NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The NCT00110461 trial for aripiprazole was conducted in the USA in patients aged between 10 and 17 years. The clinical advisers to the ERG and the ERG raised the following concerns about the baseline characteristics of the population in the trial:
  - the trial population was younger than the population seen in UK clinical practice.
  - a high proportion of patients in the trial had comorbid ADHD (51.7%).
  - patients who are at risk of suicide have been excluded from the trial population.
  - many of the patients in the trial were treated as outpatients which is different from UK clinical practice where most adolescents with bipolar I disorder would receive treatment as inpatients.

  How generalisable is the trial to UK clinical practice?

- The licensed indication for aripiprazole is for the treatment, for up to 12 weeks, of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and over. The population in NCT00110461 included patients between 10-17 years with approximately 62% aged 13 and over. Approximately 42% of patients were in a mixed state at baseline and approximately 40% were in a manic state at baseline and the status of the rest was unknown. Does the Committee expect the overall size of effect shown for the whole trial population to be reflected in the licensed population?
- The manufacturer reported results from a Bayesian network meta-analysis involving the four atypical antipsychotics. The ERG expressed concerns about the pooling of data from multiple treatment arms in trials where there was more than one treatment dose. The ERG noted that pooling data from different doses together implied an assumption of similar efficacy and safety between the doses and this assumption should have been justified. Both the ERG and the manufacturer were unable to conduct a network meta-analysis with multiple treatment arms treated as separate treatment possibilities within the available time. The ERG recommended caution in interpreting the results of the network meta-analysis based on pooled data from multiple treatment arms. Does the Committee consider the network meta-analysis based on pooled doses appropriate?

Cost effectiveness

- Incremental analysis by the ERG found that aripiprazole second-line dominated the other strategies considered, (that is no aripiprazole and aripiprazole in first- and third-line). The choice of treatment sequence in clinical practice is usually based on an individual's needs considering factors such as comorbidities, severity of symptoms, and side-effect profile. Any of the antipsychotics may be considered as first-line treatment and certain sub-groups may benefit more than others from the use of certain treatment sequences. Exploratory scenario analysis by the ERG to examine the implications of personalised medicine demonstrated that small changes in the modelled results – typically no more than 2% of either the total costs or total QALYs – for each treatment sequence were needed for that strategy

to become cost-effective compared with the aripiprazole second line strategy. The ERG concluded that these results suggest the most cost effective treatment sequence could depend on individual circumstances. Should the implications of personalised medicine in clinical practice be considered in the evaluation of the cost-effectiveness of aripiprazole?

- The structure of the economic model assumed three lines of treatment before the patient moved to a 'treatment resistant' phase. Clinical advisers to the ERG commented that it was more likely that all four antipsychotics would be tried before classifying a patient as 'treatment resistant'. The manufacturer was not able to modify the model because of time constraints. The ERG did not consider that the inclusion of a fourth treatment line would alter the conclusions from the cost effectiveness analysis. Is the model based on a three-line treatment structure reasonable to assess the cost-effectiveness of aripiprazole?
- The ERG explored two treatment durations: 12 weeks based on the CHMP recommendation and 12 months based on clinical advice to the ERG about current use of antipsychotics in this patient population. The cost-effectiveness results were similar to the manufacture's base-case results. What is the appropriate treatment duration for aripiprazole in the economic evaluation?

1 Background: clinical need and practice

1.1 Bipolar disorder is a cyclical mood disorder in which a patient's mood and energy levels can oscillate, affecting their ability to perform everyday tasks. In its more severe forms, bipolar disorder is associated with significant impairment of personal and social functioning. To achieve a diagnosis of bipolar disorder in adults, ICD-10 requires at least two episodes (one of which must be mania or hypomania) in which the person's mood and activity levels are significantly disturbed. The disturbance consists of either an elevation of mood and increased energy and activity (mania or hypomania), or a lowering of mood (depression). The Diagnostic and Statistical Manual of Mental Disorders version four (DSM-IV) classify bipolar I disorder as a single episode of mania or a single episode of hypomania plus a single major depressive episode. A

mixed episode of bipolar disorder features symptoms of both mania or hypomania and depression. NICE Clinical Guideline 38 recommends that the same criteria used for adults are used for the diagnosis of bipolar disorder in adolescents except that mania must be present, euphoria also must be present for most of the time over at least 7 days and irritability should not be used as a core criterion but it can be helpful in making a diagnosis if it is episodic, severe, results in impaired function and is out of keeping or not in character.

1.2 The prevalence of bipolar disorder in the UK was estimated to be 1% (range 0.5% to 1.6%) of the general population in 2009. Recent epidemiological surveys, report a mean age of onset of bipolar disorder of between 17.1 to 29 years, with a peak onset occurring between the ages of 15 to 19 years. Approximately 25% of people with bipolar disorder experience their first episode before the age of 18 years. The manufacturer recognised the uncertainty about the prevalence of bipolar I disorder in children and adolescents in the UK because of the lack of available data. The manufacturer estimated the prevalence to be 136 patients hospitalised per year in the UK based on a retrospective study carried out in a specialist centre between 1974 and 1996. The ERG considered that the manufacturer's estimation is not inappropriate to the decision problem and that a more recent and accurate estimate of clinical prevalence is lacking.

1.3 The current management for bipolar disorder depends on the phase of the disorder being experienced, preference for future prophylactic treatment and side effect profile. Lithium is the only drug with current UK marketing authorisation for bipolar disorder in patients younger than 18 years. The Royal College of Paediatrics and Child Health recommend that unlicensed medications may be prescribed where there are no suitable alternatives and where the use is accepted by a professional opinion. NICE clinical guideline no. 38 states that the drug treatment of acute mania for adolescents should be the same as for adults, except treatment should be

initiated at lower doses. The following factors should also be considered: height and weight should be checked and monitored regularly; prolactin levels should be monitored and the risk of increased prolactin levels with risperidone and weight gain with olanzapine should be considered; following an inadequate response to antipsychotics, adding lithium or valproate should be considered. Valproate should normally be avoided in girls and young women because of teratogenicity risks during pregnancy and risk of polycystic ovary syndrome. The clinical guideline recommends close monitoring as this population may be more susceptible to adverse events such as sedation, obesity, extrapyramidal symptoms, metabolic changes and raised prolactin.

2 The technology

2.1 Aripiprazole (Abilify, Otsuka Pharmaceuticals) is an atypical antipsychotic with partial dopamine D2 and D3 agonistic properties. It has received a positive opinion from the Committee for Human Medicinal Products (CHMP) for the treatment, for up to 12 weeks, of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and over. It already has a UK marketing authorisation for the treatment of schizophrenia in people aged 15 years and older; for the treatment of moderate to severe manic episodes in bipolar I disorder in adults and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

2.2 Aripiprazole is taken orally. The recommended dosage is 10 milligrams (mg) once daily. The summary of product characteristics states that the treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. It is recommended that doses higher than 10 mg/day should only be used in exceptional cases and with close clinical monitoring. For full details of dosage and administration, see the summary of product characteristics.

2.3 The summary of product characteristics lists the following adverse reactions in adolescents treated with aripiprazole: very common reactions (10% or more) were somnolence (23.0%), extrapyramidal disorder (18.4%), akathisia (16.0%), and fatigue (11.8%); and common reactions (between 1% and 10%) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscletwitching, and dyskinesia. The following undesirable effects had a possible dose response relationship; extrapyramidal disorder (incidences were 10 mg 9.1%, 30 mg 28.8%, placebo 1.7%); and akathisia (incidences were 10 mg 12.1%, 30 mg 20.3%, placebo, 1.7%). Mean changes in body weight in adolescents with bipolar I disorder at 12 and 30 weeks for aripiprazole were 2.4 kg and 5.8 kg, and for placebo 0.2 kg and 2.3 kg, respectively. In the paediatric bipolar population (10-17 years) with exposure up to 30 weeks, incidence of low serum prolactin levels in females and males was 28.0% and 53.3%, respectively. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 Aripiprazole is available in 5 mg, 10 mg, 15 mg and 30 mg tablets or 10 mg and 15 mg orodispersible tablets or as an oral solution (1 mg/ml). The acquisition cost of aripiprazole 5 mg, 10 mg and 15 mg is £95.74 for 28 tablets. The acquisition cost of aripiprazole 30 mg is £191.47 for 28 tablets. The acquisition cost of aripiprazole oral solution (1 mg/ml) is £102.57 for 150 ml. Costs exclude VAT and are from the British National Formulary (BNF, edition 63). For patients who respond to aripiprazole, the expected length of a course of treatment is 12 weeks. For a course of 12 weeks (84 days), the 10 mg dose would cost £287.22. This cost would be the same for a 15 mg dose. A course of 30 mg dose would cost £574.41. The manufacturer noted in the submission that a generic version of aripiprazole is expected in 2014. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of aripiprazole within its licensed indication for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Children and adolescents with acute manic or mixed episodes associated with bipolar I disorder	Adolescents with acute manic episodes associated with bipolar I disorder

3.2 The population described in the final scope issued by NICE was children and adolescents with acute manic or mixed episodes associated with bipolar I disorder. Aripiprazole received a positive CHMP opinion for the treatment (of up to 12 weeks duration) of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 years and older. The manufacturer focussed on this age group in the economic model. However the ERG noted that the population included in the manufacturer's submission for the assessment of clinical efficacy were aged between10 and17 years in accordance with the inclusion criteria of the clinical trial.

	Final scope issued by NICE	Decision problem addressed in the submission
Comparators	• Antipsychotics (e.g., olanzapine, quetiapine or risperidone) • valproate • lithium • combination treatment with any of the above	• Atypical antipsychotics (olanzapine, quetiapine or risperidone)

3.3 The manufacturer stated that mood stabilisers such as lithium and valproate are not generally used as monotherapy treatment for children with bipolar disorder and that clinical opinion is that, if used at all, they would be used as adjuncts to atypical antipsychotics. The manufacturer concluded that the only relevant comparators are atypical antipsychotics

(olanzapine, quetiapine and risperidone). The clinical advisers to the ERG agreed with this opinion.

Final scope issued by NICE	Decision problem addressed in the submission	Decision problem addressed in the submission
Outcomes	The outcome measures to be considered include: • response rate • range and severity of symptoms of mania and depression • recurrence of manic episodes • body mass index (adjusted for the child's age and gender). • adverse effects of treatment • health-related quality of life.	As in final scope

3.4 The ERG noted that data was not presented on the recurrence of manic episodes.

3.5 It is anticipated that aripiprazole would be used in the same way in the treatment pathway as the other atypical antipsychotics (olanzapine, quetiapine and risperidone) which are currently used off-label for this patient population.

4 Clinical-effectiveness evidence

4.1 The manufacturer presented direct clinical-effectiveness evidence from 2 randomised controlled trials (RCTs) comparing aripiprazole with placebo and performed a meta-analysis of these trials. The manufacturer also presented a network meta-analysis based on a network containing aripiprazole, olanzapine, risperidone, quetiapine and placebo.

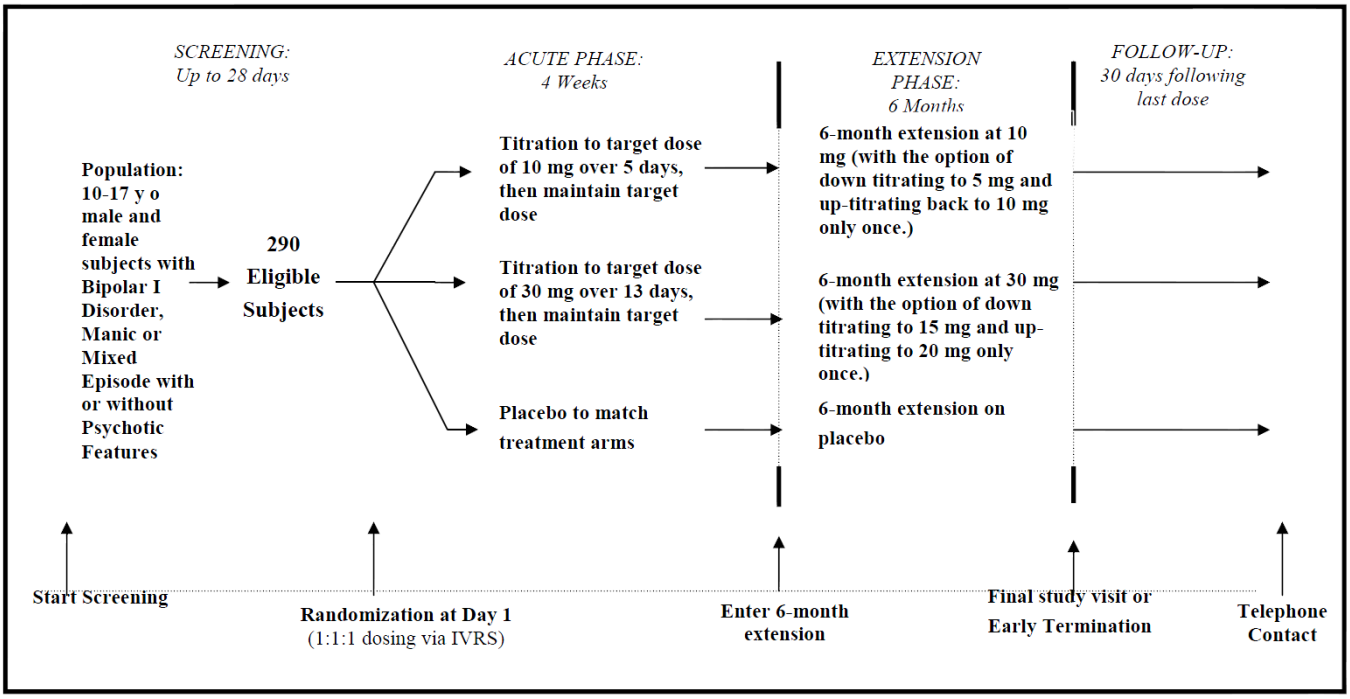
Direct evidence

4.2 The manufacturer undertook a systematic review to identify published evidence for the treatment and prevention of acute manic and mixed

episodes in bipolar disorder in children and adolescents with aripiprazole. The review identified 3 relevant RCTs (NCT00110461, NCT00194077 and NCT00116259). The NCT00194077 trial was excluded because it only included children under the age of 10 which is outside the licensed indication. The manufacturer considered NCT00110461 the main evidence for the use of aripiprazole in this patient population. The NCT00116259 trial was not discussed in detail because the manufacturer considered it to be a small trial in a specific population of children and adolescents with bipolar disorder (both types I and II) comorbid with attention-deficit hyperactive disorder (ADHD). No relevant non-RCT evidence for aripiprazole was identified from the systematic review.

4.3 NCT00110461 was a multicentre, double-blind, randomised, placebo-controlled clinical trial undertaken across 59 sites in the United States between March 2005 and February 2007. The study was designed to test the safety and efficacy of two doses of aripiprazole in children and adolescents with bipolar I disorder who experienced manic or mixed episodes with or without psychotic features. There were 296 participants randomised to receive aripiprazole 10 mg/day (n=98), aripiprazole 30 mg/day (n=99) or placebo (n=99). The study duration was 30 weeks with a 4 week acute phase followed by an extension phase of 26 weeks. Assessments took place on days 1 and 4, and at weeks 1, 2, 3 and 4 during the acute phase and [redacted].

Figure 1: Study design schematic for NCT00110461



4.4 Participants in NCT00110461 were aged between 10 and 17 years with a DSM-IV diagnosis of bipolar I disorder who were experiencing manic or mixed episodes, with or without psychotic features. Comorbid diagnoses were permitted including Attention Deficit Disorder (ADHD), Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD) and anxiety disorders. All participants had a baseline Young Mania Rating Scale (YMRS) score of more than 20. Exclusion criteria included bipolar II disorder, bipolar disorder not otherwise specified and psychosis due to other medial conditions or concomitant mediations. Participants with learning disabilities and those who were determined by the investigator to be at risk of suicide were also excluded.

4.5 In the NCT00110461 trial, 72% (296/413) patients screened were enrolled in the study. Patient characteristics at baseline were comparable between the three patient groups in the trial (see Table 1). Approximately 62% of patients were aged 13 or more and hence fell within the licensed population. In response to a clarification request, the manufacturer provided post hoc data on the proportion of patients in mixed and manic

state at baseline and on the proportion of rapid cyclers (patients who experience 4 or more manic, hypomanic or mixed episodes during the previous year). In both cases the proportions were relatively similar between the groups.

Table 1: Selected baseline characteristics

Parameter	Placebo (n=99)	ARI 10 mg (n=98)	ARI 30 mg (n=99)
Mean age (years) ± SD	13.3 ± 2.1	13.7 ± 2.2	13.3 ± 2.3
Age 13 or more at onset? (%)	61%	67%	60%
Mean duration of bipolar disease (years) ± SD	1.4 ± 1.9	1.3 ± 2.2	1.3 ± 2.5
YMRS total score, mean ± SD	30.7 ± 6.8	29.8 ± 6.5	29.5 ± 6.3
Current episode at baseline:			
Mixed (%)	43%	44%	39%
Manic (%)	38%	42%	40%
Unknown (%)	18%	14%	20%

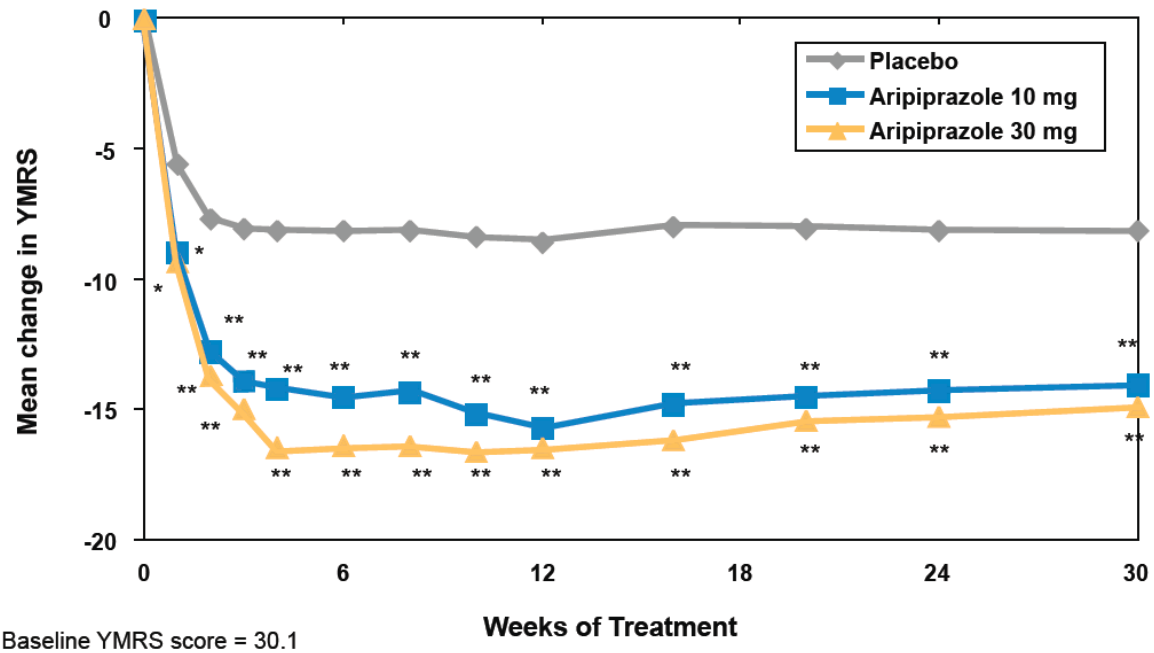
4.6 The primary outcome in NCT00110461 was the change from baseline to week 4 on the Young Mania Rating Scale (YMRS) total score. Secondary outcomes were changes from baseline scores in: Children's Global Assessment Scale (CGAS); Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity of mania, depression and overall bipolar illness; Children's Depression Rating Scale-Revised (CDRS-R) score; General Behaviour Inventory Scale (GBI) score and Attention-Deficit Hyperactivity Disorders Rating Scale (ADHD-RS-IV) score. A YMRS response rate was based on a responder definition of more than 50% reduction from the YMRS total score at baseline.

4.7 Data from all participants randomised to treatment were included in the statistical analysis. For the efficacy analysis the primary dataset used included last observation carried forward (LOCF) to handle missing data. Statistical analysis for the primary endpoint was based on an F-test for the mean change from baseline in YMRS total score at a significance level of

0.05 (two-tailed) for the aripiprazole 10 mg, aripiprazole 30 mg and placebo groups. Changes in scores from baseline were analysed using analysis of covariance with treatment as a factor and baseline score as a covariate at each time point. Least squares means were used for the treatment comparison and two-tailed Student t-tests were used to test differences between the treatment groups.

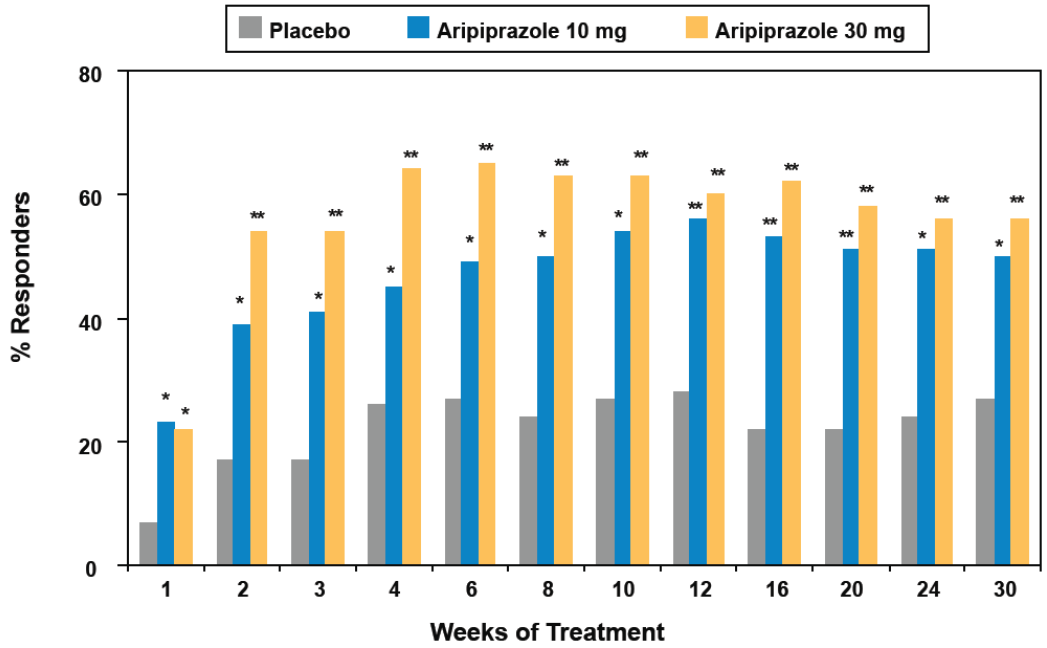
4.8 In the NCT00110461 trial, both aripiprazole doses demonstrated statistically significant improvements over placebo in the YMRS total score at week 4, with treatment differences from placebo of −5.99 (95% CI: −8.49 to −3.50; p<0.0001) for the aripiprazole 10 mg group, and −8.26 (95% CI: −10.7 to −5.77; p<0.0001) for the aripiprazole 30 mg group (see figure 2). Statistically significant improvements in YMRS total score were demonstrated at week 1 for both aripiprazole doses, and were maintained until week 30 (up to week 30, p<0.0001 at all visits). At week 30, the treatment difference in YMRS total score from placebo for the aripiprazole 10 mg dose was −5.89 (95% CI: −8.70 to −3.08), and for the aripiprazole 30 mg dose was −6.73 (95% CI: −9.53 to −3.94). The YMRS responder rates as shown in figure 3 were also significantly higher in the aripiprazole arms than in the placebo at week 4 and week 30.

Figure 2: Mean change from baseline in YMRS by week of treatment in the NCT00110461 trial



Baseline YMRS score = 30.1
*P<0.05, **P<0.0001

Figure 3: YMRS response rate by week of treatment



Response defined as ≥ 50% reduction from baseline in YMRS
*P<0.05, **P<0.0001

4.9 Both aripiprazole doses demonstrated significant improvements at week 4 compared with baseline in the secondary endpoints: CGAS core , CGI-BP Severity scores for Mania and Overall Bipolar Illness, GBI-Parent/Guard-

ian Version and Subject Version Mania Total score, and the ADHD-RS-IV Total score. Significant differences were not observed at week 4 in the CGI-BP Severity scores for depression; GBI- Patient Depression total scores or the CDRS-R score. A significant difference was observed in the 10 mg arm for the GBI-Parent/Guardian version for depression (p= 0.0430) but not in the 30 mg arm. The manufacturer considered the [redacted].

4.10 Results from a post hoc subgroup analysis based on the change in YMRS score from baseline calculated using both the observed case dataset and the LOCF dataset for age subgroups (10-12,13-17) were presented by the manufacturer (see Table 2).At the end of the acute phase of the trial (4 weeks) the proportion of drop outs was 14.3% in the aripiprazole 10 mg group, 22.2% in the aripiprazole 30 mg group and 23.2% in the placebo group. At 30 weeks the drop out rates were 65.3% in the aripiprazole 10mg group, 77.7% in the aripiprazole 30 mg group and 87.9% in the placebo group. The manufacturer highlighted the statement in the Committee for Medicinal Products for Human Use (CHMP) assessment report that results based on the observed case analysis dataset failed to show statistical significance for aripiprazole compared with placebo for both doses on all analysed efficacy endpoints at week 12. The manufacturer stated that the lack of statistically significant differences between aripiprazole and placebo at week 12 along with the high discontinuation rate, resulted in the CHMP restricting the treatment length with aripiprazole to 12 weeks.

Table 2: Results from age subgroup analysis for mean change from baseline in YMRS score

Visit/week	10 – 12 years						13 – 17 years					
	Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
	N	LS Mean[a]	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean	N	LS Mean
Observed case dataset												
Baseline	31	31.5	40	28.4	36	29.9	65	29	59	30.3	58	31.9
Week 4	25	-16.0**	30	-15.5**	26	-5.8	53	-14.9*	45	-17.9*	41	-11.1
Week 12	17	-20.4	17	-20.6	7	-15.8	34	-21.4	25	-20.5	13	-21.5
LOCF dataset												
Baseline	31	31.5	40	28.4	36	29.9	65	29	59	30.3	58	31.9
Week 4	31	-15.6**	40	-15.5**	34	-4.7	65	-13.9*	59	-16.8**	58	-10.1
Week 12	31	-16.2**	40	-15.9**	36	-6.9	65	-15.6*	59	-16.8**	58	-9.7

*p < 0.05, **p < 0.001 vs. Placebo
[a] a negative mean indicates improvement
LS = Least Squares; LOCF=last observation carried forward

4.11 The manufacturer also carried out a post hoc subgroup analysis to investigate if the efficacy of aripiprazole was influenced by the presence or absence of ADHD symptoms. Results presented in 3 age sub-groups (10-12,13-14, 15-17) suggested no change in the treatment effect.

4.12 In NCT00110461, health-related quality of life was measured by the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q). The manufacturer reported that whilst the results did not reach statistical significance, both aripiprazole arms demonstrated a trend for improvement relative to placebo.

4.13 The manufacturer presented adverse events occurring in more than 5% of any group in NCT00110461 over the acute phase and over the full trial duration. There were no deaths or suicides in the study. The manufacturer acknowledged that somnolence and extrapyramidal symptoms occurred more frequently in the aripiprazole arms than in the placebo group. In the acute phase (up to 4 weeks) extrapyramidal symptoms occurred in 12.2%

(12/98) of the aripiprazole 10 mg group, 27.3% (27/99) of the aripiprazole 30 mg group and 3.1% (3/97) of the placebo group. In the acute phase (up to 4 weeks) somnolence occurred in 19.4% (19/98) of the aripiprazole 10 mg group, 26.3% (26/99) of the aripiprazole 30 mg group and 3.1% (3/97) of the placebo group. The manufacturer concluded that most of the adverse events occurred in the acute phase of the study and were mild to moderate in severity and so were expected to be manageable.

4.14 The manufacturer presented changes in baseline metabolic parameters at 4 and 30 weeks. Differences in the treatment groups between the incidence of clinically significant weight gain (more than 7% weight gain compared with baseline) and change from baseline body mass index (BMI) were not statistically significant at week 4. [redacted] There were no differences between the treatment groups in the proportion of participants with a BMI on or above the 95th percentile for age and gender at week 4. [redacted]

4.15 The manufacturer noted that the CHMP limited the indication for aripiprazole to adolescents aged 13 and over as a result of safety concerns in younger patients. The manufacturer reported results from a post hoc subgroup analysis to assess the safety profile across age (10 to 12 years, 13 to 17 years) sub-groups. In the 10 to12 years subgroup there were significant increases in mean weight and BMI changes from baseline in the aripiprazole 30 mg treatment arm at weeks 4 and 12 (see Table 3) There were also significant increases in weight and BMI measurements in the aripiprazole 10 mg treatment arm using the LOCF analysis.

Table 3: Mean weight and BMI change from baseline by age group at week 12 (observed case dataset)

Parameter		10-12 years						13-17 years					
		Aripip 10 mg		Aripip 30 mg		Placebo		Aripip 10 mg		Aripip 30 mg		Placebo	
		N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Weight (kg) change from baseline	Baseline	32		40		39		66		59		58	
	Week 4	26	1.2	31	1.4*	26	0.4	49	0.6	42	0.9	39	0.7
	Week 12	16	2.8	16	4.0*	7	0.8	33	2.6*	25	2.1	14	0.2
BMI (kg/m2) change from baseline	Baseline	32		40		39		66		59		58	
	Week 4	26	0.5	30	0.5*	26	0	49	0.1	42	0.2	39	0.2
	Week 12	16	0.9	16	1.4*	7	0	33	0.8*	25	0.4	14	0

* $p < 0.05$, ** $p < 0.001$ vs. Placebo (Aripiprazole 10 mg and Aripiprazole 30 mg treatment group)

4.16 NCT00116259 was a double-blind randomised placebo-controlled clinical trial undertaken at a site in Brazil. There were 43 participants who were randomised to receive aripiprazole 20 mg/day (n=18) or placebo (n=25). The study duration was 6 weeks. Participants were aged between 8 and 17 years with a DSM-IV diagnosis of bipolar I or II disorder comorbid with DSM-IV ADHD. All participants were in an acutely manic or mixed state defined as a YMRS score of more than 20 at the baseline visit. Exclusion criteria included learning disabilities and severe suicide or homicide risk contraindicating outpatient treatment.

4.17 Results from study NCT00116259 showed that patients receiving aripiprazole had a significantly larger reduction in YMRS total scores from baseline to week 6 than patients on placebo (−27.22 versus. −19.52, p=0.02). A greater proportion of patients on aripiprazole compared with placebo were also responders (88.9% versus 52%, p=0.02; number needed to treat (NNT) =2.70) and achieved remission (72% versus 32%, p=0.01; NNT = 2.50).

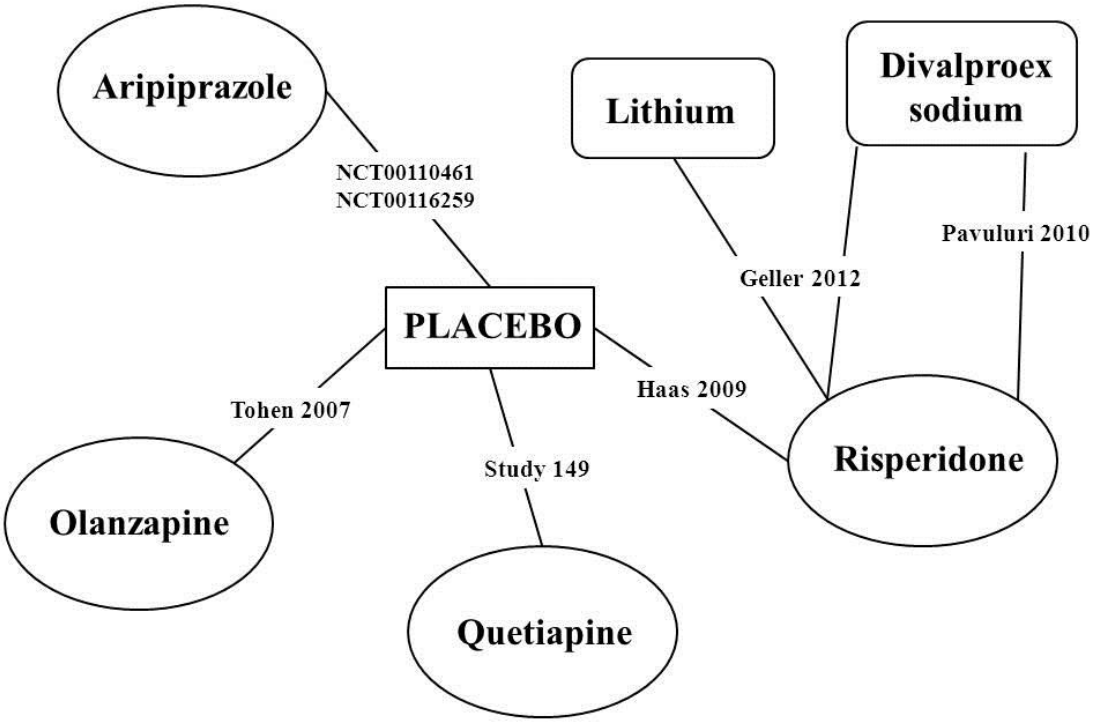
4.18 The manufacturer presented a meta-analysis of NCT00110461 (pooled 10 mg/day and 30 mg/day doses) and NCT00116259 (20 mg/day dose). Results from the meta-analysis indicated that aripiprazole was statistically significantly superior to placebo in inducing symptomatic response (as

measured by >50% change in YMRS score) at weeks 1, 2 and 4, but not at week 3. Also results from the meta-analysis showed aripiprazole to be associated with a statistically significant higher rate of extrapyramidal symptoms than placebo, but not of somnolence. More details can be found in the manufacturer's submission Appendix 17. The manufacturer commented that the meta-analysis was performed to be transparent rather than to provide meaningful results. The manufacturer stated that the results should be treated with caution because the information from the NCT00116259 trial is limited because of the small trial size and the different patient population from NCT00110461 (includes bipolar II disorders and restricted to patients with comorbid ADHD).

Indirect evidence

4.19 As there are no head-to-head trials comparing aripiprazole with the comparators specified in the final scope, issued by NICE, the manufacturer presented a network meta-analysis to determine the relative efficacy of the treatments using placebo as the common comparator. Five RCTS were identified: 3 included risperidone (Haas 2009, Pavaluri 2010 and Geller 2012);1 included quetiapine (Study 149) and 1 included olanzapine (Tohen 2007). Of the 5 identified studies, the Haas 2009, Study 149 and Tohen 2007 studies were included in the network meta-analysis (see Figure 4). Two studies were excluded but were considered in a sensitivity analysis: the Pavaluri 2010 study was excluded because it was a small study and the Geller 2012 study was excluded because unlike the other studies it was not placebo-controlled.

Figure 4: Schematic of the network meta-analysis



4.20 The network analysis was undertaken using a fixed-effects Bayesian model, as the manufacturer considered there was not enough evidence to support the estimation of a random-effects model. Results from studies which included treatment groups with different intervention doses were pooled to provide an average treatment dose effect. Efficacy outcomes considered in the network meta-analysis were the YMRS response rates at weeks 1, 2 and 3 and discontinuation at week 3. Analyses were also conducted for the following safety outcomes: extrapyramidal symptoms, clinically significant weight gain, clinically significant increase in prolactin and somnolence.

4.21 The relative risks using placebo and aripiprazole as references derived from the analyses on the included studies are shown in Table 4. Similar results for the 10 mg and 30 mg doses were also presented in the manufacturer's submission. The results indicated that all the atypical antipsychotic interventions considered (aripiprazole, risperidone and

olanzapine) were better than placebo at achieving YMRS response at weeks 1 to 3. The results also indicated that there were no statistically significant differences in YMRS response rates at weeks 1 to 3 between the atypical antipsychotics. No significant differences were found for discontinuation of treatment at week 3 between the interventions considered in the network.

Table 4 Relative risk results from network meta-analysis comparing interventions against placebo and against aripiprazole.

	Relative risk versus placebo		Relative risk versus aripiprazole	
	median	**95% CrI**	**median**	**95% CrI**
	YMRS response at week 1			
Placebo	1	-	0.29	0.14, 0.57
Aripiprazole	3.47	1.77, 7.31*	1	-
Olanzapine	2.59	1.20, 5.93*	0.74	0.27, 2.01
Risperidone	2.95	1.32, 7.07*	0.85	0.31, 2.34
	YMRS response at week 2			
Placebo	1	-	0.38	0.26, 0.55
Aripiprazole	2.63	1.83, 3.83*	1	-
Olanzapine	2.68	1.66, 4.32*	1.02	0.61, 1.67
Risperidone	2.62	1.72, 3.93*	0.99	0.62, 1.57
	YMRS response at week 3			
Placebo	1	-	0.42	0.31, 0.57
Aripiprazole	2.39	1.76, 3.24*	1	-
Olanzapine	2.12	1.39, 3.11*	0.89	0.56, 1.35
Risperidone	2.44	1.70, 3.37*	1.02	0.69, 1.47
Quetiapine	1.9	1.38, 2.54*	0.79	0.54, 1.15
	Discontinuation at week 3			
Placebo	1	-	1.37	0.80, 2.43
Aripiprazole	0.73	0.41, 1.24	1	-
Olanzapine	0.54	0.28, 0.99	0.75	0.32, 1.72
Risperidone	0.88	0.46, 1.61	1.21	0.52, 2.78
Quetiapine	0.7	0.43, 1.11	0.96	0.46, 2.01

95% CrI = 95% credible interval

4.22 Patients receiving aripiprazole were found to be statistically significantly more likely to experience extrapyramidal symptoms than patients receiving placebo. They were also more likely to experience them than patients receiving risperidone and quetiapine, but these differences were

not statistically significant (see Table 5). There was no statistically significant difference between aripiprazole and placebo in the risk of experiencing a clinically significant increase in weight. Aripiprazole (pooled dose) was significantly less likely to induce clinically significant weight gain than olanzapine and quetiapine. There was no statistically significant difference between aripiprazole and placebo in the risk of experiencing a clinically significant increase in prolactin. Patients receiving aripiprazole were significantly less likely to experience a clinically significant increase in prolactin than patients on olanzapine, risperidone and quetiapine. Patients receiving aripiprazole were significantly more likely to experience somnolence than those on placebo. They were also more likely to experience somnolence than patients receiving risperidone and quetiapine, but these differences were not statistically significant.

Table 5: Risk ratios versus placebo and aripiprazole for adverse events

	Relative risk versus placebo		Relative risk versus aripiprazole	
	median	**95% CrI**	**Median**	**95% CrI**
	Extrapyramidal symptoms			
Placebo	1	-	0.19	0.09, 0.38*
Aripiprazole	5.28	2.65, 11.74*	1	-
Risperidone	3.73	1.28, 13.84*	0.71	0.20, 2.93
Quetiapine	3.79	0.67, 44.77	0.72	0.12, 8.38
	Clinically significant weight gain			
Placebo	1	-	0.47	0.14, 1.32
Aripiprazole	2.13	0.76, 7.20	1	-
Olanzapine	26.44	7.46, 130.3*	12.52	2.31, 76.22*
Risperidone	2.54	0.78, 10.78	1.19	0.22, 6.94
Quetiapine	23.54	3.92, 217.9*	11.1	1.30, 116.1*
	Increase in prolactin			
Placebo	1	-	4.89	0.41, 140.3
Aripiprazole	0.2	0.01, 2.43	1	-
Olanzapine	33.83	9.15, 186.1*	175.7	10.86, 6414*
Risperidone	25.88	3.82, 291.8*	139.8	5.52, 7202*
Quetiapine	5.97	1.72, 32.14*	31.22	1.81, 1191*
	Somnolence			
Placebo	1	-	0.17	0.07, 0.36
Aripiprazole	5.85	2.75, 14.10*	1	-
Risperidone	3.39	1.87, 6.27*	0.58	0.23, 1.38
Quetiapine	3.47	1.90, 6.69*	0.59	0.23, 1.43

95% CrI = 95% credible interval

ERG critique and exploratory analyses

4.23 The ERG noted that the searches in the manufacturer's submission were limited to January 2012 and requested that the manufacturer update them. As a result of time constraints the manufacturer provided results from a non-systematic approach and identified 3 further trials. The ERG repeated and updated the searches until January 2013. The ERG found 3 studies not identified by the manufacturer, but none of them were phase III randomised controlled trials.

4.24 The ERG considered the NCT0011461 trial to be of reasonable methodological quality, and measured a range of outcomes that are

relevant to the decision problem. However the ERG expressed concern that the trial population presented in the manufacturer's submission are likely to be disrepant to the UK clinical population:

- Clinical advisers to the ERG considered that the age of the population in the trial to be much younger than that seen in UK clinical practice.
- Clinical advisers also raised concerns about the high proportion of patients in the trial with comorbid ADHD.
- The ERG considered it likely that many of the patients in the trials were treated in an outpatient setting which does not reflect current UK practice for this patient population.
- The ERG commented that the exclusion of patients who were at risk of suicide from the trial, may have resulted in the trial population having less severe disease than those presenting in UK clinical practice.

The ERG noted the manufacturer's acknowledgement that the inclusion and exclusion criteria for NCT0011461 could have reduced the external validity of the trial population. The ERG noted that no information was presented on the duration or maintenance of effect after 12 weeks of treatment with aripiprazole.

4.25 The ERG noted the advice in the European Medicines Agency (EMA) guidance for clinical investigation of bipolar disorder, that the occurrence of switching to depression should be investigated. In response to a clarification request, the manufacturer provided depression outcomes at weeks 4 and 30 using the CGI-BP severity depression score; the CDRS-R score; the GBI total score- parent guardian (depression); the GBI total scores- patient (depression) score. The ERG considered that while the data presented did not raise concerns about the occurrence of depression associated with aripiprazole treatment, the effect of aripiprazole on depression was not explored in depth in the submission.

4.26 Clinical advisers to the ERG highlighted that the manufacturer had not discussed the role of the caregiver in the patient's management of their illness including medication adherence as well as identifying prodromal

symptoms prior to acute episodes in its submission. Since many of the participants were treated in an outpatient setting, the impact on the carer's role in management of patients' recovery is even more relevant. The clinical advisers also noted that the impact of acute manic and mixed episodes on the patient's family or caregiver is not addressed in the submission.

4.27 The ERG considered the key clinical evidence for this appraisal came from the network meta-analysis. The ERG noted that relevant placebo-controlled trials of the anti-psychotic comparators were used for the indirect comparison. The ERG agreed with the manufacturer that the NCT00116259 trial should be excluded from the base case because of the different patient population. The ERG also agreed that the exclusion of the Geller 2012 trial was appropriate. The ERG did not consider it appropriate for the Pavuluri 2010 study to be excluded but it acknowledged that inclusion of this study would have little impact on the conclusions from the network meta-analysis.

4.28 The ERG questioned the pooling of doses from treatment arms with multiple doses in the network meta-analysis because it considered that different doses are associated with different efficacies and side effects. The manufacturer was requested to conduct a network meta-analysis with doses from multiple treatment arms separated but was unable to do so within the time available. The ERG considered that caution should be used when interpreting the results from the network meta-analysis based on pooled interventions from multiple treatment arms.

4.29 The ERG considered that a random effects model was more appropriate for the network meta-analysis rather than the fixed effects model used by the manufacturer because of the heterogeneity between the trials. The ERG undertook the network meta-analysis using a random effects model, and obtained similar results to those from the fixed effects model,

although in all cases the 95% credible intervals were wider reflecting the increased uncertainty.

5 Comments from other consultees

5.1 Statements received from professional groups reported that, within the NHS, acute manic and mixed episodes in bipolar I disorder in children and adolescents are generally treated by child and adolescent psychiatrists with support from the broader multidisciplinary child and adolescent mental health team (e.g. nurses, clinical psychologists, occupational therapists). There is some regional variation at the upper age range (16 – 18 years) with respect to transition to adult mental health services and often transition arrangements are sub-optimal. In some regions paediatricians treating patients with ADHD have begun to make diagnosis of bipolar disorder and initiate treatments for bipolar I disorder in individuals with ADHD and severe mood dysregulation. This practice is not supported by UK guidelines and it can result in patients receiving inappropriate treatments.

5.2 Professional groups stated that there is variation in practice across the UK between psychiatrists with respect to the treatments offered for bipolar disorder. They suggested that this reflects differing levels of experience and training in bipolar disorder; a lack of quality psychoeducation materials; the broad range of interpretations available to clinicians when implementing current NICE and British Association of Psychopharmacology guidance (that require a downward extrapolation of adult recommendations to children and adolescents) and differing interpretations of the available evidence with respect to pharmacological treatments.

5.3 A professional group commented that aripiprazole treatment should only be initiated in children and adolescents by a psychiatrist with age-appropriate training. While aripiprazole and the atypical antipsychotics are not yet available under licence for children and adolescents with bipolar

disorder they are used off-label. Of the current medication approaches only lithium has a marketing authorisation for this patient population. Lithium is however associated with a range of practical limitations (the need for pre and post treatment blood tests, narrow therapeutic window and significant adverse effects). Other alternatives include valproate and the atypical antipsychotics (e.g. aripiprazole, olanzapine, quetiapine, risperidone). Each intervention can be considered as a monotherapy or in combination. Usually a monotherapy would be considered first followed by an alternative monotherapy or combination treatments where response is inadequate.

5.4 A professional group noted that any trial that includes individuals with bipolar II disorder or bipolar disorder not otherwise specified or a high proportion of patients with comorbid ADHD is likely to reflect a very different population to that seen in UK clinical practice. However the main trials for the atypical antipsychotics include patients with bipolar I disorder and are likely to reflect reasonably well the type of patient seen in the UK. However as with all registration trials the subjects are relatively “clean” with respect to comorbidity and may not fully represent the population seen in clinical practice.

5.5 No statements were received from patient groups.

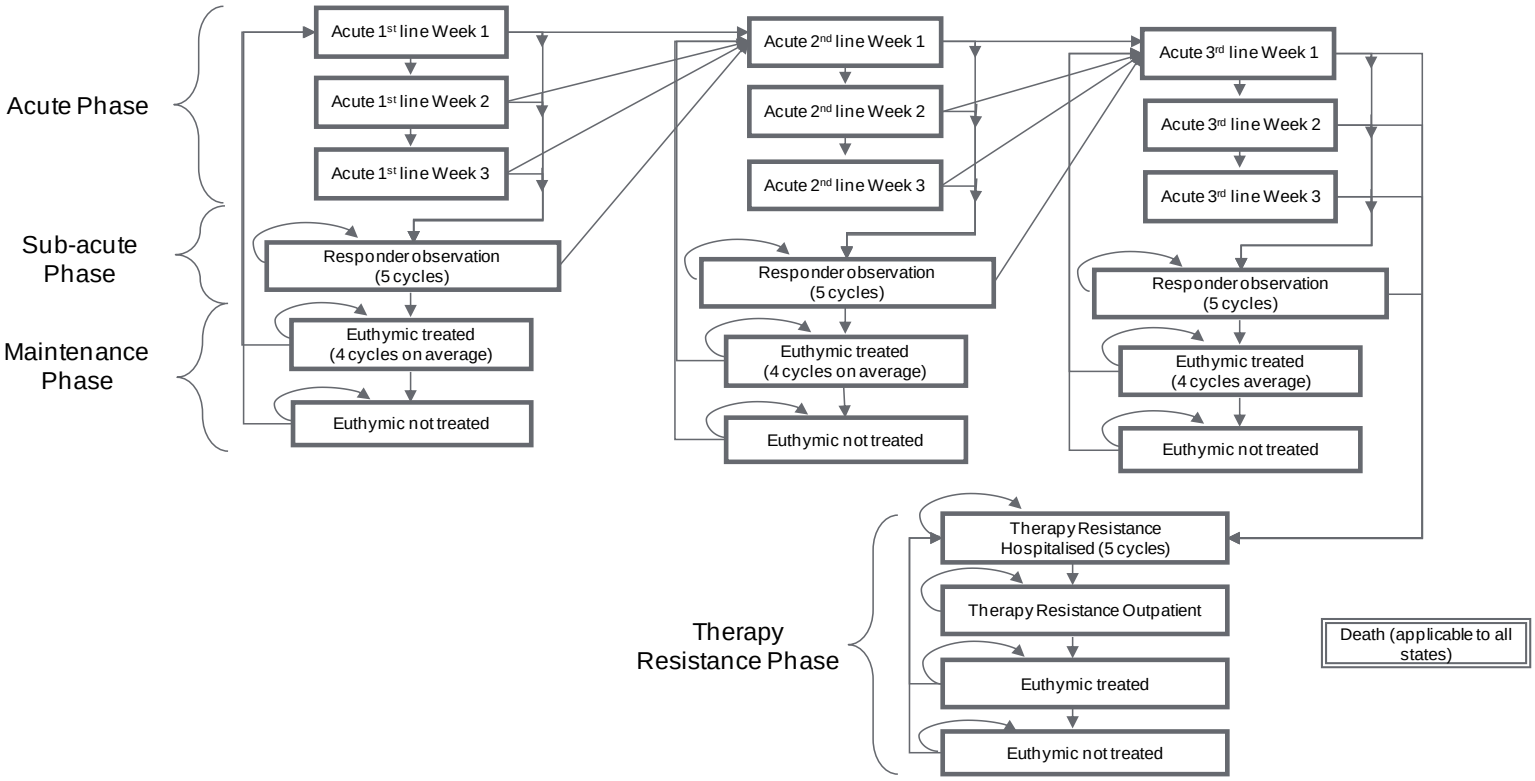
6 Cost-effectiveness evidence

6.1 The manufacturer undertook a systematic review to identify relevant cost-effectiveness or cost-utility studies. No economic evaluations were identified for the treatment of bipolar I disorder in children and adolescents. The manufacturer developed a de novo economic model to assess the cost effectiveness of aripiprazole compared with the other atypical antipsychotics. The patient population in the economic evaluation was adolescents with manic episodes of bipolar I disorder between 13 and 17 years old as specified in the marketing authorisation. The age of

onset implemented in the model was 15 years and the time horizon in the model was until the patient reached adulthood at 18 years.

6.2 The cost-effectiveness model presented by the manufacturer is a Markov cohort model with a weekly cycle length. The treatment pathway in the model was based on a sequence of up to 4 treatment lines. The first 3 related to treatment with an antipsychotic drug and the fourth included lithium treatment for patients whose disease was resistant to previous therapy (see figure 5). The antipsychotic treatment lines were identical in structure and each contained: an acute phase encompassing 3 weeks of inpatient treatment, a sub-acute phase encompassing up to 5 weeks of inpatient treatment for responders, and a maintenance phase encompassing outpatient treatment for an average of 4 weeks and then withdrawal of treatment. The structure of the model ensured that the average duration for a responding patient on each antipsychotic intervention was 10 to 12 weeks. The ‘therapy resistance’ phase contained up to 5 weeks inpatient lithium treatment, followed by outpatient lithium treatment and a maintenance phase similar to that in the antipsychotic lines for responders.

Figure 5: Schematic representation of the manufacturer's model



6.3 Patients entered the model at the start of the first treatment line. Patients moved to the next treatment line if they discontinued treatment before response during the acute phase or if they relapsed before discharge from hospital. If patients relapsed within the maintenance phase they remained on the same treatment line to which they had responded. If patients did not respond to 3 lines of antipsychotic treatment they entered the 'therapy resistance' treatment line. If patients relapsed on 'therapy resistance' treatment they returned to the inpatient lithium treatment (that is the 'therapy resistance' hospitalised state). The modelling of adverse events was included within the treatment-related health states. Patients could also die in any health state in the model.

6.4 Based on clinical opinion, the manufacturer specified the treatment sequence of risperidone, quetiapine and olanzapine to represent usual care (labelled strategy 1 in the model). The manufacturer considered either quetiapine or olanzapine could be replaced by aripiprazole. For the base case analyses, olanzapine was replaced with aripiprazole and the

position of aripiprazole in the treatment sequences was varied, giving 4 different strategies:

- Strategy 1: (S1) risperidone, quetiapine, olanzapine.
- Strategy 2: (S2) risperidone, aripiprazole, quetiapine.
- Strategy 3: (S3) aripiprazole, risperidone, quetiapine.
- Strategy 4: (S4) risperidone, quetiapine, aripiprazole.

6.5 Clinical data for the effectiveness for each antipsychotic in the 3 week acute phase were taken from the results of the network meta-analysis based on pooled dose levels (see table 6). It was assumed the effectiveness of each antipsychotic intervention is not influenced by its position in the treatment pathway and that the treatment is at a constant dose. Beyond the acute phase, it was assumed that all antipsychotics were equally effective and the common weekly relapse value was based on expert opinion. The manufacturer also assumed an identical mortality rate for all the antipsychotic interventions, based on UK life-tables adjusted to reflect the higher rates of mortality observed among patients with bipolar disorder.

Table 6: Effectiveness data used in the manufacturer's base case

	aripiprazole	risperidone	quetiapine	olanzapine
Weekly probability of discontinuation (from network meta-analysis)				
0 to 1 week	2.06%	2.48%	1.97%	1.54%
1 to 2 weeks	8.56%	10.30%	8.17%	6.37%
2 to 3 weeks	7.00%	8.43%	6.70%	5.23%
0 to 3 weeks[B]	**17.62%**	**21.21%**	**16.84%**	**13.14%**
Weekly probability of YMRS response (from network meta-analysis)				
0 to 1 week	28.09%	23.89%	22.20%	20.92%
1 to 2 weeks	22.59%	26.48%	17.86%	30.82%
2 to 3 weeks	8.40%	9.70%	6.64%	0.60%
0 to 3 weeks[B]	**59.08%**	**60.07%**	**46.70%**	**52.34%**
Weekly probability of relapse in the sub-acute and maintenance phases (expert opinion)				
Whilst treated*	0.57% for all drugs			
Not treated	0.67% for all drugs			

*In the model this corresponds to both the 'Responder observation' and 'Euthymic treated' health states.

в Numbers represent the proportion of the starting cohort. Thus summation of the three individual values equal the 0-3 week values

6.6 The model included three adverse events: extrapyramidal symptoms, somnolence and weight gain. Data for the incidence of these events were based on the results of the network meta-analysis (see table 7). There was no available data for the incidence of extrapyramidal symptoms and somnolence associated with olanzapine treatment and so these values were set equal to the lowest incidence of the other antipsychotics.

Table 7: Mean incidence of adverse events during the acute phase of the model (based on network meta-analysis results)

	EPS	Somnolence	Weight gain
Aripiprazole	0.158	0.463	0.034
Risperidone	0.112	0.266	0.041
Quetiapine	0.116	0.273	0.403
Olanzapine*	0.112	0.266	0.450

* Values for EPS and somnolence set equal to the lowest value for the other antipsychotics. EPS extrapyramidal symptoms

6.7 The health-related quality of life data collected in NCT00110461 were not based on a preference-based measure. Due to a lack of available data, for preference-based utility values from bipolar disorder in adolescents, the manufacturer based the utilities in the model on published data from adult populations with bipolar disorder. For the main analysis, the utilities were based on EQ-5D data from an adult UK population with bipolar I disorder reported by Hayhurst (2006). A multiplicative model for the utilities was employed to take into account the demographic (age and sex) of the population from which the utility was calculated. The calculated multipliers were then applied to an appropriate general population utility for the adolescent population in the mode (see table 8). The utility was also further adjusted within the model according to hospitalisation status, adverse events and the ageing of the adolescent cohort. The utility for weight gain was taken from the general population and the utilities for somnolence and extrapyramidal symptoms came from patients with schizophrenia.

Table 8: Summary of utility values applied in the base case and sensitivity analysis

Parameter	Utility type	Main analysis	Sensitivity analysis
General population	Based on formula including age. Updated every cycle	Examples (with 54% male); 15 year old: 0.951 16 year old: 0.950 17 year old: 0.948	-
Acute phase	multiplier	0.775	0.259
Responder observation	multiplier	0.954	0.849
Euthymic treated	multiplier	0.954	0.933
Euthymic not treated	multiplier	0.954	0.832
Therapy resistant inpatient	multiplier	0.809	0.292
Therapy resistant outpatient	multiplier	0.809	0.674
EPS	multiplier	0.815	-
Weight gain	multiplier	0.908	0.926
Somnolence	multiplier	0.905	-
Hospitalisation (decrement)	decrement	0.070	0 [1]

[1]assumed to be included in above values

6.8 In the economic model in-hospital costs were based on NHS reference costs 2010/1155 (code MHIPC1; NHS Trusts Mental Health Inpatients – Children). This cost was assumed to include costs relating to adverse events, but not the cost of antipsychotic treatments. Out-of-hospital resource use was based on expert opinion, with costs taken from the Personal Social Services Research Unit. Non-propriety costs were used for each of the anti-psychotics apart from aripiprazole (see table 9). The so an average dose cost was used. A weekly cost of £16.57 was included with weight gain in the euthymic treated states.

Table 9: Summary of weekly costs used within the model

Parameter	Cost (£)
In-patient care (acute and therapy resistant phases)*	4,214.68
Out-patient care; on treatment*	80.37
Out-patient care; no treatment	42.33
Out-patient care; therapy resistant*	161.84
Weight gain	16.57
Aripiprazole	35.90
Risperidone	0.40
Quetiapine	28.31
Olanzapine	9.24
Lithium	0.25
*excludes drug costs	

6.9 A summary of the base case results from an incremental analysis by cost is presented in table 10. These results show that the cost-effectiveness results are similar for the 4 strategies, but that use of aripiprazole at any point in the treatment pathway, dominated usual care which had the highest total cost (£75,066) and the lowest total quality-adjusted life years (QALYs) (2.516). Aripiprazole used as second line therapy after risperidone had the lowest total cost (£74,133) and the highest total QALYs (2.525) and dominated the other base case strategies.

Table 10: Base case results – incremental analysis by cost (produced by ERG from table B78, page 229 manufacturer's submission)

Sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
S2 (RIS, ARI, QUE)	£74,133	2.52466			
S3 (ARI, RIS, QUE)	£74,379	2.52348	£246	-0.0012	Dominated by S2
S4 (RIS, QUE, ARI)	£74,888	2.52297	£755	-0.0017	Dominated by S2
S1 (RIS, QUE, OLA)	£75,066	2.51637	£933	-0.0083	Dominated by S2

ICER; Incremental cost-effectiveness ratio (Incremental costs / incremental QALYs). Where one sequence is both less effective (results in lower total QALYs) and more costly (higher total costs) than another sequence, the former is said to be dominated by the latter.

RIS: risperidone. QUE: quetiapine. OLA: olanzapine. ARI: aripiprazole.

6.10 The manufacturer undertook a wide range of univariate sensitivity analyses for the base case and identified the rates of response applied during the acute treatment phase as the main parameters which influenced the cost-effectiveness estimates of the strategies. The manufacturer noted that this was expected because the response rates were varied by ±30% and there is not a significant difference in response rate between the four antipsychotic treatments considered. Scatterplots from probabilistic sensitivity analysis (PSA) were also presented in the submission. From these results the manufacturer noted that there is some uncertainty surrounding the cost-effectiveness results but for all 3 strategies containing aripiprazole, the majority of PSA iterations indicate cost-effectiveness or dominance.

6.11 The manufacturer presented 5 scenario analyses:

- When efficacy and safety results from the network meta-analysis based on the aripiprazole 10 mg dose rather than the pooled dose and the associated drug costs were included in the model only aripiprazole second-line (strategy 2) remained dominant over all other strategies, with the lowest costs (£74,815) and the highest QALYs (2.520). Aripiprazole first-line had the highest costs (£75,741) and usual care had the lowest QALYs (2.517).
- A second scenario analysis examined the impact of using efficacy and safety results from the network meta-analysis which included all the trials identified for the sensitivity analysis described in section 4.19. Aripiprazole second-line (strategy 2) remained dominant (total costs £72,178 and QALYs 2.534) and, first-line aripiprazole had the highest costs (£73,164) and lowest QALYs (2.532). The manufacturer highlighted that these results should be treated with caution because of the uncertainty in the network meta-analysis results by the inclusion of small trials.
- A scenario analysis investigated the impact of swapping the position of quetiapine and olanzapine in the base case treatment strategy.

Aripiprazole was then used to replace quetiapine giving four possible strategies:

- Strategy 1: (S1) risperidone, olanzapine, quetiapine.
- Strategy 2: (S2) risperidone, aripiprazole, olanzapine.
- Strategy 3: (S3) aripiprazole, risperidone, olanzapine.
- Strategy 4: (S4) risperidone, olanzapine, aripiprazole.

The results obtained from considering these strategies did not differ greatly from the base case results that indicated that the use of aripiprazole anywhere in the treatment pathway dominated usual care.

- Two further scenario analyses considered changes in the utilities values shown in table 6. Neither of these scenarios produced results which differed greatly from the base case and use of aripiprazole anywhere in the treatment pathway dominated usual care.

6.12 In response to a clarification request, the manufacturer presented 5 additional scenario analyses:

- The starting age of patients was varied from 15 years in the base case to 13 years and 17 years. Increasing the model's time horizon resulted in increased accumulated costs and QALYs for all strategies.
- The manufacturer was requested to explore the possibility that treatment efficacy reduced when the antipsychotic was not used for first line treatment. In response the manufacturer conducted a series of analyses varying the reduction in efficacy between lines 1 and 2 from 5% to 50% and between lines 2 and 3 from 10% to 75%. Results from these scenarios demonstrated that the manufacturer's original cost-effectiveness results were not substantially altered – even with reductions of 50% and 75%.
- The manufacturer was requested to include the cost of drug-related adverse events in the model. The manufacturer presented results based on somnolence and extrapyramidal symptoms requiring either 1 additional hour of consultant time per week or 3 additional hours per week. For both cases aripiprazole in second-line dominated the other strategies considered, but as in the base case results, there was only a

small difference between the total costs and QALYs between strategies.

- The manufacturer was requested to undertake a scenario analysis in which the acute and euthymic treated phases of the model were extended. In response, the manufacturer extended the acute phase from 3 weeks to 4 weeks, which had a minimal impact on the cost-effectiveness results. The effect of extending the euthymic treated phase of the model was to reduce the total costs for each health strategy but it did not impact on the cost-effectiveness results.
- The manufacturer was requested to undertake a scenario analysis investigating the impact of increasing the relapse rate from the base case value of 5% over the entire duration of the trial (0.57% per week) to 10%, 15% and 20%. The results showed that increasing relapse rates resulted in higher accumulated costs and lower accumulated QALYs for all the strategies, but the incremental analyses remained the same.

ERG critique and exploratory analyses

6.13 In general the ERG was satisfied that the economic evidence submitted by the manufacturer does not represent a biased assessment of the cost-effectiveness of aripiprazole. The ERG considered the manufacturer's model to be robust and transparent and well structured, allowing for the analysis of uncertainty in the model inputs.

6.14 The ERG highlighted that both its clinical advisers and those to the manufacturer stressed the importance of tailoring the treatment sequence to reflect an individual's needs (based on factors such as severity of symptoms; side-effect profile; or comorbidities for example). As there are limited data available to model treatment within sub-groups, the ERG conducted an exploratory scenario analysis to assess the possible implications of personalised medicine. The results, shown in table 11, showed that only small changes in the modelled results – typically no more than 2% of either the total costs or total QALYs – for each treatment

sequence were needed for the incremental cost effectiveness ratio (ICER) for that strategy to be £20,000 or £30,000 per QALY gained. The ERG stated that these results suggest that the actual place of aripiprazole within a treatment sequence is likely to depend on individual circumstances.

Table 11: QALY gains and cost offsets required to produce ICER equal to £30,000 or £20,000 per QALY gained relative to S2 (RIS, ARI, QUE)

Strategy	Additional QALYs required for:		Cost offset required for	
	ICER = £30,000	ICER = £20,000	ICER = £30,000	ICER = £20,000
S4 (RIS, QUE, ARI)	0.02759	0.03864	- £828	- £773
S1 (RIS, QUE, OLA)	0.04269	0.05567	- £1,281	- £1,113
S3 (ARI, RIS, QUE)	0.03093	0.04590	- £928	- £918

RIS: risperidone. QUE: quetiapine. OLA: olanzapine. ARI: aripiprazole

6.15 The ERG explored the potential implications of two different treatment durations for aripiprazole: one use reflected its licensed duration of a maximum of 12 weeks; the other reflected its real-life use based on clinical opinion of an average of twelve months. The ERG amended the manufacturer's model to have a maximum treatment duration (for all antipsychotics) of 12 weeks. Following a request, the manufacturer provided an amended version of its model to have an average of 12 months of antipsychotic treatment. The ERG considered that although both total costs and total QALYs showed a reduction in both of the two new models, the substantive conclusions of the manufacturer's base case analysis remained unchanged.

6.16 The ERG considered that a treatment sequence containing all 4 antipsychotics was appropriate. Clinical advisers to the ERG stated that if a patient's condition had not responded to the first 3 antipsychotic interventions, clinicians would generally try the remaining antipsychotic rather than conclude that a patient's condition was treatment resistant. This scenario was not possible to evaluate within the time frame of the

clarification process. The ERG stated that there is no evidence to suggest that a 4 line treatment sequence would substantially alter the conclusions.

6.17 The ERG made the following changes to the model in order to provide the most plausible ICER:

- use network meta-analysis results from a random-effects model.
- include a half-cycle correction
- adjust the discounting formula used
- amend the mortality rate calculations
- include a 10% reduction in efficacy between lines 1 and 2 and 15% between lines 2 and 3
- impose a logical constraint on the PSA inputs so that week 3 probability of discontinuing or responding does not exceed 1.

These amendments were incorporated into a 'licensed duration' model which reflected the maximum 12 week duration specified in the marketing authorisation and into a 'real-life' model which assumed 4 weeks of acute treatment and 12 months of euthymic treatment.

6.18 The deterministic and probabilistic cost effectiveness results from both models were similar to those obtained in the manufacturer's base case model.

- In the deterministic licensed duration model, use of aripiprazole at any point in the treatment pathway dominated usual care which had the highest total cost (£72,411) and the lowest total quality-adjusted life years (QALYs) (2.453). Aripiprazole used as second line therapy after risperidone had the lowest total cost (£70,647) and the highest total QALYs (2.469).
- In the deterministic real-world model aripiprazole used as first line therapy had the highest total cost (£63,437) and the lowest total quality-adjusted life years (QALYs) (2.485). Aripiprazole used as second line therapy had the lowest total cost (£62,257) and the highest total QALYs

(2.486). Results showed a decrease in both total costs and QALYs compared with the manufacturer's deterministic base case results.

The ERG also explored the impact on the cost-effectiveness of the amendments separately and concluded that the key drivers to changes in the cost-effectiveness results were the extension of treatment duration either to 4 weeks acute treatment or 12 months of euthymic treatment,

7 Equalities issues

7.1 No potential equality issues were identified during the scoping workshop discussion or during the two draft scope consultations. A professional group stated that is likely that those with significant intellectual disability would not be covered by this guidance as the evidence base does not extend to this population, No equality issues relating to the use of aripiprazole under its licence. were raised by the manufacturer in its submission.

8 Innovation

8.1 During the scope consultation, the manufacturer noted that aripiprazole will be the first antipsychotic to be licensed in this age group, and so presents psychiatrists with a licensed alternative to the off-licence treatment options currently available

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Aripiprazole for the treatment of schizophrenia in people aged 15-17. NICE technology appraisal guidance 213 (2011). Available from http://www.nice.org.uk/guidance/TA213
- The clinical effectiveness and cost effectiveness of electroconvulsive therapy (ECT) for depressive illness, schizophrenia, catatonia and mania. NICE technology appraisal guidance 59 (2003). Available from http://www.nice.org.uk/guidance/TA59
- The management of bipolar disorder in adults, children and adolescents, in primary and secondary care'. NICE Clinical Guideline 38 (2006). Available from http://www.nice.org.uk/guidance/CG38
- Depression in children and young people: identification and management in primary, community and secondary care'. NICE Clinical Guideline 28 (2005). Available from http://www.nice.org.uk/guidance/CG28