</td><td>The text should read:
<table><tr><td>Adverse Events, no. of events (no. of events per patient-year)</td><td>ADA (+MTX) (n=37; 15 Pt-yrs)</td><td>PBO (+MTX) (n=38; 18.3 Pt-yrs)</td></tr></table></td><td>As noted above (for items on pp 58 & 59) these data had inadvertently been extracted incorrectly. This has now been corrected. (see Erratum)</td></tr>
</table>

Adverse Events, no. of events (no. of events per patient-year)	ADA (+MTX) (n=37; 15 Pt-yrs)	PBO (+MTX) (n=38; 18.3 Pt-yrs)
Any AE	155 (10.3)	234 (12.8)
Most frequently reported AEs		
Related to injection-site reaction	57 (3.8)	73 (4.0)
Contusion	7 (0.5)	12 (0.7)
Nasopharyngitis	6 (0.4)	5 (0.3)
Upper respiratory tract infection	5 (0.3)	6 (0.3)
Viral infection	3 (0.2)	7 (0.4)
Vomiting	2 (0.1)	4 (0.2)
Excoriation	1 (0.1)	10 (0.6)
Serious AEs, possibly related to study drug1	1 (0.1) - Gastroduodenitis	0

Any AE	234 (12.8)	155 (10.3)
Most frequently reported AEs		
Related to injection-site reaction	73 (4.0)	57 (3.8)
Contusion	12 (0.7)	7 (0.5)
Nasopharyngitis	5 (0.3)	6 (0.4)
Upper respiratory tract infection	6 (0.3)	5 (0.3)
Viral infection	7 (0.4)	3 (0.2)
Vomiting	4 (0.2)	2 (0.1)
Excoriation	10 (0.6)	1 (0.1)
Serious AEs, possibly related to study drug1	0	1 (0.1) - Gastroduodenitis

Other comments

	Description of problem	Description of proposed amendment	Response
	The calculation of the discontinuation probabilities for subsequent cycles (P_{4y}-P_{1st_cycle})/15 is incorrect and underestimates the cumulative discontinuation probability at 4 years. Note that a similar error occurs in the calculations of the probability of death (mortality/4) and remission. However, it is unclear why the probability of remission is divided by 3, as this is not covered in the AR.		We acknowledge that we have used approximations that marginally underestimate the cumulative discontinuation probability. Changing this for discontinuations and mortality increases the base case ICER by about £100-£300. (not updated in Erratum) We agree there is an error in the probability of remission for methotrexate. This only affects the discontinuation due to clinical remission scenario analysis. Changing this reduces the scenario analysis ICER by about £300. (not updated in Erratum)
	Incorrect risk of disease flare is used in the first cycle in the MTX model (MTX tab, cell AB4)		We agree. Changing this reduces the base case ICER by about £100. (not updated in Erratum)
	On the Parameters tab, cell D1 has a note regarding the drop down options that will allow the user to change the parameters from deterministic to probabilistic or sensitivity analysis. However, the drop down menu does not appear populated and it is not	Correcting the drop-down menu so that the user can trigger the values	Noted. Unfortunately the options have been accidently removed but can be easily corrected by adding the values 1,2,3 in cells C56-58. None of the results are affected. Not a factual error.

	possible to overwrite the text in cell D1. This in turn does not allow the live values in column B to be changed and the user therefore can't easily verify the results for the deterministic and probabilistic sensitivity analyses.		
	No half-cycle correction was applied in the model	Half-cycle correction should be applied e.g. by halving the total costs and QALYs in the first and last cycle The changes to the ICERs are expected to be minor and in the range of £400-£600 lower depending on the biologic drug in first line use. The model was not re-run for the 2nd line biologic model or sensitivity analyses	It is not necessary to implement a half-cycle correction in a model with a short cycle length. Nemeth B., Vincziczki Á.The Role of Half-Cycle Correction in the Models Used for Health Technology Assessment. Value In Health 16 (2013) A323–A636. See also Decision Modelling for Health Economic Evaluation By Andrew H. Briggs, Karl Claxton, Mark J. Sculpher, p33-34.
	Adalimumab Tab Cell G5 contains the formula: (1-$E$4)*F5*Efficacy!$D$22 (with the remainder of the column using the same value highlighted in yellow) This is repeated in the	The formula should be: (1-E5)*F5*Efficacy!$D$22 with subsequent cells in the column referring to the corresponding value in column E It has no noticeable effect on the ICER.	We agree with this comment. The results are not affected by this error.

	methotrexate, etanercept, tocilizumab and abatacept tabs		
	MTX Tab Cell AB4 contains the formula: =DF_EtN*W4 (with the remainder of the column using the formula =DF_Pbo*W5)	The formula should be: =DF_Pbo*W5 The deterministic ICERs for the biologics are lower in Model 1: Adalimumab: £38,023 Etanercept: £32,435 Tocilizumab: £38,557 The model was not re-run for the 2nd line biologic model or for sensitivity analyses	We agree. Changing this reduces the ICERs by about £100. (not updated in Erratum)
	Disease flare risk Each of the four included randomized controlled trials (RCTs) comparing the biologic DMARDS to placebo reports a statistically significant reduction in the relative risk of disease flare. However, the CIs (presumably 95%), taken from Appendix 11 (page 229) of the assessment report imply that it is possible for the risk of disease flare for placebo (lower CI 0.16) to be less than the risk of disease flare for the biologics (whose higher CIs are greater than or equal to 0.16) when varying with 95% CIs. This should not be possible because		We acknowledge that it would be possible for the lower confidence interval used for the risk of disease flare for the placebo to be less than the risk of disease flare for the biologics. As suggested it is possible that this would affect some of the probabilistic analysis simulation runs. However we note that this happens in a very small number of runs and it unlikely to have a significant impact on model results.

	the relative risks are statistically significant at the 95% significance level. This error would increase the probability that methotrexate is cost-effective in the probabilistic analysis.		
	The AG assumes that 9.47% of abatacept patient discontinue due to lack of efficacy in the first cycle. In the RCT (Ruperto 2008), 8.95% (17 of 190) patients discontinued due to lack of efficacy. The AG model is overestimating the proportion of patients discontinuing abatacept.		We acknowledge that the patient discontinuation in the first cycle of abatacept treatment should be 8.95%, rather than 9.47%. This change would lead to a small decrease in the ICER for abatacept (approx. £55). (not updated in Erratum)
	The cost per cycle for abatacept is incorrect. The model should estimate 3.25 doses per cycle		Not a factual error. The correct dose, as applied in our model, is 4 doses for the first cycle and 3 doses for subsequent cycles.