NICE National Institute for Health and Care Excellence

NICE guidance

Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder

Technology appraisal guidance
Published: 24 July 2013

www.nice.org.uk/guidance/ta292

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Aripiprazole is recommended as an option for treating moderate to severe manic episodes in adolescents with bipolar I disorder, within its marketing authorisation (that is, up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older).

2 The technology

2.1 Aripiprazole (Abilify, Otsuka Pharmaceuticals Europe) is an antipsychotic with partial dopamine D2 and D3 agonistic properties. It has a UK marketing authorisation 'for the treatment up to 12 weeks of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older'. It also has a UK marketing authorisation 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 administered orally. The summary of product characteristics states that the recommended dosage for aripiprazole is 10 mg per day administered once daily without regard to meals. It also states that treatment should be initiated at 2 mg (using aripiprazole oral solution 1 mg/ml) for 2 days, and titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. The summary of product characteristics notes that enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated and that a daily dose of 30 mg is associated with a substantially higher incidence of significant undesirable effects. It states that doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring.

2.3 The summary of product characteristics lists the following adverse reactions specific to 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%) were upper abdominal pain, increased heart rate, increased weight, increased appetite, muscle twitching and dyskinesia. The following undesirable effects had a possible dose–response relationship: extrapyramidal disorder (incidences were: 10 mg dose 9.1%, 30 mg dose 28.8%, placebo 1.7%) and akathisia (incidences were: 10 mg dose 12.1%, 30 mg dose 20.3%, placebo 1.7%). 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, as 10 mg and 15 mg orodispersible tablets, and 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. For 30 mg it is £191.47 for 28 tablets, and for oral solution it is £102.57 for 150 ml. Costs exclude VAT and are from the BNF, edition 63. For people whose condition responds 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 the 30 mg dose would cost £574.41. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of aripiprazole and a review of this submission by the Evidence Review Group (ERG).

3.1 The manufacturer presented direct clinical-effectiveness evidence from 2 randomised controlled trials 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.

3.2 The manufacturer undertook a systematic review to identify published evidence for aripiprazole for the treatment and prevention of acute manic and mixed episodes in children and adolescents with bipolar disorder. The review identified 3 randomised controlled trials (NCT00110461, NCT00194077 and NCT00116259) that investigated aripiprazole in children and adolescents with bipolar disorder. The NCT00194077 trial was excluded because it only included children under the age of 10, a group outside the licensed indication. The manufacturer considered NCT00110461 to be the main evidence for the use of aripiprazole in children and adolescents. 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) and attention-deficit hyperactive disorder (ADHD). No relevant non-randomised controlled trial evidence for aripiprazole was identified from the systematic review.

3.3 NCT00110461 was a multicentre, double-blind, randomised, placebo-controlled clinical trial undertaken across 59 sites in the USA between March 2005 and February 2007. The study was designed to test the safety and efficacy of 2 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.

3.4 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 ADHD, conduct disorder, oppositional defiant disorder and anxiety disorders. All participants had a baseline Young Mania Rating Scale (YMRS) score of more than 20. Exclusion criteria included bipolar II disorder, unspecified bipolar disorder and psychosis caused by other medical 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.

3.5 In the NCT00110461 trial, 72% (296 out of 413) of participants screened were enrolled in the study. Participant characteristics at baseline were comparable between the 3 groups in the trial. Approximately 63% of participants were aged 13 or over and fell within the licensed population. In response to a clarification request, the manufacturer provided post-hoc data on the proportion of participants in mixed and manic states at baseline and on the proportion of 'rapid cyclers' (participants who experienced 4 or more manic, hypomanic or mixed episodes in the previous year). In both cases the proportions were relatively similar between the groups.

3.6 The primary outcome in NCT00110461 was the change from baseline to week 4 on the YMRS total score. Secondary outcomes were changes from baseline scores in the Children's Global Assessment Scale (CGAS), Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity scores for 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 a 50% or more reduction from the YMRS total score at baseline.

3.7 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% confidence interval -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. Statistically significant improvements in YMRS total score were demonstrated at week 1 for both aripiprazole doses, and were maintained until week 30. 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 it was -6.73 (95% CI -9.53 to -3.94). The YMRS responder rates were also significantly higher in the aripiprazole arms than in the placebo arm at week 4 and week 30.

3.8 Both aripiprazole doses demonstrated significant improvements at week 4 compared with baseline in the secondary end points: CGAS core, CGI-BP severity scores for mania, depression and overall bipolar illness, GBI – parent or guardian 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 aripiprazole arm for the GBI-parent or guardian version for depression (p=0.0430) but not in the 30 mg arm.

3.9 The manufacturer presented 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 last observation carried forward dataset for age subgroups (10 to 12, and 13 to 17 years). Results from the last observation carried forward data showed that participants receiving aripiprazole in both age groups had a statistically significant change in YMRS score from baseline at both weeks 4 and 12 compared with those receiving placebo. Using the observed case dataset, there was a statistically significant change in YMRS score in participants receiving aripiprazole in both age groups at week 4; however by week 12, although the change in YRMS score was still greater in participants receiving aripiprazole compared with those receiving placebo, this was not statistically significant.

3.10 At the end of the acute phase of the trial (4 weeks) the proportion of participants not completing the trial 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 10 mg group, 77.7% in the aripiprazole 30 mg group and 87.9% in the placebo group. The manufacturer noted 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 end points 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.

3.11 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 subgroups (10 to 12, 13 to 14, and 15 to 17 years) suggested no change in the treatment effect.

3.12 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 although the results did not reach statistical significance, both aripiprazole arms demonstrated a trend for improvement relative to placebo.

3.13 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 disorder occurred in 12.2% (12 out of 98) of the aripiprazole 10 mg group, 27.3% (27 out of 99) of the aripiprazole 30 mg group and 3.1% (3 out of 97) of the placebo group. In the acute phase (up to 4 weeks) somnolence occurred in 19.4% (19 out of 98) of the aripiprazole 10 mg group, 26.3% (26 out of 99) of the aripiprazole 30 mg group and 3.1% (3 out of 97) of the placebo group. In the acute phase (up to 4 weeks) akathisia occurred in 8.2% (8 out of 98) of the aripiprazole 10 mg group, 11.1% (11 out of 99) of the aripiprazole 30 mg group and 2.1% (2 out of 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 therefore were expected to be manageable.

3.14 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 (7% or more weight gain compared with baseline) and change from baseline body mass index (BMI) were not statistically significant at week 4. Data on the incidence of clinically significant weight gain at 30 weeks was considered to be academic in confidence by the manufacturer and therefore cannot be reported in this document. 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 sex at week 4. Data on the proportion of participants with a BMI on or above the 95th percentile at week 30 was considered to be academic in confidence.

3.15 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 people. The manufacturer reported results from a post-hoc subgroup analysis to assess the safety profile across age subgroups (10 to 12 years, and 13 to 17 years). In the 10 to 12 years subgroup there were statistically significant increases in mean weight and BMI changes from baseline in the aripiprazole 30 mg treatment arm at weeks 4 and 12. There were also statistically significant increases in weight and BMI measurements in the aripiprazole 10 mg treatment arm at week 12 using the last observation carried forward analysis for the 10 to 12 years subgroup.

3.16 The NCT00116259 trial was a double-blind randomised placebo-controlled clinical trial undertaken in Brazil. There were 43 participants who were randomised to receive aripiprazole 20 mg per 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 risk of suicide.

3.17 Results from NCT00116259 showed that participants receiving aripiprazole had a statistically significantly larger reduction in YMRS total scores from baseline to week 6 than participants receiving placebo (-27.22 versus -19.52, p=0.02). A greater proportion of participants on aripiprazole compared with placebo experienced a response (88.9% versus 52%, p=0.02; number needed to treat [NNT] =2.70) and experienced remission (72% versus 32%, p=0.01; NNT=2.50).

3.18 The manufacturer presented a meta-analysis of NCT00110461 (pooled 10 mg per day and 30 mg per day) and NCT00116259 (20 mg per day). Results from the meta-analysis indicated that aripiprazole was statistically significantly superior to placebo in inducing symptomatic response (as measured as a 50% or more 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. 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 by the small trial size and the different population compared with NCT00110461 (that is, it included people with bipolar II disorder and was restricted to participants with comorbid ADHD).

3.19 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 randomised controlled trials were identified in addition to the 2 studies including aripiprazole (NCT00110461 and NCT00116259). The 5 studies were as follows: 3 studies for risperidone (risperidone compared with placebo, risperidone compared with divalproex sodium [valproate semisodium] and risperidone compared with divalproex sodium and lithium), 1 study for quetiapine (quetiapine compared with placebo), and 1 study for olanzapine (olanzapine compared with placebo). The network meta-analysis included NCT00110461, one of the studies for risperidone (risperidone compared with placebo), and the studies for quetiapine and olanzapine (both compared with placebo). The manufacturer undertook a sensitivity analysis in which the NCT00116259 trial and the remaining 2 studies for risperidone (risperidone compared with lithium and divalproex sodium) were also included.

3.20 The network analysis used a fixed-effects Bayesian model, because the manufacturer considered there was not enough evidence to support the estimation of a random-effects model. Results from studies that 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.

3.21 The manufacturer presented results from the network meta-analysis as relative risks using placebo and aripiprazole (pooled dose) as references. These results indicated that all the antipsychotics considered (aripiprazole, risperidone, quetiapine and olanzapine) were statistically more effective 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 antipsychotics. No statistically significant differences were found for discontinuation of treatment at week 3 between the interventions considered in the network.

3.22 Participants receiving aripiprazole were found to be statistically significantly more likely to experience extrapyramidal symptoms than those receiving placebo. They were also more likely to experience them than participants receiving risperidone and quetiapine, but these differences were not statistically significant. 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 statistically significantly less likely to cause clinically significant weight gain than olanzapine and quetiapine. Participants receiving aripiprazole were less likely to experience a clinically significant increase in prolactin than those on olanzapine, risperidone or quetiapine. Participants receiving aripiprazole were found to be statistically significantly more likely to experience somnolence than those receiving placebo. They were also more likely to experience somnolence than participants receiving risperidone and quetiapine, but this was not statistically significant.

Cost effectiveness

3.23 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 antipsychotics. The population in the economic evaluation was adolescents with manic episodes of bipolar I disorder between 13 and 17 years as specified in the marketing authorisation. The age of onset used in the model was 15 years and the time horizon was until the person reached adulthood at 18 years.

3.24 The cost-effectiveness model presented by the manufacturer was 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 participants whose condition was resistant to previous therapy. The antipsychotic treatment lines were identical in structure and each contained an acute phase of 3 weeks of inpatient treatment, a sub-acute phase of up to 5 weeks of inpatient treatment for participants who experienced a response, a maintenance phase of outpatient treatment for an average of 4 weeks, and then withdrawal of treatment. 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 participants who experienced a response.

3.25 Participants entered the model at the start of the first treatment line. They moved to the next treatment line if they discontinued treatment before response during the acute phase, if they did not respond to current treatment by the end of week 3, or if they relapsed before discharge from hospital. If participants relapsed within the maintenance phase they remained on the same treatment line to which they had responded. If participants did not respond to 3 lines of antipsychotic treatment they entered the 'therapy resistance' treatment line. If participants 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 in the treatment-related health states. Participants could also die in any health state in the model.

3.26 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: risperidone, quetiapine, olanzapine.
- Strategy 2: risperidone, aripiprazole, quetiapine.
- Strategy 3: aripiprazole, risperidone, quetiapine.
- Strategy 4: risperidone, quetiapine, aripiprazole.

3.27 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. It was assumed the effectiveness of each antipsychotic intervention was not influenced by its position in the treatment pathway and that the treatment was 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 participants with bipolar disorder.

3.28 The model included 3 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. There were no available data for the incidence of extrapyramidal symptoms or somnolence associated with olanzapine treatment, and so these values were set equal to the lowest incidence of the other antipsychotics.

3.29 The health-related quality of life data collected in NCT00110461 were not based on a preference-based measure. As a result of 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 utility values for the bipolar health states were based on EQ-5D data from a study of an adult UK population with bipolar I disorder. A multiplicative model for the utility values was used 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 value for the adolescent population in the model. The utility values were also further adjusted according to hospitalisation status, adverse events and the ageing of the cohort. The utility value for weight gain was taken from a cohort of children who are overweight or obese and the utility values for somnolence and extrapyramidal symptoms came from participants with schizophrenia.

3.30 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. Outpatient 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 antipsychotics apart from aripiprazole. The base case was based on the pooled dose efficacy and safety results and so an average dose cost was used.

3.31 In the base case, the cost-effectiveness results were similar for the 4 strategies. The use of aripiprazole at any point in the treatment pathway dominated usual care (that is, was more effective and less costly), 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.

3.32 The manufacturer undertook a wide range of univariate sensitivity analyses and identified the rates of response applied during the acute treatment phase as the main parameters that influenced the cost-effectiveness estimates of the strategies. The manufacturer noted that this was expected because the response rates were varied by ±30%, and the differences in the base-case response rates between the 4 antipsychotic treatments considered were not substantial. Scatterplots from probabilistic sensitivity analysis were also presented in the submission. From these results the manufacturer noted that there was some uncertainty surrounding the cost-effectiveness results, but that for all 3 strategies containing aripiprazole, the majority of probabilistic sensitivity analysis iterations indicated cost effectiveness or dominance.

3.33 The manufacturer presented various scenario analyses in its submission and in response to a clarification request. These included:

- Using 10 mg aripiprazole rather than a pooled dose.
- Using results from the network meta-analysis sensitivity analysis based on all trials identified in the manufacturer's review.
- Swapping the position of quetiapine and olanzapine in the base-case treatment strategy.
- Using utility values from a different source.
- Changing the starting age of participants to 13 years and 17 years.

- Reducing treatment efficacy between lines 1 and 2 and between lines 2 and 3.
- Including the cost of drug-related adverse events in the model.
- Extending the acute and euthymic treated phases of the model.

None of these scenarios produced results that differed greatly from the base case, and use of aripiprazole in the treatment pathway always dominated usual care.

Evidence Review Group comments

3.34 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 3 randomised controlled trials.

3.35 The ERG considered that the NCT0011461 trial was 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 described in the manufacturer's submission is not likely to represent the UK clinical population:

- Clinical advisers to the ERG considered that the age of the population in the trial was much younger than that seen in UK clinical practice.
- Clinical advisers also raised concerns about the high proportion of participants in the trial with comorbid ADHD.
- The ERG considered it likely that many of the participants in the trials were treated as outpatients, which does not reflect current UK practice for this population.
- The ERG commented that excluding from the trial participants who were at

risk of suicide 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. It also noted that no information was presented on the duration or maintenance of effect after 12 weeks of treatment with aripiprazole.

3.36 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 or guardian (depression), and the GBI total scores – patient (depression) score. The ERG considered that although 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.

3.37 The ERG stated that the key clinical evidence for this appraisal came from the network meta-analysis. The ERG noted that relevant placebo-controlled trials of the antipsychotic 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 participant population. The ERG also agreed that excluding the study comparing risperidone with lithium and divalproex sodium was appropriate. The ERG did not consider it appropriate for the study comparing risperidone with divalproex sodium to be excluded but acknowledged that including this study would have little impact on the conclusions from the network meta-analysis.

3.38 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 in 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.

3.39 The ERG considered that a random-effects model was more appropriate for the network meta-analysis 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.

3.40 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 analysis of uncertainty in the model inputs.

3.41 The ERG explored the manufacturer's probabilistic sensitivity analysis. The ERG noted that all changes in the total costs and QALYS between the deterministic and mean probabilistic sensitivity analysis results were less than 0.1% of the deterministic value. Although second-line aripiprazole (strategy 2) dominated all the other strategies in the deterministic analysis and mean probabilistic sensitivity analysis results, the probabilistic 95% confidence intervals included the possibility of each strategy dominating this strategy. The ERG summarised the results to show that the strategy that excludes aripiprazole (strategy 1) was dominated by each of the other strategies in over half of the probabilistic sensitivity analysis results: strategy 2 dominated strategy 1 in 72.1% of iterations, strategy 3 dominated strategy 1 in 54.4% of iterations, and strategy 4 dominated strategy 1 in 57.2% of iterations. The cost-effectiveness acceptability curve indicated that the probability that strategy 1 is cost effective is roughly half that of the probabilities for strategy 2 or strategy 3 for all the thresholds explored.

3.42 The ERG highlighted that its clinical advisers and those of 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 and comorbidities). As there are limited data available to model treatment within subgroups, the ERG conducted an exploratory scenario analysis to assess the possible implications of treatment sequences tailored to reflect an individual's needs. The results showed that only small changes in the modelled results 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.

3.43 The ERG explored the potential implications of 2 different treatment durations for aripiprazole: 1 use reflected its licensed duration of a maximum of 12 weeks, the other reflected clinical opinion of its real-life use based on an average of 12 months. The ERG amended the manufacturer's model to have maximum treatment duration (for all antipsychotics) of 12 weeks. Responding to 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 total costs and total QALYs showed a reduction in both of the 2 new models, the substantive conclusions of the manufacturer's base case analysis remained unchanged.

3.44 The ERG considered that a treatment sequence containing all 4 antipsychotics was appropriate. Clinical advisers to the ERG stated that if a person's condition had not responded to the first 3 antipsychotic interventions, clinicians would generally try the remaining antipsychotic rather than conclude that a person's condition was treatment resistant. It was not possible to evaluate this scenario 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.

3.45 The ERG made the following changes to the model to explore the plausibility of the manufacturer's results:

- it used network meta-analysis results from a random-effects model
- it included a half-cycle correction
- it adjusted the discounting formula used
- it amended the mortality rate calculations
- it included a 10% reduction in efficacy between lines 1 and 2, and 15% between lines 2 and 3

- it included a logical constraint on the probabilistic sensitivity analysis inputs so that week 3 probability of discontinuing or responding did not exceed 100%.

  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-world' model, which assumed 4 weeks of acute treatment and 12 months of euthymic treatment.

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

- The probabilistic sensitivity analysis results from the 'licensed duration' model indicated that the use of aripiprazole at any point in the treatment pathway dominated usual care, which had the highest total cost (£72,157) and the lowest total QALYs (2.458). Aripiprazole used as second-line therapy after risperidone had the lowest total cost (£70,707) and the highest total QALYs (2.471).
- The probabilistic sensitivity analysis results from the 'real-world' model indicated that aripiprazole used as first-line therapy had the highest total cost (£63,384) and the lowest total QALYs (2.428). Aripiprazole used as second-line therapy had the lowest total cost (£62,138) and the highest total QALYs (2.429).

3.47 The ERG also explored the impact on the cost effectiveness of the amendments (described in section 3.45) 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.

3.48 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of aripiprazole, having considered evidence on the nature of acute manic episodes in bipolar I disorder in adolescents and the value placed on the benefits of aripiprazole by people with the condition, and clinical specialists. It also took into account the effective use of NHS resources.

4.1 The Committee discussed the nature of acute manic episodes in bipolar I disorder. The clinical specialists explained that acute manic episodes can have a large impact on adolescents and their families. Symptoms of mania may include poor concentration, little need for sleep, poor temper control, irritability, reckless behaviour and lack of self-control. For adolescents, the symptoms may impact on schooling, work and social life. The impact on families may include sleep deprivation, financial pressures and family wellbeing. The Committee heard that there is often a need to resolve the manic episode quickly so that adolescents can return to normal functioning in terms of schooling, work and family life.

4.2 The Committee discussed current standard clinical management of manic episodes in bipolar I disorder in adolescents. The clinical specialists highlighted that the main aim of treatment is to maximise control of the mania and minimise the adverse reactions to treatment that are most troublesome for each individual. The Committee heard from the clinical specialists that drug treatment options for adolescents who develop acute mania include antipsychotic drugs such as aripiprazole, risperidone, olanzapine or quetiapine. The clinical specialists explained that lithium is associated with a range of practical limitations, including the need for pre- and post-treatment blood tests, a narrow therapeutic range, and significant adverse effects. The clinical specialists further explained that although lithium can be prescribed as a monotherapy, it is usually prescribed in combination with antipsychotics. They also highlighted that valproate is rarely used as a monotherapy and is usually not given to women of childbearing age because of fetal malformation risks during pregnancy and risk of polycystic ovary syndrome.

4.3 The clinical specialists confirmed that in UK clinical practice, the routinely prescribed antipsychotics for this indication are olanzapine, aripiprazole,

risperidone and quetiapine, and they acknowledged that all are prescribed off-label for the adolescent population (except aripiprazole, which received its marketing authorisation for this indication in January 2013). The Committee was aware that NICE's guideline on bipolar disorder (now replaced by NICE's guideline on bipolar disorder: assessment and management) recommends following the recommendations for adults with bipolar disorder when prescribing medication for adolescents with acute manic episodes, except that drugs should be started at lower doses. The Committee understood from the clinical specialists that no single antipsychotic drug is considered to be more clinically effective than the others, but that tolerability and adverse reactions vary between the treatments. The Committee heard from the clinical specialists that there is substantial variation between the antipsychotics in the adverse reactions associated with each treatment including weight gain, hyperprolactinaemia and sexual dysfunction, aggression, and akathisia or extrapyramidal symptoms. The clinical specialists explained that it is important for adolescents with moderate to severe manic episodes to have a range of treatment options available. This is in order to individualise treatment and to minimise adverse treatment effects, as adolescents are often less tolerant of adverse reactions than adults, leading to problems with adherence to medication.

4.4 The Committee discussed the manufacturer's decision problem, noting that the manufacturer had excluded lithium and valproate as comparators even though they were specified in the final scope issued by NICE. The Committee noted the comments from the manufacturer, ERG and the clinical specialists highlighting that lithium and valproate monotherapy are rarely used in UK clinical practice. The Committee accepted that these 2 treatments are rarely used as monotherapy and agreed that it was appropriate to consider only risperidone, olanzapine and quetiapine as the comparators, as listed in the manufacturer's decision problem.

Clinical effectiveness

4.5 The Committee considered the relevance of the USA-based NCT00110461 trial to UK clinical practice. It discussed whether the population in the trial reflected that seen in UK clinical practice. The Committee noted that the trial recruited people who were aged between 10 and 17 years and that approximately 63% of the trial

participants were aged 13 or older, and so were within the UK marketing authorisation. The Committee heard from the clinical specialists that the diagnosis criteria for bipolar I disorder in children and adolescents in the UK differed from those used in the USA and it is likely that some of the participants with bipolar I disorder comorbid with ADHD in the trial would not have been diagnosed with bipolar I disorder in the UK. The clinical specialists also confirmed that it was usual in clinical trials involving children and adolescents with bipolar I disorder to exclude people with learning disabilities and those at risk of suicide. The Committee discussed the concerns raised by the ERG that most of the participants recruited to the trial were treated as outpatients, whereas in UK clinical practice, they would be usually treated as inpatients. The Committee heard from the clinical specialists that a significant proportion of people in the NHS are managed as outpatients, especially outside the major cities where there is often limited availability of inpatient facilities for this age group. The Committee concluded that the results from the NCT00110461 trial were generalisable to UK clinical practice.

4.6 The Committee then considered the clinical-effectiveness results of the NCT00110461 trial, which showed that aripiprazole was associated with a statistically significant reduction in total YMRS score when compared with placebo throughout the 30-week study duration based on the last observation carried forward dataset. The Committee understood that the marketing authorisation is restricted to 12 weeks' treatment because of high discontinuation rates and the lack of a statistically significant difference in efficacy outcomes beyond 12 weeks when the analysis was based on the observed case dataset. The Committee discussed the usefulness of the YMRS score as the primary outcome and heard from the clinical specialists that this score is a well-recognised tool used in clinical trials for assessing symptoms of mania but that the tool is not routinely used by all clinicians in the UK. The clinical specialists explained that any changes in the YMRS are clearly evident in the change in severity of the symptoms of the individual. The Committee accepted that the YMRS is a valid tool for measuring the severity of symptoms of mania. It concluded that evidence from the trial demonstrated a reduction in manic symptoms in those receiving aripiprazole for 12 weeks compared with those receiving placebo.

4.7 The Committee considered the adverse event data from the NCT00110461 trial.

Extrapyramidal disorder and somnolence were statistically significantly more common in those receiving either 10 mg or 30 mg aripiprazole compared with those receiving placebo. Akathisia was statistically significantly more common, but only in those receiving the 30 mg dose of aripiprazole compared with those receiving placebo. It noted there were no statistically significant increases in weight gain or BMI in those receiving aripiprazole compared with those receiving placebo at 4 weeks. The Committee heard from the clinical specialists that the patterns of adverse events seen in the trial were consistent with the use of aripiprazole in other indications. The clinical specialists also stated that for this group, in the short term, somnolence may help in the management of acute mania. The Committee noted the lack of long-term safety data for aripiprazole, but was aware that the risk management plan agreed with the EMA included a long-term (up to 2 years) study to evaluate the safety and tolerability of aripiprazole as maintenance treatment in adolescents with schizophrenia, and children and adolescents with bipolar disorder. The Committee concluded that current evidence suggests that the tolerability and range of adverse reactions associated with aripiprazole are acceptable. The Committee was aware that the population in the NCT00110461 trial was broader than that in the UK marketing authorisation, because the trial included children aged younger than 13 years and those with mixed episodes. The Committee understood that the EMA had restricted the licence for aripiprazole to adolescents aged 13 or older because of safety concerns in younger people. The Committee noted that the manufacturer had presented clinical efficacy and safety results in its submission by age group, that is, for ages 10 to 12 years and 13 to 17 years. The Committee noted that the subgroup analysis by age group suggested that there was no change in treatment effect between the age subgroups, but that the younger age group experienced a greater increase in mean weight and BMI changes from baseline at week 12. The Committee noted that the manufacturer provided baseline data on the current episode type (manic or mixed) but a subgroup analysis by age group and episode type was not presented. The Committee understood that these subgroups were post hoc subgroups. It was also aware that the subgroup analyses were based on small numbers of people in the groups, which increased the uncertainty in the results. The Committee therefore concluded that evidence of treatment effect should be based on the whole trial population of NCT00110461.

4.8 The Committee noted that there were no head-to-head comparisons of

aripiprazole with the other comparator antipsychotics. The Committee considered the manufacturer's approach to conducting a network meta-analysis to determine the relative efficacy and tolerability of aripiprazole, risperidone, olanzapine and quetiapine. The Committee noted and accepted the ERG's concerns about the network meta-analysis (see sections 3.37 to 3.39). The Committee was aware that using a random-effects model in the network meta-analysis as suggested by the ERG produced results similar to those obtained by the manufacturer. The Committee therefore accepted the results of the network meta-analysis as a reasonable basis for the economic model given the evidence available.

4.9 The Committee considered the clinical effectiveness evidence of aripiprazole compared with risperidone, olanzapine and quetiapine obtained from the network meta-analysis. It noted that the results suggested that aripiprazole and the other antipsychotics showed greater efficacy than placebo but that no statistically significant differences in efficacy were found between aripiprazole and the other antipsychotics. It then considered the adverse-event profile of aripiprazole compared with risperidone, olanzapine and quetiapine. It was aware that the results suggested that the extrapyramidal symptoms and somnolence occurred more frequently with aripiprazole than with risperidone or quetiapine but that these results were not statistically significant. The Committee also noted that the results suggested that clinically significant weight gain was statistically significantly less likely with aripiprazole than with olanzapine or quetiapine. The Committee was aware of the testimony from the clinical specialists about the importance of having a range of treatments available in order to individualise treatment, minimise adverse treatment effects and therefore increase adherence to medication. The Committee heard from the clinical specialists that avoiding weight gain may be of considerable importance to adolescents. The Committee concluded that based on the evidence available, aripiprazole was as effective as other antipsychotics for treating acute mania and had a comparable and acceptable adverse reaction profile.

Cost effectiveness

4.10 The Committee considered the manufacturer's economic model and the ERG's critique and exploratory analysis. It noted that the ERG considered the

manufacturer's model to be transparent, robust, and well structured. The Committee agreed that the model structure was appropriate.

4.11 The Committee considered the manufacturer's base case in which strategies with aripiprazole used at any stage of the treatment pathway (that is, strategies 2 to 4) were compared with a treatment strategy without aripiprazole (strategy 1). The Committee noted that the manufacturer had undertaken a number of deterministic sensitivity analyses (see section 3.32). The Committee was aware that the main parameters that could make the strategies including aripiprazole become less cost effective were the rates of response applied during the treatment phase. The Committee noted that a higher response rate during the treatment phase resulted in people leaving hospital earlier, which had both cost and health-related quality-of-life benefits. The Committee was also aware that the manufacturer's probabilistic sensitivity analyses suggested that there was uncertainty surrounding the ICERs and it understood that this may be a result of the lack of statistically significant differences in response rates obtained from the network meta-analysis for the 4 antipsychotics. The Committee noted that the results from the manufacturer's probabilistic sensitivity analyses indicated that for the 3 strategies that include aripiprazole, the majority of the probabilistic sensitivity iterations indicated cost effectiveness or dominance. The Committee therefore agreed that the base-case results suggested that a treatment strategy that includes aripiprazole is a cost-effective option when compared with a treatment strategy without it.

4.12 The Committee then considered the impact of the position of aripiprazole within the treatment pathway on the cost effectiveness results. The Committee discussed the results of the manufacturer's base case as presented in the incremental analysis. The Committee noted that the pathway in which aripiprazole was positioned second, that is strategy 2, dominated all of the other strategies. The Committee also noted that a comparison of the ranges of costs and QALYs (in the base case, costs ranged from £74,133 to £75,066, and QALYs ranged from 2.516 to 2.525) across the strategies showed that they were similar. The Committee noted that the treatment pathway without aripiprazole (strategy 1) was dominated by each of the other treatment pathways including aripiprazole in over half of the probabilistic sensitivity analysis iterations, and that the probability of strategy 1 being the most cost-effective strategy was half the probabilities for strategy 2 and strategy 3 for all of the thresholds explored by the

ERG (see section 3.41). Given that each of the strategies was dominated by every other strategy in at least some of the probabilistic iterations, the Committee agreed that the results were not sufficiently robust to make a recommendation on the position of aripiprazole in the treatment pathway. The Committee concluded that aripiprazole should be recommended as an option for the treatment of moderate to severe manic episodes in bipolar I disorder in adolescents.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if an adolescent has moderate to severe manic episodes in bipolar I disorder and the healthcare professional responsible for their care thinks that aripiprazole is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Department of Diagnostic Radiology, St George's Hospital

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Dr Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Fiona Duncan
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Professor Jonathan Grigg

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Brian Hawkins
Chief Pharmacist, Cwm Taf Health Board, South Wales

Dr Peter Heywood
Consultant Neurologist, Frenchay Hospital

Dr Sharon Saint Lamont
Head of Quality and Innovation, North East Strategic Health Authority

Dr Louise Longworth
Reader in Health Economics, HERG, Brunel University

Professor John McMurray
Professor of Medical Cardiology, University of Glasgow

Dr Mohit Misra
General Practitioner, Queen Elizabeth Hospital, London

Ms Sarah Parry
CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees
Lay Member

Dr Ann Richardson
Lay Member

Dr Paul Robinson
Medical Director, Merck Sharp & Dohme

Mr Stephen Sharp
Senior Statistician, MRC Epidemiology Unit

Dr Peter Sims
General Practitioner, Devon

Dr Eldon Spackman
Research Fellow, Centre for Health Economics, University of York

Mr David Thomson
Lay Member

Dr John Watkins
Clinical Senior Lecturer and Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Olivia Wu
Reader in Health Economics, University of Glasgow

6.1 Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing NICE's guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

Mrs Carol Paton (GDG member)
Chief Pharmacist, Oxleas NHS Foundation Trust

Professor Richard Morriss (GDG Chair)
Professor of Psychiatry

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Bernice Dillon
Technical Lead

Nicola Hay
Technical Adviser

Bijal Joshi
Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health and Related Research (ScHARR), The University of Sheffield:

- Uttley L, Kearns B, Stevenson M et al. Aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar disorder in children and adolescents. A Single Technology Appraisal. School of Health and Related Research (ScHARR), The University of Sheffield, March 2013.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups gave their expert views on aripiprazole by providing a written statement to the Committee. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Otsuka Pharmaceuticals (aripiprazole)

Professional or specialist and patient or carer groups:

- British Association for Psychopharmacology
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Psychiatrists
- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health
- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Collaborating Centre for Mental Health (NCCMH)
- National Institute for Health Research Health Technology Assessment Programme
- School of Health & Related Research Sheffield (ScHARR)

The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on aripiprazole by providing oral evidence to the Committee.

- Dr Anthony James, Consultant Child and Adolescent Psychiatrist, nominated by organisation representing Royal College of Psychiatrists – clinical specialist
- Dr David Coghill, Reader in child and adolescent psychiatry, University of Dundee, nominated by organisation representing Royal College of Psychiatrists and British Association for Psychopharmacology – clinical specialist

Representatives from the following manufacturer or sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Otsuka Pharmaceuticals

ISBN 978-1-4731-0230-9