

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

- 1.1 Aripiprazole is recommended as an option for the treatment of schizophrenia in people aged 15 to 17 years who are intolerant of risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone.
- 1.2 People aged 15 to 17 years currently receiving aripiprazole for the treatment of schizophrenia who do not meet the criteria specified in 1.1 should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician and the person with schizophrenia, and if appropriate, their parents or carers.

2 The technology

- 2.1 Aripiprazole (Abilify, Bristol-Myers Squibb and Otsuka Pharmaceuticals) has a UK marketing authorisation for the treatment of schizophrenia in people aged 15 years and older. The initial marketing authorisation for aripiprazole was for the treatment of schizophrenia in adults. Subsequently an extension was sought to include the treatment of schizophrenia in adolescents aged 13 to 17 years. The Committee for Human Medicinal Products concluded

that the proposed extension was approvable provided the population is restricted to people aged 15 years and older.

- 2.2 Aripiprazole is administered orally. The summary of product characteristics (SPC) states that the recommended dosage for aripiprazole is '10 mg/day administered on a once-a-day schedule without regard to meals'. It also states: 'Treatment should be initiated at 2 mg (using aripiprazole oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg'.
- 2.3 The SPC lists the most commonly reported adverse reactions associated with aripiprazole treatment to include akathisia and nausea. For full details of adverse reactions, contraindications, special warnings and precautions for use, see the SPC.
- 2.4 Aripiprazole is available in 5 mg, 10 mg, 15 mg and 30 mg tablets. The acquisition cost of aripiprazole 5 mg, 10 mg and 15 mg is £97.67 for 28 tablets. The acquisition cost of aripiprazole 30 mg is £195.33 for 28 tablets. The acquisition cost of aripiprazole oral solution 1 mg/ml is £104.64 for 150 ml. Costs exclude VAT and are from the British national formulary [BNF] 59th edition. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submissions

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

Clinical effectiveness

Original submission

- 3.1 The decision problem defined the population as people with schizophrenia aged 15 to 17 years, in line with the marketing authorisation. Consideration of the population with schizophrenia aged 18 years and older was outside the remit of this appraisal. The manufacturer considered only one antipsychotic treatment, olanzapine, as a comparator to aripiprazole, despite the decision problem listing risperidone, quetiapine and amisulpride as other comparators. The manufacturer justified these omissions on the grounds that data for these comparators from randomised controlled trials (RCTs) in adolescents were not available.
- 3.2 The manufacturer performed a systematic review to identify RCTs comparing aripiprazole with antipsychotic drugs (olanzapine, risperidone, quetiapine, haloperidol, and amisulpride) or with placebo. Clozapine was listed as a comparator in the decision problem but was excluded from the systematic review because the manufacturer received clinical advice that clozapine is not routinely prescribed for the first-line treatment of schizophrenia in adolescents.
- 3.3 Six RCTs were identified, none of which compared aripiprazole with another antipsychotic drug. Only one RCT on the use of aripiprazole in adolescents (study 31-03-239) compared with placebo was identified. Study 31-03-239 was a phase III, multicentre, randomised, double-blind, placebo-controlled trial that enrolled 302 people aged between 13 and 17 years with schizophrenia (diagnosed using the 'Diagnostic and statistical manual of mental disorders, 4th edition' ['DSM-IV'] and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia-

Present and Lifetime Version [K-SADS-PL]). Participants were randomly assigned to one of three study arms: a once-daily fixed dose of either 10 mg or 30 mg of aripiprazole, or matching placebo. Supporting data on adverse events were from two open-label single-arm extension studies.

- 3.4 The primary outcome in study 31-03-239 was mean change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at 6-week follow-up. PANSS scores range from 7 (symptoms absent) to 49 (extreme symptoms), with reductions in score indicating improvements in symptoms. Secondary outcomes included PANSS positive and negative subscale scores, Children's Global Assessment Scale (CGAS), Clinical Global Impression for Severity (CGI-severity) and Improvement (CGI-improvement), and time to discontinuation (for all reasons). The number of hospitalisations was also included. Health-related quality of life was assessed using the Paediatric Quality of Life and Enjoyment and Satisfaction Questionnaire (P-QLES-Q) total and overall scores at baseline and at 6-week follow-up.
- 3.5 The results from study 31-03-239 showed that at 6-week follow-up reductions in PANSS score (that is, improvements in symptoms) occurred in all three groups. Statistically significant differences in the degree of improvement versus placebo were observed in the group who received aripiprazole 10 mg (-5.5 ; $p = 0.05$) and the group who received aripiprazole 30 mg (-7.4 ; $p = 0.007$). At 6-week follow-up all three groups showed reductions in PANSS positive subscale scores, and these reductions were statistically significant in the two groups who received aripiprazole compared with the group who received placebo. All three groups also showed reductions in PANSS negative subscale scores at 6-week follow-

up; compared with placebo these reductions were statistically significant only in the group who received 10 mg aripiprazole.

3.6 At 6-week follow-up mean change in CGAS scores showed statistically significant increases (improvements) from baseline in the groups in study 31-03-239 who received 10 mg and 30 mg aripiprazole compared with the group who received placebo. Mean CGI-severity and CGI-improvement scores at 6-week follow-up showed statistically significant decreases (improvements) from baseline in the groups who received 10 mg or 30 mg aripiprazole compared with the group who received placebo. Health-related quality of life as assessed by P-QLES-Q total and overall scores at baseline and at 6-week follow-up showed statistically significant changes in both the group who received 10 mg aripiprazole and the group who received 30 mg aripiprazole compared with the group who received placebo.

3.7 The manufacturer presented a post-hoc subgroup analysis of the results in participants aged 15 to 17 years in study 31-03-239 (which included participants as young as 13 years). The manufacturer used a cut-off age of 15 years to separate participants aged 15 to 17 years from those aged 13 to 14 years in the trial. From this analysis the manufacturer concluded that efficacy improvements in the subgroup aged 15 to 17 years were comparable to those in the overall dataset, and that the observed effect was maintained during the trial period. The manufacturer also compared side effects in adolescents aged 15 to 17 years with side effects in adults treated with aripiprazole for schizophrenia and concluded that the tolerability and safety profiles were similar in the two age groups.

3.8 Data on adverse events were taken from study 31-03-239 comparing aripiprazole with placebo and from two open-label

single-arm extension studies (31-03-241 and 31-05-243).

Participants who completed study 31-03-239 were eligible to enter an open-label extension study of aripiprazole for 6 months (31-03-241). The second open-label extension study (31-05-243) included participants who had completed the first extension study (31-03-241).

3.9 The most common treatment-related adverse events observed in study 31-03-239 comparing aripiprazole with placebo were extrapyramidal disorder, somnolence and tremor. Overall, a higher percentage of participants in the groups who received aripiprazole experienced treatment-related adverse events (71.0% of those who received 10 mg aripiprazole and 72.5% of those who received 30 mg aripiprazole) compared with the placebo group (57.0%). The majority of treatment-related adverse events were mild or moderate in severity. The rates of serious treatment-emergent adverse events were low for all groups; with an incidence of 3% in the placebo group and 4% in the groups who received 10 mg and 30 mg aripiprazole. Mean weight and body mass index z-scores at each visit were within 0.5 standard deviations of the general population for all three groups. A 'significant' weight gain (defined as a weight gain of 7% or more from baseline) was seen at 6-week follow-up in 4% of the participants who received 10 mg aripiprazole, 5.2% of those who received 30 mg aripiprazole and 1% of participants in the placebo group. A 'significant' weight loss (defined as a weight loss of 7% or more from baseline) was seen at 6-week follow-up in 3% of the participants who received 10 mg aripiprazole, 2.1% of those who received 30 mg aripiprazole and 6.1% of participants in the placebo group.

3.10 Changes from baseline in extrapyramidal symptoms as shown by the Simpson–Angus scale showed a statistically significant

difference between the aripiprazole groups and the placebo group (0.5 in the group who received aripiprazole 10 mg [$p < 0.007$], 0.3 in the group who received aripiprazole 30 mg [$p < 0.05$] and -0.3 in the placebo group). In this study, the Barnes scale and the Abnormal Involuntary Movement scale were also analysed and showed no statistically significant differences (data not reported). Mean serum prolactin levels relative to baseline were -8.45 ng/ml for the group who received placebo, -11.93 ng/ml for the group who received 10 mg aripiprazole and -15.14 ng/ml for the group who received 30 mg aripiprazole. The aripiprazole groups showed significantly greater changes in prolactin levels compared with the placebo groups (10 mg aripiprazole group, $p = 0.003$; 30 mg aripiprazole group, $p < 0.0001$). The manufacturer's submission stated that overall, aripiprazole has no impact on cardiac conduction, and the available literature suggests that the impact on metabolic parameters and prolactin levels appears to be less than with other atypical antipsychotics.

- 3.11 The results of the first open-label study (31-03-241) showed that the majority of treatment-related adverse events were mild or moderate in severity. In the subgroup of participants with schizophrenia, 69% had at least one treatment-related adverse event and 5.9% had a serious adverse event. At 6-week follow-up, 24.5% of participants had a weight gain from baseline of 7% or more and 4.6% had a weight loss from baseline of 7% or more. There were no clinically meaningful changes reported in mean QT or QTc intervals or other ECG abnormalities.
- 3.12 The results of the second open-label extension study (31-05-243) showed that the majority of treatment-related adverse events were mild or moderate in severity. Approximately 48% of participants who received long-term treatment with aripiprazole reported at least

one treatment-related adverse event. Influenza, vomiting and headache were the only treatment-related adverse events reported by 5% or more of the participants. Serious adverse events occurred in 5.9% of participants. The manufacturer's submission stated that data were insufficient to draw conclusions about the impact of aripiprazole treatment on clinical chemistry parameters such as prolactin levels. At 6-week follow-up 12.7% of participants had a weight gain from baseline of 7% or more and 7.0% had a weight loss from baseline of 7% or more. No clinically meaningful changes in mean QT or QTc intervals or other ECG abnormalities were observed.

- 3.13 The manufacturer's systematic review also attempted to identify studies that could be included in an adjusted indirect comparison to provide data comparing aripiprazole with olanzapine, the chosen comparator in the manufacturer's submission. Of the six trials identified, two were deemed eligible for inclusion in an indirect comparison by the manufacturer: study 31-03-239 that compared aripiprazole with placebo, and an RCT by Kryzhanovskaya et al. (2009) that compared olanzapine with placebo; both studies were in adolescents with schizophrenia aged 13 to 17 years. The other four trials identified were deemed by the manufacturer to be unsuitable for inclusion in the indirect comparison as they either did not include a placebo group or did not contain sufficient data for comparison. The olanzapine RCT was a phase III, multicentre, randomised, double-blind, placebo-controlled trial that enrolled 107 participants aged between 13 and 17 years with schizophrenia (diagnosed using the 'Diagnostic and statistical manual of mental disorders, 4th edition text revision' ['DSM-IV-TR']). Participants were randomly assigned to either flexible doses of olanzapine (2.5–20 mg/day) or placebo.

- 3.14 Data on clinical efficacy (withdrawals because of adverse events, lack of efficacy or other reasons, weight gain of 7% or more, somnolence and treatment with benzodiazepines [used as a surrogate for extrapyramidal symptoms]) were extracted from the RCTs and analysed for use in the economic evaluation. Data from the study of olanzapine were compared with data from the study of aripiprazole using the placebo arm of each trial as a common comparator. Data were also extracted from the clinical study reports for aripiprazole. No further details on the methodological approach taken to data extraction for the indirect comparison were provided in the manufacturer's submission.
- 3.15 The results of the adjusted indirect comparison were reported as an odds ratio (OR) and relative risk (RR), each with 95% confidence intervals (CI). The manufacturer's submission did not provide further details on how these results were generated from the ORs and RRs of the individual RCTs. The estimates of the effectiveness of aripiprazole relative to olanzapine were used primarily to inform the economic model. These estimates included the probability of discontinuation of olanzapine compared with aripiprazole 10 mg (due to adverse events OR 1.57, lack of efficacy OR 5.00, and other reasons OR 4.00), the probability of adverse events with olanzapine compared with aripiprazole 10 mg (weight gain OR 0.51 and somnolence OR 5.34) and the probability of relapse with aripiprazole or olanzapine (information provided as commercial in confidence).
- 3.16 The ERG noted that the evidence of clinical effectiveness was based on only one RCT (study 31-03-239), which compared aripiprazole with placebo. The ERG considered that the RCT was relevant to the decision problem and provided evidence that is generalisable to the UK population. However, the trial included

adolescents aged 13 to 17 years, which is broader than the population defined in the decision problem and in the UK marketing authorisation for aripiprazole (which is for people aged 15 years and older). The ERG also noted that there were differences in the three treatment arms of the trial, with a greater proportion of white people, people who had previously received antipsychotic treatment and females in the 10 mg aripiprazole group compared with the 30 mg aripiprazole group. The ERG noted that the two open-label extension studies included adolescents and adults with schizophrenia and with bipolar disorder.

- 3.17 The ERG commented on the clinical outcomes presented in the manufacturer's submission. The ERG noted that there are no agreed parameters by which clinically meaningful changes or differences in PANSS, CGI, CGAS, and P-QLES-Q can be pre-defined. The ERG noted that the clinical significance of the differences observed in PANSS score, which was the manufacturer's chosen primary outcome, was not explained by the manufacturer. The ERG commented that no explanation was given by the manufacturer of the apparent placebo effect observed in the trial. The ERG also noted that data from three scales used to assess the clinical effects of aripiprazole were reported in the 31-03-239 study and clinical study report, but were not included in the manufacturer's submission.
- 3.18 The ERG noted that only a subset of the relevant outcomes reported in the RCTs was used in the indirect comparison. The ERG also commented that no formal assessment of heterogeneity was carried out on the indirect comparison by the manufacturer. The ERG further noted that the manufacturer's submission did not provide an interpretation of the results of the adjusted indirect comparison or any critical assessment of the results of the analysis.

It noted that a trial reported by Haas and colleagues comparing standard and subtherapeutic (that is, lower doses than the indicated dosage regimen) doses of risperidone in adolescents with schizophrenia was not identified in the systematic review or included in the indirect comparison because it was published after the manufacturer's systematic review of the literature was carried out.

Additional submission after consultation

3.19 In response to the appraisal consultation document issued in July 2010 in which the Committee was minded not to recommend aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years, the manufacturer was asked to submit further clinical data to incorporate into an updated indirect comparison. Data from two additional RCTs were provided, one comparing quetiapine with placebo (Findling et al. 2008) and the other comparing risperidone with placebo (Haas et al. 2009). Both RCTs included people aged 13 to 17 years with schizophrenia, a wider population than that defined in the decision problem (which specified an age range of 15 to 17 years). No studies were identified that compared amisulpride with placebo. Three studies were identified that compared clozapine with placebo. However, the manufacturer did not consider clozapine to be a main comparator and therefore deemed these three studies unsuitable for inclusion in its analysis. No clinical data on the use of aripiprazole in adolescents with learning difficulties were identified.

3.20 The manufacturer also reported conclusions from a systematic review of head-to-head and placebo-controlled comparisons of atypical antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders (Fraguas et al. 2010). The systematic review found differences in mean weight gain across

second-generation antipsychotics. Olanzapine was associated with the largest mean weight gain (3.8 to 16.2 kg) and aripiprazole was associated with the smallest (0 to 4.4 kg). The systematic review also reported that the greatest increase in prolactin levels occurred in people receiving risperidone (mean change from 8.3 to 49.6 ng/ml) followed by people receiving olanzapine (-1.5 to 13.7 ng/ml). The manufacturer also presented results from a study of children and adolescents aged 4 to 19 years that reported hyperprolactinaemia (> 25.7 ng/ml) in 84.1% of participants who received risperidone, 52.9% of those who received olanzapine, 14.4% of those who received quetiapine and 9.5% of those who received aripiprazole (Correll 2007).

- 3.21 The trials for each comparator all reported significant differences in PANSS total score at 6-week follow-up. The largest differences were reported in the trials with risperidone 1–3 mg per day (-12.7 versus placebo; $p < 0.001$) and risperidone 4–6 mg per day (-13.4 versus placebo; $p < 0.001$), followed by the trial with olanzapine 2.5–20 mg per day (-12.5 versus placebo; $p = 0.005$) and the trial with quetiapine 800 mg per day (-9.29 versus placebo; $p = 0.009$) and 400 mg per day (-8.16 versus placebo; $p = 0.043$). The smallest differences were reported in the trials with aripiprazole 10 mg per day (-5.5 versus placebo; $p = 0.05$) and aripiprazole 30 mg per day (-7.4 versus placebo; $p = 0.007$).
- 3.22 The trials for each comparator (except quetiapine) reported data on PANSS subscores. Reductions in PANSS positive subscores at 6-week follow-up were reported in each of these trials: olanzapine 2.5–20 mg per day (-3.9 versus placebo), risperidone 1–3 mg per day (-3.3 versus placebo), risperidone 4–6 mg per day (-3.5 versus placebo), aripiprazole 10 mg per day (-2.0 versus placebo) and aripiprazole 30 mg per day (-2.5 versus placebo). Similarly,

reductions in PANSS negative subscores at 6-week follow-up were reported in each of these trials: risperidone 1–3 mg per day (–3.5 versus placebo), risperidone 4–6 mg per day (–3.0 versus placebo), olanzapine 2.5–20 mg per day (–2.0 versus placebo), aripiprazole 10 mg per day (–1.5 versus placebo) and aripiprazole 30 mg per day (–1.2 versus placebo). PANSS subscores were not reported in the trial comparing quetiapine with placebo (Findling et al. 2008).

- 3.23 CGI-severity and CGI-improvement scores were reported only in the trials that compared olanzapine and aripiprazole with placebo. The reported mean CGI-severity scores at 6-week follow-up showed a decrease (improvement) in the group who received olanzapine 2.5–20 mg per day (–0.6 versus placebo; $p = 0.004$), the group who received aripiprazole 10 mg per day (–0.3 versus placebo; $p = 0.008$) and the group who received aripiprazole 30 mg per day (–0.4 versus placebo; $p = 0.002$). The reported mean CGI-improvement scores at 6-week follow-up showed a decrease in the group who received olanzapine 2.5–20 mg per day (–1.1 versus placebo; $p < 0.001$). Reductions in CGI-improvement scores at 6-week follow-up were also reported in the groups who received aripiprazole 10 mg per day (–0.4 versus placebo; $p = 0.02$) and aripiprazole 30 mg per day (–0.6 versus placebo; $p = 0.0004$). CGAS scores were reported only in the risperidone and aripiprazole trials. The risperidone trial reported increases (improvements) in mean change in CGAS scores at 6-week follow-up in the group who received risperidone 1–3 mg per day (+9.0 versus placebo; $p = 0.006$) and risperidone 4–6 mg per day (+11.0 versus placebo; $p < 0.001$). The aripiprazole trial also reported increases in mean change in CGAS scores at 6-week follow-up in the group who received aripiprazole 10 mg per day (+4.9 versus placebo; $p = 0.006$) and aripiprazole 30 mg per day (+5.0 versus placebo; $p = 0.005$).

- 3.24 The trials for each comparator all reported data on weight. The difference in weight gain at 6-week follow-up was lowest in the groups who received aripiprazole 10 mg per day (+0.8 kg versus placebo) and aripiprazole 30 mg per day (+1.0 kg versus placebo), followed by the groups who received risperidone 0.5–2.5 mg per day (+1.18 kg versus placebo) and risperidone 3–6 mg per day (+1.38 kg versus placebo) and those who received quetiapine 400 mg per day (+2.6 kg versus placebo) and quetiapine 800 mg per day (+2.2 kg versus placebo). The highest weight gain was reported in the olanzapine trial (+4.2 kg versus placebo).
- 3.25 Increases in the level of prolactin at 6-week follow-up were reported in the group who received risperidone 0.5–2.5 mg per day (+46.1 ng/ml in females and +19.2 ng/ml in males, versus placebo), risperidone 3–6 mg per day (+86.5 ng/ml in females and +29.6 ng/ml in males, versus placebo), olanzapine 2.5–20 mg per day (+12.1 ng/ml versus placebo), quetiapine 400 mg per day (+7.7 ng/ml versus placebo) and quetiapine 800 mg per day (+10.42 ng/ml versus placebo). Reductions in prolactin levels were reported only in the groups who received aripiprazole 10 mg per day (–3.4 ng/ml versus placebo) and aripiprazole 30 mg per day (–6.6 ng/ml versus placebo). No differences in akathisia compared with placebo were reported in the group who received aripiprazole 10 mg per day. Differences in akathisia were reported in the groups who received aripiprazole 30 mg per day (+7.0% versus placebo), risperidone 0.5–2.5 mg per day (+5.0% versus placebo), quetiapine 400 mg per day (+1.4% versus placebo) and quetiapine 800 mg per day (+1.4% versus placebo).
- 3.26 The ERG noted that the additional studies identified by the manufacturer include people aged 13 to 17 years with schizophrenia, which is wider than the population defined in the

scope (people aged 15 to 17 years). The ERG also noted that the systematic review and the two other data sources identified by the manufacturer encompassed people with conditions other than schizophrenia and included non-randomised studies. The ERG concurred with the manufacturer that data on the use of aripiprazole specifically for people with learning difficulties are unlikely to be available.

- 3.27 The ERG commented that comparable data on PANSS scores for aripiprazole, quetiapine, risperidone and olanzapine could have been included in an indirect comparison. It noted that the manufacturer provided no explanation of its calculation or interpretation of the odds ratios for the indirect comparison. The ERG also noted that three of the RCTs reported prolactin concentration in a standard format that could have been included in an indirect comparison. Comparable data on weight change from the risperidone trial could also have been included in an indirect comparison. The ERG agreed with the manufacturer that there were insufficient data for analysis of the other clinical outcomes.

Cost effectiveness

Original submission

- 3.28 The manufacturer carried out a systematic review of the literature to identify cost-effectiveness studies of aripiprazole for the treatment of schizophrenia in adolescents. No such studies were identified; however, four economic evaluations that included aripiprazole in adults with schizophrenia were identified and reviewed. Since Given that there were no economic evaluations assessing the cost effectiveness of aripiprazole in adolescents, the manufacturer carried out a de novo economic evaluation.

3.29 The manufacturer presented a decision tree followed by a Markov model to estimate the cost effectiveness of first-line aripiprazole compared with first-line olanzapine for the treatment of schizophrenia in adolescents. The model incorporates first-line, second-line and third-line treatments and allows people to switch to the next treatment when one treatment is discontinued or a relapse occurs. In the first two cycles of the model, people undergoing treatment may discontinue and switch to another antipsychotic drug (from aripiprazole to olanzapine or vice versa). These cycles are represented as two health states in the decision tree: stable schizophrenia and withdrawal (because of lack of efficacy, adverse events or other reasons). In the second cycle there may also be a relapse, which is reflected as an additional health state in this cycle. People in whom there is no relapse or who discontinue treatment are assumed to continue treatment in the stable schizophrenia state. Discontinuation is assumed to occur only in the first two cycles. From the third treatment cycle onwards, people are assumed to either continue in a stable condition or a relapse occurs and they may subsequently switch antipsychotic treatment. This is reflected by using a Markov process that involves only two states – maintenance on treatment and relapse. People who discontinue treatment or in whom a relapse occurs on the second treatment are assumed to receive clozapine as a last-resort treatment and to continue receiving clozapine after relapse. The model adopted a 3-year time horizon on the basis that this is the maximum duration an individual would remain in this group before being considered an adult (at which point other treatment options may be available). Death was not modelled because of the short time horizon and a lack of efficacy data on death rates.

3.30 The manufacturer's base-case analysis compared first-line aripiprazole with first-line olanzapine in people aged 13 to 17 years

with schizophrenia, which is broader than the UK marketing authorisation for aripiprazole (which is for adolescents aged 15 to 17 years with schizophrenia). Results were presented in terms of total and incremental costs and quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for the two strategies.

- 3.31 The model used withdrawal and adverse event data, but not primary outcome data, from published RCTs and the indirect comparison. The probabilities of withdrawals and adverse events were calculated directly from study 31-03-239 on aripiprazole and from the manufacturer's adjusted indirect comparison. The manufacturer stated that no long-term data on treatment effects, including rates of relapse with aripiprazole and olanzapine, were identified in the literature for the adolescent population. Data on rates of relapse were therefore taken from a study of adults with schizophrenia that compared aripiprazole with other atypical antipsychotics. The study reported a relative risk of relapse with aripiprazole of 0.92 (95% CI 0.67 to 1.26) compared with other atypical antipsychotics. However, the manufacturer stated that this value is an error, as it does not equal the ratio of the proportion of people in whom there is a relapse after treatment with other atypical antipsychotics divided by the proportion of people in whom there is a relapse after treatment with aripiprazole. The manufacturer adjusted the value (which was provided as commercial in confidence) and used this higher adjusted relative risk of relapse (that is, a relapse is more likely to occur) in the economic model.
- 3.32 The manufacturer also found limited or no data on adolescents with schizophrenia concerning utility values and resource use. Utilities for the health states were taken from a study of adults with

schizophrenia in the UK. The study reported separate utilities for patients and non-patients. The manufacturer used the utilities derived from patients in its economic model.

- 3.33 The model included four types of resource use and costs: drug acquisition, on-treatment monitoring and switching of medication, management of adverse events, and health state costs. Treatment costs were calculated using daily drug dosages from the SPCs supported by the mean and median dosages in study 31-03-239 and the RCT reported by Kryzhanovskaya et al. (2009) respectively. Resource use associated with switching medication was based on three 20-minute visits to a psychiatrist. Resource use associated with adverse treatment effects was based on assumptions made in NICE clinical guideline 82 (CG82), 'Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care' (2009) about weight gain and extrapyramidal symptoms, and clinical opinion on somnolence. Resource use associated with relapse was also based on CG82.
- 3.34 In the manufacturer's base-case analyses, first-line treatment with aripiprazole is estimated to dominate first-line treatment with olanzapine (that is, first-line treatment with aripiprazole is more effective and less costly than first-line treatment with olanzapine; incremental cost -£69.21, incremental benefit 0.004). The manufacturer conducted a number of one-way deterministic sensitivity analyses, which showed that varying the relative risk of relapse and the daily cost of aripiprazole had the greatest effect on the ICERs. The ICERs varied between -£123,663 and £628,706 per QALY gained for a relative risk of relapse of 0.679 to 1.261 and from -£64,755 and £130,723 per QALY gained for a daily cost of aripiprazole of £2.28 to £6.84. The probabilistic sensitivity analysis

suggested that first-line aripiprazole had a 96% probability of being cost effective at £20,000 per QALY gained when compared with first-line olanzapine.

3.35 The ERG considered that in general the manufacturer's approach to the economic evaluation was appropriate. However, the ERG noted a number of concerns about the cost-effectiveness analysis, including the approach used to compare sequential treatment strategies. These concerns included:

- for both treatment strategies the major contribution to the total cost was the cost of managing relapses
- the exclusion of risperidone, which is currently the most common first-line treatment for schizophrenia in adolescent populations in the UK
- the exclusion of relevant adverse events such as extrapyramidal symptoms and sexual dysfunction in the economic model
- the appropriateness of applying data derived from adult populations, such as relative risk values, to adolescents, and the uncertainty this generates in the model
- the appropriateness of using a re-derived relative risk value based on crude relative risk reported in the published paper.

3.36 The ERG made revisions to the manufacturer's model to correct errors (relating to the cost of relapse in cycle 2 and the Health Resource Group [HRG] cost code that was applied). When the cost of relapse in cycle 2 was revised it resulted in a higher ICER than was reported in the manufacturer's base case for the comparison of first-line aripiprazole with first-line olanzapine (£6231 per QALY gained; incremental cost £27.15, incremental benefit 0.004). Revising the HRG cost code had no effect on the result (aripiprazole dominated olanzapine in the revised result and the

base case). The ERG also noted there was an error in the presentation of all the probabilistic sensitivity results relating to the inclusion of total undiscounted cost for first-line olanzapine. Revising this error resulted in considerably higher ICERs than those reported in the manufacturer's base case (ranging from £22,182 per QALY gained in the ERG analysis after correcting for this error to £47,103 per QALY gained after correcting for this error and applying a relative risk of relapse of 0.92).

- 3.37 The ERG performed a number of analyses on the corrected model to apply alternative estimates for parameter inputs and explore the impact of alternative structural assumptions and the methods used in the adjusted indirect comparison. The cumulative results presented by the ERG showed that adjusting medication costs for people with schizophrenia in whom there is a relapse approximately doubles the incremental costs without affecting the incremental QALYs, increasing the ICER from £6231 to £13,763 per QALY gained. The ICER increases from £13,763 to £23,144 per QALY gained when the disutility for people discontinuing treatment because of adverse events is reduced and the disutility associated with weight gain is continued while people remain on a given treatment. When the proportion of people in whom there is a relapse and who are admitted as inpatients is increased to 50% and applied to the assumptions already considered, it results in aripiprazole dominating olanzapine (that is, aripiprazole is more effective and less expensive than olanzapine). However, when the length of stay for admitted patients is increased to 107.7 days, the ICER increases to £69,638 QALY gained, and increases further to £232,981 per QALY gained when the relative risk of relapse of 0.92 reported by Moeller and colleagues is used.

3.38 The ERG also presented exploratory analyses in which the unit costs of risperidone for the treatment of adolescents with schizophrenia and the odds ratios relating to early discontinuations with risperidone (based on an adjusted indirect comparison) were applied to the manufacturer's economic model. In the first analysis, the cost of first-line treatment with risperidone was substituted for the cost of first-line treatment with olanzapine in the manufacturer's model. This caused the ICERs for aripiprazole as a first-line treatment to increase significantly, rising to £89,114–£112,012 per QALY gained compared with risperidone. The ERG noted that this analysis did not use any clinical data specific to risperidone, and implicitly assumed that the odds ratios derived for olanzapine (relative to aripiprazole) could be applied to risperidone. To examine the impact of applying odds ratios derived from an alternative data source, an adjusted indirect comparison was conducted using data from an RCT on the use of risperidone in adolescents aged 13 to 17 years reported by Haas and colleagues (2009) to estimate the odds ratios for discontinuation (due to adverse events, lack of efficacy and other reasons) and for treatment-related adverse effects (weight gain, somnolence and extrapyramidal symptoms). The ERG noted that the risperidone RCT was not placebo controlled; rather, it compared the standard dosage of risperidone (1.5–6.0 mg/day) with a dosage that (although not proven ineffective) was tenfold lower (0.15–0.6 mg/day). The ERG therefore cautioned that the occurrence of treatment discontinuations associated with risperidone may have been underestimated in the study, and hence the odds ratios derived in the adjusted indirect comparison may be biased against aripiprazole. Using these data in the manufacturer's economic model, the ERG's analysis suggested that first-line risperidone

dominated first-line aripiprazole (that is, first-line aripiprazole is a less cost-effective option compared with first-line risperidone).

Additional submission after consultation

3.39 In response to the Appraisal Consultation Document issued in July 2010 in which the Committee was minded not to recommend aripiprazole for the treatment of schizophrenia in adolescents aged 15 to 17 years, the manufacturer provided a revised economic model. The revised model contained four additional treatment sequences specified in the Appraisal Consultation Document:

- treatment strategy A (aripiprazole then risperidone then olanzapine then clozapine [A, R, O, C])
- treatment strategy B (risperidone then aripiprazole then olanzapine then clozapine [R, A, O, C])
- treatment strategy C (risperidone then olanzapine then aripiprazole then clozapine [R, O, A, C])
- treatment strategy D (risperidone then olanzapine then quetiapine then clozapine [R, O, Q, C]).

The revised economic model also included a range of doses for the comparators, including low doses (which are commonly prescribed for adolescents), lay utility values (rather than patient values) from Briggs and colleagues (2008), an unadjusted relative risk of relapse of 0.937 (rather than an adjusted value), and additional adverse treatment effects (akathisia, tremor and agitation). The manufacturer's submission stated that, although requested by the Committee, sexual dysfunction could not be included in the model because this outcome was not reported in the studies identified and that prolactin levels (which are thought to be related to sexual dysfunction) were reported in different ways. Furthermore, data on aggression were not consistently reported in the studies identified,

although rates of agitation were available for aripiprazole, risperidone and quetiapine and included as a sensitivity analysis. The manufacturer's submission justified the exclusion of PANSS scores in the revised model on the basis that clinicians do not use the PANSS questionnaire in clinical practice and that in CG82 PANSS was used to inform utility values and not as a separate outcome measure. The manufacturer carried out corrections for inaccuracies identified by the ERG in the original model, which included the cost of an acute hospital stay (changed to £513 per day), the costs during the second cycle of the model, the values for the proportion of patients with an acute hospitalisation, and the number of patients receiving olanzapine following relapse.

3.40 The manufacturer's revised model included a number of assumptions to inform gaps in the outcome measures. If data were not available for any outcome measure, equivalence with aripiprazole was assumed (that is, relative risk = 1.0). For quetiapine, the odds ratio of withdrawal due to lack of efficacy was assumed to be captured in withdrawal due to other reasons. Costs and disutility associated with extrapyramidal symptoms were applied to other adverse events included in the model (akathisia, benzodiazepine use, agitation and tremor). The manufacturer's model included several available formulations of each of the antipsychotic treatments. In the base-case analysis, UK prescription cost analysis was used to provide the most commonly prescribed formulation, which was then used to calculate the daily cost of the antipsychotics included in the analysis. The most commonly prescribed formulation of aripiprazole was the 28-tablet pack of 10 mg at a cost of £95.74. Based on a dose of 10 mg per day (dose escalated according to the SPC and according to the dose used in the clinical trial), aripiprazole was costed at £3.42 per day in the model. The most commonly prescribed formulation of

olanzapine was the 28-tablet pack of 10 mg at a cost of £79.45. Based on a dose of 12.5 mg per day (mean modal dose according to the clinical trial), olanzapine was costed at £3.55 per day in the model. The most commonly prescribed formulation of quetiapine was the 60-tablet pack of 25 mg at a cost of £33.83. Based on a dose of 400 mg per day, quetiapine was costed at £9.02 per day in the model. The most commonly prescribed formulation of risperidone was the 20-tablet pack of 0.5 mg at a cost of £1.06. Based on a dose of 2 mg per day, risperidone was costed at £0.21 per day in the model. The most commonly prescribed clozapine formulation was 100 mg tablets. At a dose of 325 mg per day (based on a usual dose for people aged under 18 years of 200–450 mg daily), clozapine was costed at £2.86 per day in the model.

3.41 The manufacturer's revised model included deterministic sensitivity analyses of the doses for each treatment:

- Dosing scenario 1 examined the following: aripiprazole 10 mg, olanzapine 12.5 mg (as in the base case), risperidone 4–6 mg and quetiapine 800 mg (both costs and efficacy were varied).
- Dosing scenario 2 examined the following: aripiprazole 10 mg, olanzapine 10 mg (tablets are available in 10 mg doses; efficacy remains the same as in the base case), risperidone 4–6 mg and quetiapine 800 mg (both costs and efficacy were varied).

The manufacturer also carried out sensitivity analyses of adverse events including weight gain, somnolence, extrapyramidal symptoms (represented by tremor and akathisia) and agitation.

3.42 The results of the manufacturer's revised deterministic base case showed that treatment strategy D (R, O, Q, C) was dominated by strategy C (R, O, A, C), and treatment strategies B (R, A, O, C) and A (A, R, O, C) resulted in ICERs ranging from £51,600 per QALY

gained to £108,800 per QALY gained respectively compared with treatment strategy C (R, O, A, C). The results of the manufacturer's sensitivity analyses showed that treatment strategy D (R, O, Q, C) was dominated by treatment strategy C (R, O, A, C) in all scenarios presented. Results of the manufacturer's dosing scenarios showed that in the first scenario, treatment strategies A (A, R, O, C) and B (R, A, O, C) resulted in ICERs ranging from £38,500 to £49,000 per QALY gained respectively compared with treatment strategy C (R, O, A, C). In the second dosing scenario, treatment strategies B (R, A, O, C) and A (A, R, O, C) resulted in ICERs ranging from £203,000 to £350,000 per QALY gained respectively compared with treatment strategy C (R, O, A, C). The results of the manufacturer's sensitivity analysis of adverse events showed that treatment strategies A (A, R, O, C) and B (R, A, O, C) resulted in ICERs ranging from £38,300 per QALY gained to £49,000 per QALY gained respectively compared with treatment strategy C (R, O, A, C).

- 3.43 The ERG commented that its original concern regarding the application of disutility due to weight gain only in the first cycle of each line of treatment was not addressed in the manufacturer's revised model. The ERG noted that the manufacturer's revised deterministic analyses showed that treatment strategy D (R, O, Q, C) was dominated by first-line risperidone strategies B (R, A, O, C) and C (R, O, A, C), and that aripiprazole was associated with higher ICERs compared with first-line risperidone sequences. The ERG noted that the results of the manufacturer's revised probabilistic sensitivity analysis showed consistently better outcomes (total QALYs increased by 0.05 and 0.06 for each strategy) and slightly lower costs than the deterministic analysis,

and that small changes in the model resulted in large changes in the results.

- 3.44 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

- 4.1 The Committee reviewed the data available on the clinical and cost effectiveness of aripiprazole, having considered evidence on the nature of schizophrenia in people aged 15 to 17 years and the value placed on the benefits of aripiprazole by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee discussed current standard clinical management of schizophrenia in adolescents. It heard from clinical specialists and patient experts that antipsychotics are prescribed only after a psychological assessment and a discussion with the person with schizophrenia together with their family or carer. The choice of treatment is negotiated with the person and depends on a number of factors, including adverse events associated with the treatment, previous treatments the person has received and their responses to them, and adverse events experienced while on those treatments. Adolescents with schizophrenia are usually treated with atypical antipsychotics at a low dose and are closely monitored.
- 4.3 The clinical specialists noted that the main aim of treatment is to maximise the control of schizophrenia and minimise the adverse events that are the most troublesome for each individual. The Committee heard from the patient experts that effective control of schizophrenia with aripiprazole would allow adolescents to return to

normal functioning in terms of work or schooling. The Committee understood from the clinical specialists that no single atypical antipsychotic drug is considered to be more clinically effective than the others. Risperidone is the most widely used first-line atypical antipsychotic in UK clinical practice because clinicians have extensive experience of using it to treat schizophrenia, and often achieve control with low doses and without troublesome adverse events. The clinical specialists stated that when an atypical antipsychotic medication is prescribed, control of schizophrenia and adverse events is assessed over a period of 6 weeks or more and an alternative atypical antipsychotic can be considered if the first antipsychotic proves unsatisfactory. Other atypical antipsychotics such as aripiprazole, olanzapine, quetiapine or amisulpride may be used if control of schizophrenia is not achieved with risperidone. The clinical specialists also explained that clozapine is sometimes prescribed; however, because it needs careful monitoring for particular side effects, it is prescribed as rescue therapy only if the schizophrenia is refractory to at least three other antipsychotic treatments. The Committee noted that some of the atypical antipsychotics described by the clinical specialists do not have a marketing authorisation for the treatment of schizophrenia in adolescents, but acknowledged that specific licensing in adolescents is not a prerequisite to prescribing licensed adult medicines, particularly if there is widespread experience of their use. The Committee agreed with the clinical specialists that it is important for adolescents with schizophrenia to have a range of treatment options before considering rescue therapy with clozapine, and therefore considered that aripiprazole may be a suitable treatment option for people aged 15 to 17 years with schizophrenia.

4.4 The Committee heard from the clinical specialists and patient experts that there are a number of dose-related adverse events associated with atypical antipsychotic treatments, including weight gain, hyperprolactinaemia and sexual dysfunction, aggression and akathisia/extrapyramidal symptoms. Adolescents are often less tolerant of adverse events than adults, leading to problems with adherence to medication. The Committee heard from the clinical specialists that some treatments are more likely to be associated with particular adverse events than others: olanzapine is more likely associated with weight gain, risperidone and amisulpride are more likely associated with hyperprolactinaemia, and aripiprazole is more likely associated with akathisia and a subjective feeling of aggression (for which benzodiazepine co-treatment may be used). The clinical specialists stated that these adverse events are dose related and therefore it is preferable to start prescribing any atypical antipsychotic at a low dose. The Committee accepted that all atypical antipsychotics are associated with adverse events and that accounts from the clinical specialists on the use of aripiprazole suggest that it may be as safe and well tolerated as the other treatments.

Clinical effectiveness

4.5 The Committee noted that the clinical effectiveness evidence presented in the manufacturer's submission was derived mainly from one RCT (study 31-03-239) that studied treatment with aripiprazole at two different doses compared with placebo, with supporting data on adverse events from two open-label single-arm extension studies. The Committee noted that the 31-03-239 study was placebo controlled and did not provide a head-to-head comparison of aripiprazole with any other atypical antipsychotics.

- 4.6 The Committee noted that the 31-03-239 study showed a reduction in total PANSS score (that is, an improvement in symptoms) at week 6 in all three study arms. Statistically significant differences in the degree of improvement were observed in the aripiprazole groups compared with the placebo group ($p = 0.0414$ and $p = 0.0061$ for the 10 mg and 30 mg doses versus placebo). The Committee heard from the clinical specialists that the PANSS score is a well-recognised tool used in clinical trials for the measurement of positive, negative and general psychopathology symptoms in schizophrenia. However, the results are often difficult to relate to UK clinical practice as the tool is not routinely used by clinicians. The Committee accepted that the PANSS score is a valid tool for the measurement of positive, negative and general psychopathology symptoms and that evidence from the 31-03-239 study demonstrates a reduction in schizophrenic symptoms in the aripiprazole groups.
- 4.7 The Committee was aware that the manufacturer's original submission included a very limited evidence base. However, the manufacturer's additional analyses provided some evidence for each of the atypical antipsychotics (risperidone, quetiapine and olanzapine) routinely used in UK clinical practice. The Committee noted that the trials for olanzapine, quetiapine and, most notably, risperidone showed greater relative risks in PANSS positive and negative scores in their treatment arms compared with their placebo arms than were seen in the aripiprazole trial. The Committee also noted that there appears to be a large placebo effect in the aripiprazole trial, but heard from the manufacturer that the precise cause of this effect is unknown. The Committee was aware that, insofar as evidence is available, the CGI and CGAS findings from the trials are not better for aripiprazole than for the comparator treatments.

4.8 The Committee considered the evidence on adverse events for aripiprazole and each of the comparators presented in the manufacturer's additional analyses. The Committee noted that there is substantial variation between the atypical antipsychotics in the adverse events associated with each treatment. The Committee was aware of the clinical specialists' view that it is important for adolescents with schizophrenia to have a range of treatment options before considering rescue therapy with clozapine, in order to individualise treatment and to minimise adverse treatment effects. The Committee noted that olanzapine is associated with substantial weight gain, as to a lesser extent are quetiapine and risperidone, but that only very small changes in weight gain are seen with aripiprazole. It considered that weight gain may be of considerable importance to adolescents and was concerned that weight gain associated with olanzapine may not be just a short-term problem, but could be a long-term health risk. In terms of changes in prolactin levels, the Committee heard from the clinical specialists that risperidone is associated with higher levels of prolactin, as to a lesser extent is olanzapine. Prolactin levels with aripiprazole treatment are generally lower than seen with the other comparator treatments. The Committee heard that a change in prolactin level is one of a number of contributors to potential sexual dysfunction.

Cost effectiveness

4.9 The Committee considered the manufacturer's economic model and the critique and exploratory analyses performed by the ERG. It noted that the manufacturer used a decision tree, followed by a Markov model, to estimate the cost effectiveness of first-line aripiprazole compared with first-line olanzapine for the treatment of schizophrenia in adolescents. Data were derived from the

manufacturer's adjusted indirect comparison using secondary outcome data for aripiprazole and olanzapine. The Committee also considered an updated adjusted indirect comparison from the manufacturer that incorporated risperidone, quetiapine and olanzapine as comparators.

- 4.10 The Committee had concerns about a number of aspects of the economic model, including the exclusion of comparators specified in the final scope, primary (PANSS) outcome data and data on relevant adverse events (such as extrapyramidal symptoms and sexual dysfunction). The Committee was also aware that the ERG had identified a number of technical errors in the manufacturer's model. The Committee heard from the ERG that in the absence of data specific to the population in the scope, data on health state utility at relapse, disutility associated with treatment-related adverse events and resource use assumptions were all derived from studies of adults rather than adolescents.
- 4.11 The Committee noted that the manufacturer's initial base-case ICER (provided for the first Appraisal Committee meeting and following revisions from the ERG) for first-line aripiprazole (in a three-drug sequence) compared with first-line olanzapine of £6200 per QALY gained (incremental costs -£69, incremental QALYs 0.004) was based on a number of assumptions that were inappropriate; and that sensitivity analyses conducted by the ERG suggested the ICER could be as high as £233,000 per QALY gained if certain assumptions were varied. Furthermore, it noted that aripiprazole is dominated by risperidone in all of the ERG's exploratory analyses. It concluded that the ICERs presented by the manufacturer could not be accepted without revision. The Committee requested further clarification from the manufacturer.

4.12 The Committee considered the manufacturer's updated economic model that compared sequences of treatments starting with aripiprazole with sequences starting with risperidone. The Committee still had concerns about the primary outcome data not being included in the model. It did not agree with the manufacturer's argument that this omission could be justified on the grounds that trial outcomes were not used in ordinary clinical practice; nor did it agree with the manufacturer's reference to NICE clinical guideline 82 ('Core interventions in the treatment and management of schizophrenia in primary and secondary care (update)'), in which PANSS scores were used to inform utility values and not considered as a separate outcome measure as an argument for not including PANSS scores in the model. The Committee noted that as aripiprazole is associated with smaller changes in PANSS scores than risperidone, olanzapine and quetiapine, the omission clearly favoured aripiprazole. The Committee also noted that some adverse events (sexual dysfunction and aggression) were not included in the model, and was aware that there was an error in the manufacturer's adjusted indirect comparison that resulted in the odds ratios of withdrawals (for other reasons) from risperidone compared with withdrawals from aripiprazole being higher in the manufacturer's analysis. The Committee noted that the manufacturer's updated base-case analysis shows that treatment sequences in which aripiprazole is used first result in ICERs ranging from £52,750 per QALY gained to £108,800 per QALY gained when compared with treatment sequences in which risperidone is used first. It considered that, in view of the PANSS scores not being included in the model, these ICERs were likely to be underestimated. Furthermore, they are outside the range considered to be a cost-effective use of NHS resources.

- 4.13 In view of the results from the manufacturer's updated base-case analysis and the testimony of the clinical specialists, which highlighted that routine clinical practice is to start treatment with risperidone, the Committee concluded that starting treatment with aripiprazole rather than risperidone would not be a cost-effective use of NHS resources.
- 4.14 However the Committee was mindful that in people aged 15 to 17 years with schizophrenia who are intolerant of or have a contraindication to risperidone, or whose schizophrenia has not been adequately controlled with risperidone, the case for aripiprazole is more plausible. The Committee considered whether there was any evidence to suggest that aripiprazole should be used ahead of, or only after olanzapine or quetiapine in the treatment pathway for schizophrenia. It noted that the economic analyses suggest little difference between sequences in which aripiprazole precedes olanzapine and vice versa; and although sequences that contain aripiprazole are suggested to be more cost effective than the sequence that contains quetiapine (sequence D), the Committee was concerned that the cost of quetiapine was unfairly calculated in the manufacturer's economic model, as optimal packs and doses may not have been considered. The Committee agreed that the differences in side effects between these drugs were a more important consideration than the (small) differences in their costs and primary outcomes. Therefore the Committee agreed that aripiprazole should be available on equal terms with other antipsychotic comparators (apart from risperidone), given its good side-effect profile and comparable price to olanzapine and quetiapine
- 4.15 The Committee considered whether its recommendations were associated with any potential issues related to equality. The

Committee was aware that consultees and commentators suggested that one area of potential discrimination was that the diagnosis of schizophrenia requires a definitive methodological approach using precise diagnostic criteria detailed in a number of tools, including DSM-IV and K-SADS-PL. The Committee noted that although some people with learning difficulties may exhibit psychoses, unless they fulfil the DSM-IV and K-SADS-PL criteria for schizophrenia they do not (by definition) have schizophrenia, and therefore are not appropriate for inclusion in this technology appraisal. It noted that both the DSM-IV and K-SADS-PL criteria are used in clinical practice, as well as in studies of schizophrenia. The Committee concluded that there are not sufficient data to provide evidence on how the clinical and cost effectiveness of aripiprazole may differ for people with schizophrenia who have learning difficulties.

Summary of Appraisal Committee’s key conclusions

TAXXX (STA)	Appraisal title: Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years	FAD section
Key conclusions		
Aripiprazole is recommended as an option for the treatment of schizophrenia in people aged 15 to 17 years who are intolerant of risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone.		1.1
People aged 15 to 17 years currently receiving aripiprazole for the treatment of schizophrenia who do not meet the criteria specified in 1.1 should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician, the person with schizophrenia, and if appropriate, their parents or carers.		1.2
Current practice		
Clinical need of patients including the availability of alternative	The Committee agreed with the clinical specialists that it is important for adolescents with schizophrenia to have a range of treatment options before considering rescue therapy with	4.3

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treatments	clozapine, and therefore considered that aripiprazole may be a suitable treatment option for people aged 15 to 17 years with schizophrenia.	
The technology		
Proposed benefits of the technology	The Committee heard from the patient experts that effective control of schizophrenia with aripiprazole would allow adolescents to return to normal functioning in terms of work or schooling.	4.3
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee understood from the clinical specialists that no single atypical antipsychotic drug is considered to be more clinically effective than the others.	4.3
What is the position of the treatment in the pathway of care for the condition?	The Committee heard from the clinical specialists that risperidone is the most widely used first-line atypical antipsychotic in UK clinical practice for adolescents with schizophrenia. Other atypical antipsychotics, such as aripiprazole, olanzapine, quetiapine or amisulpride may be used if control of schizophrenia is not achieved with risperidone. It was noted that clozapine is prescribed as a rescue therapy only if the schizophrenia is refractory to at least three other antipsychotic treatments.	4.3
Adverse events	The Committee heard from the clinical specialists and patient experts that there are a number of dose-related adverse events associated with atypical antipsychotic treatments, including weight gain, hyperprolactinaemia and sexual dysfunction, aggression and akathisia/extrapyramidal symptoms. The Committee heard from the clinical specialists that some treatments are more frequently associated with particular adverse events than others. The Committee accepted that accounts from the clinical specialists on of the use of aripiprazole suggest	4.4

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	that it may be as safe and well tolerated as the other treatments.	
Evidence for clinical effectiveness		
Availability, nature and quality of the evidence	The clinical evidence presented in the manufacturer's submission was derived mainly from one RCT (study 31-03-239) that studied treatment with aripiprazole at two different doses compared with placebo. Supporting data on adverse events was obtained from two open-label single-arm extension studies.	4.5
	An indirect comparison was also conducted to compare first-line aripiprazole with first-line olanzapine.	3.13
	The 31-03-239 study was placebo controlled and did not provide a head-to-head comparison of aripiprazole with any other atypical antipsychotics.	4.5
	The Committee was aware that the manufacturer's original submission included a very limited evidence base. However, the manufacturer's additional analyses provided some evidence for each of the atypical antipsychotics (risperidone, quetiapine and olanzapine) routinely used in UK clinical practice. The Committee noted that the trials for olanzapine, quetiapine and, most notably, risperidone showed greater relative risks in PANSS positive and negative scores in their treatment arms compared with their placebo arms than were seen in the aripiprazole trial. The Committee also noted that there appears to be a large placebo effect in the aripiprazole trial, but heard from the manufacturer that the precise cause of this effect is unknown. The Committee was aware that, insofar as evidence is available, the CGI and CGAS findings are not better for aripiprazole than for the comparator treatments.	4.7
	The Committee noted that there is substantial variation between the atypical antipsychotics in	4.8

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	<p>the adverse events associated with each treatment.</p> <p>The Committee heard that a change in prolactin level is one of a number of contributors to potential sexual dysfunction. The Committee considered that weight gain may be of considerable importance to adolescents and was concerned that weight gain associated with olanzapine may not be just a short-term problem, but could be a long-term health risk.</p>	4.8
Relevance to general clinical practice in the NHS	The Committee heard from the clinical specialists that choice of treatment depends on a number of factors. Adolescents with schizophrenia are usually treated with atypical antipsychotics at a low dose and are closely monitored.	4.2
Uncertainties generated by the evidence	<p>The Committee heard from the clinical specialists that the PANSS score (primary outcome) is a well-recognised tool used in clinical trials, however the results are often difficult to relate to UK clinical practice as the tool is not routinely used by clinicians.</p> <p>The Committee noted that there appears to be a large placebo effect in the aripiprazole trial, but heard from the manufacturer that the precise cause of this effect is unknown.</p>	4.6 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Not applicable.	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee accepted that PANSS score is a valid tool for the measurement of positive, negative and general psychopathology symptoms and that evidence from the 31-03-239 study demonstrates a reduction in schizophrenic symptoms in the aripiprazole groups.	4.6

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Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the manufacturer's economic model and the critique and exploratory analyses performed by the ERG.	4.9
	The Committee heard from the ERG that some data used in the model were derived from adults rather than adolescent populations in the absence of data specific to adolescents.	4.10
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee had concerns about a number of aspects of the economic model, such as the exclusion of comparators specified in the final scope, primary PANSS outcome data, and data on relevant adverse events (such as EPS and sexual dysfunction).	4.10
	The Committee considered the manufacturer's updated economic model that compared sequences of treatments starting with aripiprazole with sequences starting with risperidone. The Committee still had concerns about the primary outcome data not being included in the model. It did not agree with the manufacturer's argument that this omission could be justified on the grounds that trial outcomes were not used in ordinary clinical practice; nor did it agree with the manufacturer's reference to NICE clinical guideline 82 ('Core interventions in the treatment and management of schizophrenia in primary and secondary care (update)'), in which PANSS scores were used to inform utility values and not considered as a separate outcome measure as an argument for not including PANSS scores in the model. The Committee noted that as aripiprazole is associated with smaller changes in PANSS scores than risperidone, olanzapine and quetiapine, the omission clearly favoured aripiprazole. The Committee also noted that some adverse events (sexual dysfunction and aggression) were not included in the model, and was aware that there is an error in the adjusted	4.12

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	indirect comparison that results in the odds ratios of withdrawals (for other reasons) from risperidone compared with withdrawals from aripiprazole being higher in the manufacturer's analysis.	
<p>Incorporation of health-related quality of life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee heard from the ERG that in the absence of data specific to the population in the scope, data on health state utility at relapse, disutility associated with treatment-related adverse events and resource use assumptions were all derived from studies of adult rather than adolescent populations.</p>	4.10
<p>Are there specific groups of people for whom the technology is particularly cost-effective?</p>	<p>Not applicable.</p>	-
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee noted that the manufacturer's updated base-case analysis shows that treatment sequences in which aripiprazole is used first result in ICERs ranging from £52,750 per QALY gained to £108,800 per QALY gained when compared with treatment sequences in which risperidone is used first. It considered that, in view of the PANSS scores not being included in the model, these ICERs were likely to be underestimated. Furthermore, they are outside the range considered to be a cost-effective use of NHS resources.</p> <p>In view of the results from the manufacturer's updated base-case analysis and the testimony</p>	<p>4.12</p> <p>4.13</p>

TAXXX (STA)	Appraisal title: Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years	FAD section
	<p>of the clinical specialists, which highlighted that routine clinical practice is to start treatment with risperidone, the Committee concluded that starting treatment with aripiprazole rather than risperidone would not be a cost-effective use of NHS resources.</p> <p>The Committee was mindful that in people aged 15 to 17 years with schizophrenia who are intolerant of or have a contraindication to risperidone, or whose schizophrenia has not been adequately controlled with risperidone, the case for aripiprazole is more plausible. The Committee considered whether there was any evidence to suggest that aripiprazole should be used ahead of, or only after olanzapine or quetiapine in the treatment pathway for schizophrenia. It noted that the economic analyses suggest little difference between sequences in which aripiprazole precedes olanzapine and vice versa; and although sequences that contain aripiprazole are suggested to be more cost-effective than the sequence that contains quetiapine (sequence D), the Committee was concerned that the cost of quetiapine was unfairly calculated in the manufacturer's economic model, as optimal packs and doses may not have been considered. The Committee agreed that the differences in side effects between these drugs were a more important consideration than the (small) differences in their costs and primary outcomes. Therefore the Committee agreed that aripiprazole should be available on equal terms with other antipsychotic comparators (apart from risperidone), given its good side-effect profile and comparable price to olanzapine and quetiapine.</p>	4.14
Additional factors taken into account		
Patient Access Schemes (PPRS)	Not applicable to this appraisal.	-

TAXXX (STA)	Appraisal title: Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years	FAD section
End-of-life considerations	Not applicable to this appraisal.	-
Equalities considerations, social value judgements	The Committee was aware that consultees and commentators suggested that one area of potential discrimination was that the diagnosis of schizophrenia requires a definitive methodological approach using precise diagnostic criteria which may not be met by people with learning difficulties. The Committee concluded that there are not sufficient data to provide evidence on how the clinical and cost effectiveness of aripiprazole may differ for people with schizophrenia who have learning difficulties.	4.15

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX).

- Slides highlighting key messages for local discussion.

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Published

- Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. NICE clinical guideline 82 (2009). Available from www.nice.org.uk/guidance/CG82
- Guidance on the use of electroconvulsive therapy. NICE technology appraisal guidance 59 (2003). Available from www.nice.org.uk/guidance/TA59

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in November 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens
Chair, Appraisal Committee
October 2010

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A *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 four 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 Kathryn Abel

Reader and Consultant Psychiatrist/Director of Centre for Women's Mental Health, University of Manchester

Dr David Black

Director of Public Health, Derbyshire County Primary Care Trust, Chesterfield

Dr Daniele Bryden

Consultant in Intensive Care Medicine/Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett

Director for Health Improvement/Medical Director, NHS Barnet, London

David Chandler

Lay member

Dr Mary Cooke

Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

Dr Chris Cooper

General Practitioner, St John's Way Medical Centre, London

Professor Peter Crome

Consultant Physician, Bucknall Hospital. Stoke-on-Trent

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance Research and Development Unit, York

Richard Devereaux-Phillips

Public Affairs and Reimbursement Manager UK and Ireland, Medtronic, Watford

Dr Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Wasim Hanif

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Henry Marsh

Consultant Neurosurgeon, St George's Hospital, London

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Eugene Milne

Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Dr Neil Myers

General Practitioner, Glasgow

Dr Richard Nakielny

Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Dr Katherine Payne

National Institute for Health and Clinical Excellence

Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy

Lay member

Dr Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Dr Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

Professor Paul Trueman

Health Economics Research Group, Brunel University, Uxbridge

Dr Judith Wardle

Lay member

B Guideline representative

The following individual, representing the Guideline Development Group responsible for developing NICE's clinical guideline related to this topic, was invited to attend the meeting to observe and to contribute as an adviser to the Committee.

- Peter Pratt, Sheffield Health and Social Care NHS Foundation Trust

C NICE project team

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

Fay McCracken/Scott Goulden

Technical Leads

Fiona Rinaldi

Technical Adviser

Lori Farrar

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessment Centre:

- Jones J, Mendes D, Frampton GK et al. Aripiprazole for the treatment of schizophrenia in adolescents (aged 15–17 years), July 2010.

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Bristol Myers Squibb/Otsuka Pharmaceuticals

II Professional/specialist and patient/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

III Other consultees:

- Betsi Cadwaladr University Health Board
- Department of Health
- Welsh Assembly Government

IV 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
- Hafal
- Medicines and Healthcare Products Regulatory Agency
- NHS Quality Improvement Scotland
- AstraZeneca
- Eli Lilly and Company
- Cochrane Schizophrenia Group
- National Institute for Health Research Health Technology Assessment Programme
- Southampton Health Technology Assessment Centre
- National Collaborating Centre for Mental Health

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer consultees and commentators. They gave their expert personal view on aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Clare Lamb, Consultant Psychiatrist, nominated by Welsh Assembly Government – clinical specialist
- Tim McDougall, Nurse Consultant, nominated by Royal College of Nursing – clinical specialist
- Clive Travis – patient expert
- Janey Antoniou (written statement only, unable to attend the meeting) – patient expert

We would like to offer our condolences to Janey Antoniou's family; sadly, Janey died during the development of this technology appraisal. Janey was a great help during this appraisal and will be sadly missed by her family and colleagues alike.

D Representatives from the following manufacturers attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy. They were also invited to comment on the ACD.

- Bristol Myers Squibb and Otsuka Pharmaceuticals