24 January 2013

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Dear [redacted]

Re: Single Technology Appraisal – Aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents

The Evidence Review Group (School of Health and Related Research [ScHARR], University of Sheffield) and the technical team at NICE have now had an opportunity to take a look at submission received on the 2 January 2013 by Bristol-Myers Squibb and Otsuka. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm, 7th February 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

[redacted]

Yours sincerely

Janet Robertson
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

General request

1. **Priority request:** Please supply the trial protocol for NCT00110461.

2. **Priority request:** Please supply the draft CHMP assessment report.

3. **Priority request:** Please supply electronic versions of all the mixed treatment comparisons undertaken.

Literature searching

4. **Priority question:** Please clarify why adult data was not deemed as relevant to this review of aripiprazole. Could inferences from such data be made for older children?

5. **Priority question:** Searches were conducted up to January 19th 2012 (pages 267 and 280 of the submission). The ERG's enquires indicate that for the period from 2012 to current there are 307 unique records for the clinical effectiveness search; 705 unique records for the cost effectiveness search; and 216 unique records in clinicaltrials.gov register. Please update the searches and associated results to include data published before January 2013 and confirm that no further studies have been missed.

6. **Priority question:** Searches for adverse events were limited to RCT evidence. Whilst one MeSH term-"Epidemiologic study characteristics/" was used within the RCT filter in the identification of studies search strategies to capture non-RCTs - this term used alone is inadequate. The subject heading is not recognised in a number of databases searched. The ERG's own search strategies (see appendix to this clarification letter) for adverse events have found a further 400 records for non-RCTs records in Medline and Embase (direct and comparators). Please provide the reasons for not carrying out separate adverse events searches and confirm that no non-RCT evidence has been missed.

7. **Priority question:** Please provide any relevant study data (regarding YMRS response or adverse events) for the following trials. If any of the trials were identified and subsequently excluded from the searches in the submission please state the explicit reasons for exclusion:
   - NCT00194012 -"Study of Aripiprazole (Abilify) Versus Placebo in Children (5-17) With Subsyndromal Bipolar Disorder" http://www.clinicaltrials.gov/ct2/show/record/NCT00194012
   - NCT00102518- "Aripiprazole Open-Label, Safety and Tolerability Study (APEX 241)" http://www.clinicaltrials.gov/ct2/show/NCT00102518
   - NCT00181779- "Aripiprazole for the Treatment of Mania in Children and Adolescents With Bipolar Disorder" http://www.clinicaltrials.gov/ct2/show/NCT00181779
   - NCT00221416- "An Open-Label Trial of Aripiprazole in Children and Adolescents With Bipolar Disorder" http://www.clinicaltrials.gov/ct2/show/NCT00221416

8. Please clarify whether the references of the full economic evaluations were checked for appropriate utility / cost data.

Section A: Clarification on effectiveness data

A1. **Priority question:** Please clarify the purpose and conduct of the 28 day screening period prior to randomisation referred to on page 51 of the submission.

Patients in NCT00110461

A2. Please clarify the following:

- How many patients were inpatients throughout the screening period, at baseline and throughout the study?
- If patients were not inpatients at baseline, how day 1 of the acute phase (page 52 of the submission) was observed.

A3. Please clarify how many patients at baseline were in a manic state and how many patients were in a mixed state.

A4. Please clarify what percentage of patients were rapid cyclers, that is patients who experience four or more episodes a year.

A5. **Priority question**: Please clarify if patients in the trial received psychotherapy and if so, please provide the numbers involved in each of the trial arms.

Outcomes in NCT00110461

A6. **Priority question**: On page 271 of the submission it is stated that medication adherence and well-being were measured but not reported.

- Please describe and provide the data for adherence.
- Please describe and provide the data for well-being.

A7. Please clarify why relapse/recurrence of manic episode was not measured in this trial as stated on page 80 of the submission.

A8. Please clarify whether recurrence of depression was measured and not reported, or if it was not measured in the trial.

Statistical analysis of NCT00110461

A9. **Priority question:** In table B8, page 70 of the submission, it is stated that an intention-to-treat analysis was not done for this trial.

- Please explain why an intention-to-treat analysis was not undertaken.
- If the evidence is available, please conduct an intention-to-treat analysis.

Results from NCT00110461

A10. **Priority question:** Please clarify why the number of patients in the placebo group at week 30 in Table B95 (page 321of the submission) is higher than the number of patients at week 4 in table B9 (page75 of the submission).

A11. Please confirm why the observed case analysis was not available as stated on page 74 of the submission, but appeared to be available for quality of life (page 82) and also for Tables B13, B14 and B15 on pages 83-84.

Mixed treatment comparison

A12. **Priority question**: Page 110 states that "data are available in very few studies for this analysis, and each study compares a different pair of treatments. There is therefore not enough evidence to support the estimation of a random-effects model." Please conduct a random effects model assuming a homogeneous between-study variance model, which should be subject to sensitivity analyses. Suggested priors for the between study standard deviation are U(0, 0.6), U(0, 1) and U(0, 2). Please conduct this for both the base-case model and the sensitivity analyses which include the Pavaluri and Geller trials.

A13. Please clarify why the mixed treatment comparison was not undertaken for 13-17 year olds. Does 'point 4 on page 146 refers to the treatments other than aripiprazole as the efficacy for aripiprazole is in Table B13 (page 83).

A14. **Priority question:** Please clarify the following:

- How the results based on 50,000 iterations of the WinBUGS model (page 110 of the submission) relate to the sample of 1,000 values used within the PSA.
- Why it was deemed necessary to generate 50,000 samples.

A15. Please clarify how convergence of the MCMC chains was assessed and confirm that the chains had converged within the burn-in phase.

A16. Please clarify what goodness-of-fit tests were performed to assess the adequacy of the model to the data.

A17. The summary data are expressed as relative risks, however the WinBugs model is constructed using odds ratios. Please clarify how the transformation from odds ratios to relative risks was performed.

A18. Please clarify the inclusion of the paediatric schizophrenia trial used alongside Study 149 referred to in Table B25 (page 108 of the submission)

- Did this provide any further data that could be pooled if deemed appropriate?
- Were similar studies sought for each intervention / comparator?

A19. Please clarify how the placebo rates in the MTC were populated to obtain the results in Table B30 (page 114 of the submission).

A20. Pooling of all doses of interventions may not be appropriate given the potential different side effect profile and acquisition cost of each intervention. Please undertake an MTC assuming that different doses represent different treatment possibilities.

A21. Please provide, as far as possible, adverse event information corresponding to Tables B36 to B39 (pages 123-128 of the submission), for each of the studies used in the mixed treatment comparison.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Please clarify, with evidence, whether the ICER reported in the submission for the population experiencing manic episodes is assumed to be applicable to a population experiencing mixed episodes.

B2. **Priority Question:** Please clarify whether the model structure was intended to replicate the licensed duration (of 12 weeks for aripiprazole) or if it was intended to replicate real life prescribing (the ERG have been advised by its clinical experts that antipsychotics are typically used for more than 12 weeks). Within the model it is currently possible for patients to receive treatment for more than 12 weeks.

B3. **Priority Question:** Please comment on why depression was not included in the model, as the occurrence of depression is likely to vary with health state, and hence with treatment strategy.

B4. Please clarify why only 4 adverse events were discussed in the model.

Model parameters

B5. On page 145 it is stated that the starting age of 15 years is not based on the trial data. Please provide sensitivity analyses using 13 and 17 years and the mean age from the trial.

B6. Please clarify whether mean or median values were used to calculate the proportion of responders at weeks 1 and 2. Table B54 (pages 168-172 of the submission) indicates the former, Section 6.6.3 (page 214) the latter.

B7. Where values from the mixed treatment comparison are reported in Table B54, please clarify if the point estimates relate to means or medians.

B8. Please clarify whether the non-proprietary costs for quetiapine were used or the costs for branded Seroquel in Table 57 (page 177 of the submission).

B9. Please clarify how the standard errors for the first five rows of Table B62 (page 192 of the submission) have been derived.

B10. Please clarify how the 'age of population' and 'proportion male in population' values for the Hospitalisation state in Table B62 (page 192 of the submission) have been derived.

Results from the model

B11. Please report results with a half cycle correction.

B12. **Priority question**: Please provide cost-effectiveness results using results from a Bayesian random effects model rather than a fixed effect model (see question A12). Please do this for both the base-case random effects results and the sensitivity analyses results which include the Pavaluri and Geller trials.

B13. Regarding section 6.6.3 (page 214 of the submission), please comment, supported by appropriate evidence, on whether including uncertainty in both resource use for maintenance states and unit costs would significantly alter the results.

B14. Regarding section 6.6.3 (page 214 of the submission), please comment, supported by appropriate evidence, on whether including uncertainty in the utility multiplier would significantly alter the results.

Additional sensitivity analyses

B15. Where additional sensitivity analyses are performed, please provide details of the input data / assumptions used, with the resulting costs, and QALYs and ICERs for each strategy.

B16. **Priority question:** Please provide sensitivity analyses assuming that there is a reduction in efficacy as the drug moves further down the treatment line, thus for example there is X% reduction between lines 1 and 2, and between lines 2 and 3.

B17. **Priority question:** Please provide sensitivity analyses using 4 treatment lines.

B18. **Priority question:** The ERG have been advised by clinical experts that switching treatment at 3 weeks due to <50% YMRS response is unlikely to happen in clinical practice. Please provide sensitivity analysis where patients are maintained on initial treatment for a longer duration.

B19. **Priority question:** The ERG has been advised by its clinical experts that patients are likely to be maintained on antipsychotics for at least 6 -12 months. Please provide sensitivity analyses whilst treatment is maintained during euthymic state for 6 and 12 months.

B20. **Priority question:** Please provide a sensitivity analysis that combines all of the previous 4 sensitivity analyses described in B15-B19.

B21. **Priority question:** Please provide sensitivity analyses where the costs of drug-related adverse events in the inpatient setting is not assumed to be incorporated into the HRG.

B22. The ERG has been advised by its clinical experts that the estimated 5% relapse rate (page 160 of the submission) is too low. Please conduct sensitivity analyses with higher relapse rate values.

Section C: Textual clarifications and additional points

C1. Please confirm the typing errors in Table B1 (page 47 of the submission)

- RCT NCT00110461 has 11 associated articles
- RCT NCT00116259 has 2 associated articles.

C2. Please confirm the valproate dose in Geller 2012. On page 98 of the submission, it is stated that the dose of divalproex is 111-125 µg/mL and on page 107 the dose of valproate is 110-125 µg/mL.

C3. On page 102 of the submission, it is stated that the dose of divalproex is 15mg/kg/day plus placebo and the dose of risperidone is 0.5-2.0 mg/day plus placebo. On page 107 it is stated that the dose of valproate in the Pavaluri 2010 study is 60-120 µg and the dose of risperidone is 0.5-2.5mg. Please clarify the typing error for the risperidone dose and confirm the valproate doses are equivalent.

C4. Please clarify why valproate is included in Table B24 (page 107 of the submission) but not lithium.

C5. Please confirm the typing error in Table B36, on page 123 of the submission, where in the 6th column “relative risk for aripiprazole 10mg” should be 30mg instead of 10mg.

C6. Please confirm the typing error on page 138 of the submission, where section 5.9.4 is referenced instead of section 5.10.4.

C7. Please clarify that the reported utility for hospitalisation is a decrement in Table B54 (pages 168-172 of the submission).

C8. Please include the treatment costs for lithium in Table B54 (pages 168-172 of the submission).

C9. Please confirm a typing error in Table B60 (page 184 of the submission) in the first exclusion criteria ‘QoL/utilities some patients < 18’ which should be >18.

C10. Please clarify the discrepancy between Table B8 (page 70) where it is stated that there is no evidence to suggest outcomes were measured and not reported and the table in section 9.3.1 (page 271), in which it is stated that medication adherence and well-being outcomes were measured and not reported.

Appendix

Embase strategy (340 records)

1. exp Bipolar Disorder/
2. ((bipolar or bi polar) adj5 (disorder$ or depress$)).tw.
3. (hypomania$ or mania$ or manic$).tw.
4. (((cyclothymi$ or rapid or ultradian) adj5 cycl$) or RCBD).tw.
5. or/1-4
6. exp clinical trials/ or exp clinical trial/ or exp controlled clinical trials/
7. exp crossover procedure/ or exp cross over studies/ or exp crossover design/
8. exp double blind procedure/ or exp double blind method/ or exp double blind studies/
9. exp single blind procedure/ or exp single blind method/ or exp single blind studies/
10. exp random allocation/ or exp randomization/ or exp random sample/
11. exp randomized controlled trials/ or exp randomized controlled trial/
12. (clinical adj2 trial$).tw.
13. (((single$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$)).tw.
14. (placebo$ or random$).mp.
15. exp epidemiologic study characteristics/
16. animals/ not (animals/ and human$.mp.)
17. animal$/ not (animal$/ and human$/)
18. (or/6-15) not (or/16-17)
19. exp child/ or exp adult children/ or exp adolescent/
20. (child$ or adolescen$ or youth$ or preschool or juvenile or pediatric or paediatric).tw.
21. (young adj3 (person$ or people)).tw.
22. under 18.tw.
23. under eighteen.tw.
24. or/19-23
25. 5 and 18
26. 24 and 25
27. limit 26 to yr="2005 -Current"
28. exp Bipolar Disorder/
29. ((bipolar or bi polar) adj5 (disorder$ or depress$)).tw.
30. (hypomania$ or mania$ or manic$).tw.
31. (((cyclothymi$ or rapid or ultradian) adj5 cycl$) or RCBD).tw.
32. or/28-31
33. exp child/ or exp adult children/ or exp adolescent/
34. (child$ or adolescen$ or youth$ or preschool or juvenile or pediatric or paediatric).tw.
35. (young adj3 (person$ or people)).tw.
36. under 18.tw.
37. under eighteen.tw.
38. or/33-37
39. 32 and 38
40. limit 39 to yr="2005 -Current"
41. ((side or adverse or undesirable) adj2 (event$ or effect$ or reaction$ or outcome$)).ti.
42. (safe or safety).ti.
43. (harm$ or complication$).ti.
44. risk$.ti.
45. (treatment adj emergen$).ti.
46. tolerability.ti.
47. mortality.ti.
48. or/41-47
49. 40 and 48
50. aripiprazole/ae, to [Adverse Drug Reaction, Drug Toxicity]
51. aripiprazole.ti,ab.
52. 50 or 51
53. 40 and 52
54. extrapyramidal symptom/
55. (extrapyramidal symptom$ or EPS).ti,ab.

56. 54 or 55
57. weight gain/
58. weight gain$.ti,ab.
59. 57 or 58
60. somnolence/
61. somnolence.ti,ab.
62. 60 or 61
63. nausea/
64. nause$.ti,ab.
65. 63 or 64
66. 56 or 59 or 62 or 65
67. 40 and 66
68. dopamine receptor stimulating agent/ae, to [Adverse Drug Reaction, Drug Toxicity]
69. 40 and 68
70. 49 or 53 or 67 or 69
71. 70 not 27

Medline strategy (254 records)

1. Bipolar Disorder/
2. ((bipolar or bi polar) adj5 (disorder$ or depress$)).tw.
3. (hypomania$ or mania$ or manic$).tw.
4. (((cyclothymi$ or rapid or ultradian) adj5 cycl$) or RCBD).tw.
5. or/1-4
6. exp clinical trial/ or exp controlled clinical trials/
7. exp cross over studies/ or exp crossover design/
8. exp double blind method/ or exp double blind studies/
9. exp single blind method/ or exp single blind studies/
10. exp random allocation/ or exp randomization/
11. exp randomized controlled trials/ or exp randomized controlled trial/
12. (clinical adj2 trial$).tw.
13. (((single$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$)).tw.
14. (placebo$ or random$).mp.
15. (clinical trial$ or clinical control trial or random$).pt.
16. exp epidemiologic study characteristics/
17. animals/ not (animals/ and human$.mp.)
18. animal$/ not (animal$/ and human$/)
19. (or/6-15) not (or/17-18)
20. exp child/ or exp adult children/ or exp adolescent/
21. (child$ or adolescen$ or youth$ or preschool or juvenile or pediatric or paediatric).tw.
22. (young adj3 (person$ or people)).tw.
23. under 18.tw.
24. under eighteen.tw.
25. or/20-24
26. 5 and 19
27. 25 and 26
28. Bipolar Disorder/
29. ((bipolar or bi polar) adj5 (disorder$ or depress$)).tw.
30. (hypomania$ or mania$ or manic$).tw.
31. (((cyclothymi$ or rapid or ultradian) adj5 cycl$) or RCBD).tw.
32. or/28-31
33. exp child/ or exp adult children/ or exp adolescent/
34. (child$ or adolescen$ or youth$ or preschool or juvenile or pediatric or paediatric).tw.
35. (young adj3 (person$ or people)).tw.
36. under 18.tw.
37. under eighteen.tw.
38. or/33-37
39. 32 and 38
40. limit 39 to yr="2005 -Current"

41. ((side or adverse or undesirable) adj2 (event$ or effect$ or reaction$ or outcome$)).ti.
42. (safe or safety).ti.
43. (harm$ or complication$).ti.
44. risk$.ti.
45. (treatment adj emergen$).ti.
46. tolerability.ti.
47. mortality.ti.
48. or/41-47
49. 40 and 48
50. (extrapyramidal symptom$ or EPS).ti,ab.
51. Weight Gain/
52. weight gain$.ti,ab.
53. 51 or 52
54. somnolence.ti,ab.
55. Nausea/
56. nause$.ti,ab.
57. 55 or 56
58. 50 or 53 or 54 or 57
59. 40 and 58
60. Dopamine Agonists/ae, to [Adverse Effects, Toxicity]
61. 40 and 60
62. 49 or 59 or 61
63. 62 not 27