Issue Number	Description of problem	Description of proposed amendment	Justification for amendment	ERG's responses
1	Page 12 (paragraph 2), page 15 (paragraph 4), page 28 (paragraph 4): The ERG raises the issue that the pivotal aripiprazole trial had a younger age group and higher ADHD rate than would be seen in UK clinical practice. Whilst this is a valid stand-alone point, it is misleading for the ERG to imply that because the age and ADHD status in the trial differs from clinical practice, this then limits the applicability of the results to clinical practice. It is important that this statement is placed in proper context.	When the age and ADHD status of the pivotal aripiprazole trial is mentioned, the following points should also be mentioned: - Age and ADHD comorbidity subgroups were presented in the MS, which showed that the efficacy of aripiprazole was similar across age groups and in both patients with and without ADHD. - Approximately two thirds of the trial population were over the age of 13 - Only the 10-12 year old age group presents with a very high rate of comorbid ADHD in the studies, the rate then declining with increasing age.	The age and ADHD subgroup analyses demonstrate that the clinical efficacy in the whole trial population can be deemed applicable to an older population with lower ADHD comorbidity. This is justifiable based on the following facts: - Age and ADHD comorbidity subgroups were presented in the MS, which showed that the efficacy of aripiprazole was similar across age groups and in both patients with and without ADHD. - Approximately two thirds of the trial population were over the age of 13 - Only the 10-12 year old age group presents with a very high rate of comorbid ADHD in the studies, the rate then declining with increasing age. This is in line with Appendix 19 of NICE CG38 on the management of bipolar disorder: 'There are major issues in the diagnosis of bipolar I disorder in prepubertal children and adolescents relating to ADHD. For example, in one study 88.9% of subjects less than 13 years old with mania also had ADHD (Geller et al., 2003).	This is not a factual error but is a matter of interpretation. The Appraisal Committee will discuss the generalisability of the patients within the pivotal trial to those within the scope.
2	Page 14 (paragraph 3, line 2), page 68 (paragraph 2, bullet 1): A '≥' sign is required before the '50%'	The sentence should read: "(as measured by ≥50% change in YMRS score)"	The response rate using YMRS score is calculated as the proportion of patients with a 50% or more change from baseline.	Agreed. The text has been amended.

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3	[redacted]	[redacted]	[redacted]	We have marked the text as AIC as proposed, although are not convinced that the problem stated by the manufacturers is evident.
4	Page 15 (paragraph 3, bullet 3): For the other safety outcomes, the ERG presents the RRs and 95% CIs. However, they do not do this for EPS and somnolence.	Add RRs and 95% CIs for EPS and somnolence	The ERG makes the statement that "aripiprazole performed less favourably than risperidone and quetiapine, but not significantly so." In the interest of balance, the RRs should be reported with this statement, as they are for the other adverse events, so that the reader is left in no doubt as to what the relative difference was.	This is not a factual error. The clinical effectiveness section of the ERG does not report non-significant differences as stated on page 87.
5	Page 16 (paragraph 6), page 145 (paragraph 4): The statement "It is noted that not all the information requested by the ERG were made available…" followed by "…the categories for which incomplete information was provided included…" could be interpreted as the manufacturer choosing not to provide data on the categories listed. This was not the case.	Change the sentence "…the categories for which incomplete information was provided included…" to: "The categories for which incomplete information was available from the pivotal aripiprazole trial were..:"	The pivotal aripiprazole trial collected some outcomes post-hoc and therefore there are some missing data. All the information collected in the trial has been reported to NICE.	For clarity we have amended the text as suggested.
6	Page 16 (paragraph 6): The ERG list 'numbers in age subgroups' under the list of incomplete information that they had previously requested.	Remove 'numbers in age subgroups' from the list.	The ERG did not previously request this information. Complete data is available for this category and is provided below:[1] Number of subjects	Agreed. The text has been amended.

<table>
<tr><th>Issue Number</th><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG's responses</th></tr>
<tr><td></td><td>The ERG did not previously request this information. Complete data is available for this category and is provided in the justification column. This information is freely available in the CHMP report.[1]</td><td></td><td>
<table>
<tr><th>Age</th><th>Aripiprazole 10 mg</th><th>Aripiprazole 30 mg</th><th>Placebo</th><th>Total</th></tr>
<tr><td>10</td><td>10</td><td>16</td><td>12</td><td>38</td></tr>
<tr><td>11</td><td>8</td><td>9</td><td>9</td><td>26</td></tr>
<tr><td>12</td><td>14</td><td>13</td><td>18</td><td>45</td></tr>
<tr><td>13</td><td>12</td><td>14</td><td>17</td><td>43</td></tr>
<tr><td>14</td><td>13</td><td>11</td><td>14</td><td>38</td></tr>
<tr><td>15</td><td>19</td><td>7</td><td>9</td><td>35</td></tr>
<tr><td>16</td><td>10</td><td>16</td><td>12</td><td>38</td></tr>
<tr><td>17</td><td>12</td><td>9</td><td>8</td><td>29</td></tr>
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</td><td></td></tr>
<tr><td>7</td><td>Page 17 (paragraph 4), page 110 (paragraph 3):
The ERG state that "The utility weight for weight gain was taken from the general population".
This is misleading. The utility weight for weight gain was taken from a cohort of overweight and obese children.</td><td>Change the sentence to:
"The utility weight for weight gain was taken from a cohort of overweight and obese children."</td><td>This utility was in fact derived from a population who suffered specifically with weight gain and therefore claiming that it was taken from the general population is misleading.</td><td>Agreed. The text has been amended.</td></tr>
<tr><td>8</td><td>Page 18 (paragraph 5), page 20 (paragraph 5):
The ERG state that "The manufacturers did not present any of their results as incremental</td><td>Page 18:
The beginning of the paragraph should be changed to:
"The manufacturers presented their base case as incremental</td><td>The manufacturer did in fact present the base case as an incremental analysis as requested by the STA template.</td><td>Agreed. The text has been amended.</td></tr>
</table>

Issue Number	Description of problem	Description of proposed amendment	Justification for amendment	ERG's responses
	analyses" This is incorrect.	analyses. The ERG recalculated the scenario analysis results as incremental analyses." Page 20: The beginning of the paragraph should be changed to: "The ERG redisplayed the manufacturers' original scenario analysis results as incremental analyses"		
9	Page 24 (paragraph 1): The ERG state that "approval by the European Medicines Agency (EMA) is expected in Q1 2013." Approval has now been granted (on 24th January 2013, pending that the agreed Risk Management Plan is implemented locally).	The sentence should be changed to: "Approval was granted by the European Medicines Agency (EMA) on 24th January 2013, pending that the agreed Risk Management Plan is implemented locally"	Approval was granted following submission of the MS	This data was not presented to the ERG until the Fact Check process, and scant detail on the risk management plan has been provided. At the time of writing our statement was correct. It would be a dangerous precedent to amend submitted reports based on new data. For this reason we have not changed the report.
10	Page 112 (paragraph 3): The ERG state that "The	Remove the following sentence:	This was clearly stated on pages 15 and 229 of the original submission.	Agreed. Sentence removed.

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	manufacturers did not declare that the use of aripiprazole second-line (after risperidone first-line) dominates all of the other treatment strategies considered" This is incorrect.	"The manufacturers did not declare that the use of aripiprazole second-line (after risperidone first-line) dominates all of the other treatment strategies considered"		
11	Page 115 (paragraph 2): The ERG state that "it is noted that the manufacturers have ignored uncertainty in their multipliers and hence also in their assessment of uncertainty in the utility values." This uncertainty was investigated as requested at the clarification stage.	The fact that varying the multiplier had no impact on the results should be mentioned here.	In analyses requested at the clarification stage, it was demonstrated that varying the multiplier had no impact on the results. The investigation of uncertainty surrounding the utility multiplier has now been performed and should be mentioned here in order to report a complete picture.	Additional text has been added to clarify the analyses undertaken.
12	Page 129 (paragraph 3): Reference to table 74 seems to be incorrect	Change to Table 76	Incorrect table reference	Agreed. The text has been amended.
13	Page 141 (paragraph 4): The ERG state: "Both of these will create a small bias disfavouring aripiprazole." This comment should be placed in full context.	When the ERG discusses the bias disfavouring aripiprazole in the adverse events in the model, they should also mention the following additional points: - The safety data from the whole trial population has been used in the model, including children aged 10-12 in whom the	To allow the Committee to have a full picture of all the bias in the model, all sources of bias should be reported.	Additional text has been added

Issue Number	Description of problem	Description of proposed amendment	Justification for amendment	ERG's responses
		CHMP consider aripiprazole to have a worse safety profile In the NMA, the adverse event rates at week 4 for aripiprazole were compared to the rates at week 3 for all other comparators, which is also disfavourable for aripiprazole		