NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Aripiprazole for the treatment of schizophrenia in people aged 15-17

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide clarification on:

- The methodology of the evidence synthesis (searching and assessment of studies)
- The population with respect to individuals with learning disabilities
- The approach to data analysis and reasons for inconsistencies in reporting
- Clinically significant changes in outcome measures such as the PANSS, CGI, CGAS, and P-QLES-Q
- Methods, quality and results of studies used to inform the economic model.

The manufacturer was also asked to provide:

- Clinical study reports.

Licensed indication

Aripiprazole (Abilify, Bristol-Myers Squibb and Otsuka Pharmaceuticals) is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

Key issues for consideration

Clinical effectiveness

- The manufacturer's submission focussed on a broader population (adolescents aged 13–17 years) than outlined in the scope. What is the Committee's view on the impact of including the younger adolescent cohort on the effectiveness of aripiprazole?
- The manufacturer's submission presented a limited and uncritical interpretation of the evidence base, which for clinical effectiveness is restricted primarily to a single RCT comparing aripiprazole with placebo. What is the Committee's view on the clinical evidence presented from the 31-03-239 study and the analysis of the data?
    - Was the intention-to-treat analysis carried out appropriately?
    - What are the implications of only using this study to derive the clinical effectiveness estimates?
- The manufacturer's adjusted indirect comparison consists of two RCTs and there is a lack of methodological information on how the adjusted indirect comparison was conducted. What is the Committee's view on the appropriateness of the adjusted indirect comparison?

Cost effectiveness

- There was a lack of data specific to adolescents to populate the model. As a result, health state utility, disutility associated with treatment-related side effects and resource use assumptions were all derived from studies of adults rather than adolescent populations. What is the Committee's view on the appropriateness of this approach?
- The manufacturer's submission does not directly include any of five eligible active comparators; it includes only one of these (olanzapine) in an adjusted indirect comparison.
    - What is the Committee's view on the limited comparisons in the manufacturer's economic model?
    - What is the Committee's view on the impact of omitting risperidone as a comparator despite its wide use in clinical practice?

  - What is the Committee's view on the applicability of olanzapine to current routine UK clinical practice for the treatment of adolescents with schizophrenia?
- The manufacturer transformed 6-month relapse risks (taken from a published study on adult populations) to 6-week relapse risks, however the relative risk of relapse reported in the original publication was not used. Instead, an estimated value based on crude risks reported in the paper was used. What is the Committee's view on the appropriateness of applying relapse risks observed in adult populations to adolescents? Is it appropriate to assume that the relative risk of relapse estimated from crude risks should be used rather than the value reported in the study publication?
- Clinical outcomes in the model are based on withdrawal from first and second line treatment and on relapse. What is the Committee's view on the appropriateness of this approach?
- The manufacturer's submission acknowledges uncertainty over the applicability of utility estimates derived in adult populations to adolescents. What is the Committee's view on the appropriateness of this approach?
- The manufacturer's model takes account of the impact of side effects on a patient's quality of life impact, but does not consider any other aspects of quality of life. In addition, the model does not take account of symptomatology, other than that which will be associated with relapse. What is the Committee's view on the appropriateness of this approach?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	People aged 15–17 years with schizophrenia
Intervention	Aripiprazole 10 or 15 mg/day, with a maintenance dose of 15 mg/day administered once daily without regard to meals.
Comparators	Olanzapine
Outcomes	• Treatment response • Positive symptoms • Negative symptoms • Mortality • Adverse effects of treatment • Health-related quality of life
Economic evaluation	The cost effectiveness of aripiprazole is expressed in terms of incremental cost per quality-adjusted life year (QALY). The time horizon for estimating clinical and cost effectiveness is 3 years, as this reflects the maximum time period before adolescents (15–17 years) are considered adults. Costs are considered from the perspective of the NHS and of personal and social services.
Other considerations	With the exception of amisulpride, which is infrequently prescribed in the adolescent population, aripiprazole is the only licensed treatment for the patient group under consideration. The comparator treatments currently used in clinical practice are not licensed for adolescent use.

1.2 Evidence Review Group comments

1.2.1 Population

The randomised controlled trial data used in the manufacturer's submission to inform the clinical effectiveness of aripiprazole comprised of adolescents aged 13–17 years with schizophrenia, which was a broader population than that defined in the marketing authorisation and the final scope, that is adolescents aged 15–17 years with schizophrenia. The ERG stated that a post-hoc subgroup analysis of adolescents aged 15–17 years confirmed the

comparable clinical improvements of this age group with the overall adolescent dataset in the trial. This was reported in section 5.3.6 and section 6.2.1 of the manufacturer's submission.

1.2.2 Intervention

Aripiprazole is an atypical antipsychotic that is administered orally.

The ERG stated that the description of the intervention defined in the manufacturer's decision problem reflects the use of the aripiprazole in UK clinical practice and in line with its marketing authorisation.

1.2.3 Comparators

The manufacturer's submission selected olanzapine as the main comparator and clozapine as the third-line rescue treatment. The manufacturer's submission acknowledged that olanzapine does not have a UK marketing authorisation for the treatment of adolescents aged 15–17 years, and that the other treatments outlined in the scope as possible comparators are either not licensed for adolescents aged 15–17 years (such as quietapine and risperidone), or are infrequently used in these patients due to adverse events experienced (such as amisulpride).

The ERG expressed concern that the exclusion of most of the comparators listed in the decision problem is not sufficiently justified in the manufacturer's submission. They quoted clinical opinion suggesting that risperidone is frequently used for the first-line treatment of schizophrenia in adolescents aged 15–17 years in UK clinical practice. They also acknowledged that although there are no clinical trial data for these treatments in adolescents, it may have been appropriate to use other types of data. They also noted that historically risperidone held a UK marketing authorisation for the treatment of people aged 15 years and over, but there was no discussion in the manufacturer's submission about the availability of risperidone data in this population.

1.2.4 Outcomes

The ERG noted that the majority of outcomes defined in the final scope were addressed in the manufacturer's submission. The manufacturer stated that recurrence of psychosis was excluded as an outcome measure due to lack of data.

The ERG stated that the chosen primary outcome (positive and negative syndrome scale [PANSS] total score) is within the scope of the decision problem, but the manufacturer's submission does not justify how to interpret the included outcomes in a clinically meaningful way. The ERG was mindful of clinical advice that clinicians rarely use specific tools such as the outcomes in the manufacturer's submission, to assess adolescents with schizophrenia.

1.2.5 Economic evaluation

The manufacturer provided a cost-utility analysis to estimate the cost-effectiveness of first-line aripiprazole compared to first-line olanzapine for the treatment of adolescents with schizophrenia. The ERG noted that the economic evaluation in the manufacturer's submission appears to be appropriate and is consistent with the approach adopted in previous economic evaluations of drug treatment for schizophrenia. .

1.3 Statements from professional/patient groups and nominated experts

The clinical specialists stated that UK clinical practice varies in the treatment of schizophrenia in adolescents aged 12–18 years, and there is substantial use of medicines outside their licensed age range. Treatment is usually with atypical antipsychotics together with psychological, family and social interventions. The most commonly used atypical antipsychotic is risperidone, but quetiapine, olanzapine or clozapine are also used, and in some cases adolescents may receive the typical antipsychotic haloperidol. However, clinical specialists noted that aripiprazole is increasingly used due to a lower risk of weight gain and hence greater acceptability by adolescents.

The clinical specialists stated that adolescents with very early onset psychosis generally have a worse prognosis, and younger patients are usually more sensitive to the side effects of atypical antipsychotics. For these reasons, the choice of an atypical antipsychotic usually depends on the side-effect profile.

The clinical specialists stated that use of aripiprazole in adolescents aged 12–18 years would not significantly alter current clinical practice in the UK or the use of concomitant treatments. The clinical specialists highlighted that aripiprazole should be used in secondary care in specialist CAMHS or early onset psychosis teams. The clinical specialists noted that NICE clinical guideline 82 on core interventions in the treatment and management of schizophrenia in primary and secondary care (March 2009) is highly relevant but only applies to individuals over the age of 18 years.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer's submission presented clinical effectiveness data from one main randomised clinical trial (RCT) (study 31-03-239), with supporting data on adverse events from two open-label single-arm extension studies (31-03-241 and 31-05-243). Study 31-03-239 was a phase III, multicentred, randomised, double-blind, placebo-controlled trial that enrolled 302 adolescents 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]). Adolescents were randomly assigned to one of three study arms: a once-daily fixed dose of either 10mg or 30mg of aripiprazole, or matching placebo.

The primary outcome was mean change from baseline in PANSS score at six weeks follow up, with reductions in score indicating an improvement in symptoms. Secondary outcomes included: positive and negative syndrome

scale (PANSS), children's global assessment scale (CGAS), clinical global impression for severity (CGI-severity) and improvement (CGI-improvement), and time to discontinuation (for all reasons). Number of hospitalisations was also included. Health-related quality of life was assessed in terms of the change in the paediatric quality of life and enjoyment and satisfaction questionnaire (P-QLES-Q) total score at baseline and at six weeks follow-up, and in terms of the change in the P-QLES-Q overall score at baseline and at six weeks follow-up.

The manufacturer's submission stated that as part of their post-marketing activities, a post-hoc subgroup analysis of adolescents aged 15–17 years was performed in study 31-03-239 to assess the similarities between this population and adults with schizophrenia treated with aripiprazole.

The manufacturer's submission stated that adolescents who completed the 31-03-239 study were eligible to enter an open-label extension study of aripiprazole for 6 months (31-03-241). A second open-label extension study (31-05-243) consisted of people who completed the first extension study (31-03-241). The manufacturer's submission presented adverse event data from both studies as supporting information.

Manufacturer's indirect comparison

The manufacturer carried out a systematic review of RCTs comparing aripiprazole against antipsychotic treatments (olanzapine, risperidone, quetiapine, haloperidol, and amisulpride) or placebo for adolescent schizophrenia. Studies were excluded if a placebo group was not included, or if they lacked sufficient data for comparison. The systematic review included six studies; however there were no head-to-head RCTs of aripiprazole compared with any other atypical antipsychotics in adolescents, and data in a conference abstract for risperidone were deemed insufficient to be included in the indirect comparison. The manufacturer stated that two RCTs were suitable for inclusion in the indirect comparison to provide comparative data between

aripiprazole and olanzapine, the manufacturer's chosen comparator in their submission.

Data were extracted and analysed for clinical efficacy (withdrawals [due to adverse events, lack of efficacy, or other reasons], weight gain [equal to or greater than 7%], somnolence, and patients receiving benzodiazepines [which were used as a surrogate for extrapyramidal symptoms]) for use in the economic evaluation. Data from the study of olanzapine were compared with data from the study of aripiprazole using the placebo arms 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.

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.

Datasets analysed

Two datasets from the 31-03-239 study were analysed; all adolescents who had a baseline and post-baseline efficacy measurement were included in an analysis of change in PANSS total score from baseline, and all subjects having a post-baseline measurement were included in an analysis of CGI-I based only on post-baseline measurements.

The core dataset for all efficacy analyses was the intention-to-treat (ITT) dataset (that is, the dataset containing data from all randomised subjects regardless of protocol violation). To account for missing data and restrictions imposed by different types of analyses (such as change from baseline analysis), other datasets derived from the ITT dataset were used for the

efficacy analyses. These included observed cases (OC) and last observation carried forward (LOCF). LOCF datasets were used in the primary analysis.

Results of the 31-03-239 study

For the primary outcome of mean change from baseline in the PANSS total score, as outlined in Table 1, the results of the 31-03-239 study (using LOCF data) demonstrated that at 6 weeks, adolescents in all three study arms showed reductions in their PANSS score (that is, an improvement in symptoms). Statistically significant differences in the degree of improvement were observed for adolescents randomised to receive aripiprazole (10 mg or 30 mg) compared with adolescents randomised to receive placebo.

Table 1 PANSS change from baseline total score at six weeks (ERG report page 31)

	Aripiprazole 10mg n=99	**Aripiprazole 30mg n=97**	**Placebo n=98**	**Aripiprazole 10mg versus placebo**	**Aripiprazole 30 mg versus placebo**
Least-squares mean - (SE)	-26.7 (1.9)	-28.6 (0.9)	-21.2 (1.9)	Difference 5.5 p value 0.05[a]	Difference 7.4 p value 0.007[a]

[a] Minor differences between manufacturer's submission, trial publication and clinical study reports noted

For the secondary outcome of mean change in the PANSS total score at all visits, the interim analysis demonstrated [redacted]

For the change from baseline in PANSS positive subscale score, as outlined in Table 2, the results of the 31-03-239 study demonstrated that at 6 weeks, adolescents in all three study arms had a reduction in score (that is, an improvement on the PANSS positive subscale). Furthermore, adolescents randomised to receive 10 mg or 30 mg of aripiprazole showed statistically significant reductions in PANSS scores compared with adolescents randomised to receive placebo. For the change from baseline in PANSS

negative subscale score, similar results were observed, showing that at 6 weeks, adolescents in all three study arms showed reductions in PANSS negative subscale scores. This improvement was larger in adolescents randomised to receive either dose of aripiprazole than in adolescents randomised to receive placebo. However there was only a statistically significant reduction in PANSS negative subscale score for adolescents randomised to receive 10 mg aripiprazole.

Table 2 PANSS positive and negative subscale scores at 6 weeks (ERG report page 32)

Aripiprazole 10 mg n = 99	**Aripiprazole 30 mg n = 97**	**Placebo n = 98**	**Aripiprazole 10 mg versus placebo**	**Aripiprazole 30 mg versus placebo**
PANSS positive subscale score, LS mean change (SE)				
-7.6 (0.6)	-8.1 (0.6)	-5.6 (0.6)	Difference 2.0 p value 0.02[a]	Difference 2.5 p value 0.002
PANSS negative subscale score, LS mean change (SE)				
-6.9 (0.6)	-6.6 (0.6)	-5.4 (0.6)	Difference 1.5 p value 0.05	Difference 1.2 p value 0.10

For the mean change from baseline in the CGAS scores, as outlined in Table 3, the results of the 31-03-239 study (using LOCF data) demonstrated that at 6 weeks, adolescents in all three study arms showed increases in scores (that is, an improvement in CGAS), and that there were statistically significant increases in CGAS scores for adolescents randomised to receive either dose of aripiprazole compared with adolescents randomised to receive placebo.

Table 3 CGAS change from baseline score at six weeks (ERG report page 32)

	Aripiprazole 10 mg n = 97	**Aripiprazole 30mg n = 94**	**Placebo n = 98**	**Aripiprazole 10mg versus placebo**	**Aripiprazole 30 mg versus placebo**
Least-squares mean - (SE)	14.7 (1.5)	14.8 (1.3)	9.8 (1.3)	Difference 4.9 p value 0.005	Difference 5.0 p value 0.004

For the change from baseline in CGI-severity scores, as outlined in Table 4 , the results of the 31-03-239 study (using LOCF data) demonstrated that at 6

weeks adolescents randomised to receive 10 mg aripiprazole showed a statistically significant decrease in scores (that is, an improvement in CGI-severity scores) compared with adolescents randomised to receive placebo. An improvement in CGI-severity scores was also seen in adolescents randomised to receive 30 mg aripiprazole compared with adolescents randomised to receive placebo.

In the interim analyses

[redacted]

For the CGI-improvement scores, the data presented in the manufacturer's submission were end-point scores rather than change from baseline scores. These results showed that adolescents randomised to receive either 10 mg or 30 mg aripiprazole had a statistically significant reduction in mean scores (that is, an improvement) compared with adolescents randomised to receive placebo.

[redacted]

Table 4 CGI severity (change from baseline) and CGI improvement score at 6 weeks (ERG report page 33)

Aripiprazole 10mg n=99	**Aripiprazole 30mg n=97**	**Placebo n=98**	**Aripiprazole 10mg versus placebo**	**Aripiprazole 30 mg versus placebo**
CGI severity score, least-squares mean (SE) change from baseline				
-1.2 (0.1)	-1.3 (0.1)	-0.9 (0.1)	Difference 0.3 p value 0.007	Difference 0.4 p value 0.0016
CGI improvement score, least-squares mean (SE)[†]				
2.7 (0.1)	2.5 (0.1)	3.1 (0.1)	Difference 0.4 p value 0.02	Difference 0.6 p value 0.0004

For time to discontinuation (due to all reasons), the manufacturer's submission stated that there were no statistically significant differences between any of the study arms.

Health-related quality of life was assessed in terms of the change in P-QLES-Q total score at baseline and at 6 weeks, and by the change in P-QLES-Q overall score at baseline and at 6 weeks. For the change in P-QLES-Q total score (using LOCF data), no statistically significant differences in health-related quality of life were seen between the aripiprazole treatment groups and the placebo group at baseline compared with week 6. For the change in P-QLES-Q overall score (using LOCF data), increases in scores (that is, improvements in health-related quality of life) were observed in all three study arms at week 6. Adolescents randomised to receive either 10 mg or 30 mg aripiprazole showed a statistically significant change in baseline scores compared to adolescents randomised to receive placebo (Table 5).

Table 5 P-QLES-Q total and overall scores at 6 weeks (ERG report pages 33 and 34)

Aripiprazole 10 mg n=95	**Aripiprazole 30 mg n=87**	**Placebo n=89**	**Aripiprazole 10 mg versus placebo**	**Aripiprazole 30 mg versus placebo**
P-QLES-Q total score, least-squares mean change (SE)				
5.2 (0.9)	5.9 (0.9)	4.5 (0.9)	Difference 0.7 p value 0.55	Difference 1.4 p value 0.26
P-QLES-Q overall score, least-squares mean change (SE)				
0.6 (0.1)	0.6 (0.1)	0.1 (0.1)	Difference 0.5 p value 0.005	Difference 0.5 p value 0.003

The manufacturer's submission also presented data on the number of hospitalisations which occurred due to worsening of schizophrenia. Adolescents started the study as either inpatients or outpatients and [redacted]

The manufacturer's submission presented results from a post-hoc subgroup analysis of adolescents aged 15–17 years in study 31-03-239 which showed that improvements in efficacy were comparable between the adolescent 15–17 year subgroup and the overall adolescent dataset for aripiprazole. Maintenance of effect was also observed in the adolescent 15–17 year

subgroup. Reports of the safety and tolerability of aripiprazole were similar between adolescent and adult patients.

An overview of the safety of aripiprazole was provided in the manufacturer's submission based on evidence from the 31-03-239 study, and two open-label extension studies (31-05-243 and 31-03-241). The most common treatment-related adverse events observed in the 31-03-239 study (more than 5% in adolescents receiving 10 mg or 30 mg aripiprazole and a combined incidence at least twice that for placebo) were extrapyramidal disorder, somnolence, and tremor. For further details please refer to table 34 in the manufacturer's submission (page 69). Overall, a higher percentage of adolescents randomised to receive aripiprazole experienced treatment-related adverse events (71% of those receiving 10 mg and 72.5% receiving 30 mg) compared with adolescents randomised to receive placebo (57%). The majority of treatment-related adverse events were mild or moderate in severity. The publication of the 31-03-239 study reported that the rates of serious treatment-emergent adverse events were low for all groups, with an incidence of 3% in adolescents randomised to receive placebo, 4% in adolescents randomised to receive 10 mg aripiprazole, and 4% in adolescents randomised to receive 30 mg aripiprazole.

The manufacturer's submission stated that the mean weight and body mass index (BMI) z-scores for each visit were within 0.5 standard deviations of the general population for all three arms of the study. At week 6, the percentage of adolescents who experienced a potentially clinically significant weight gain (defined as 7% or more weight gain compared to baseline) was [redacted] for those randomised to receive 10 mg aripiprazole, 5.2% for those randomised to receive 30 mg aripiprazole, and 1% for those randomised to receive placebo. Conversely, the percentage of adolescents who experienced a potentially clinically significant weight loss (defined as 7% or more weight loss compared to baseline) was 3% for those randomised to receive 10 mg aripiprazole, 2.1%

for those randomised to receive 30 mg aripiprazole, and 6.1% for those randomised to receive placebo.

The publication of the 31-03-239 study reported that changes from baseline in extrapyramidal symptoms differed significantly between aripiprazole and placebo for the Simpson–Angus scale (0.5 aripiprazole 10 mg, 0.3 aripiprazole 30 mg, -0.3 placebo; $p < 0.007$ aripiprazole 10 mg compared with placebo; $p < 0.05$ aripiprazole 30 mg compared with placebo). The publication stated that there were no statistically significant differences for the Barnes scale and abnormal involuntary movement scale (AIMS), although data were not reported.

The manufacturer's submission reported a mean decrease in serum prolactin levels relative to baseline. The mean decreases at 6 weeks were -8.45, -11.93, and -15.14 ng per ml for adolescents randomised to receive placebo; 10 mg or 30 mg of aripiprazole respectively. The publication of the 31-03-239 study reported that adolescents randomised to receive 10 mg and 30 mg aripiprazole had statistically significantly greater reductions in prolactin levels compared with adolescents randomised to receive placebo (10 mg aripiprazole, $p = 0.003$; 30 mg aripiprazole, $p < 0.0001$). Low prolactin levels were defined as those below 3 ng per ml for females and below 2 ng per ml for males. Hence the rates of low prolactin levels observed were 8% for adolescents randomised to receive placebo, 34% for adolescents randomised to receive 10 mg of aripiprazole (statistically significantly different from placebo, $p < 0.0001$), and 26% for adolescents randomised to receive 30 mg of aripiprazole ($p = 0.001$). The manufacturer's submission stated that overall, aripiprazole has no impact on cardiac conduction, and the impact on metabolic parameters and prolactin levels appears to be less than for other atypical antipsychotics.

The results of the first of the two open-label extension studies (study 31-05-243) showed that the majority of treatment-related adverse events were mild or moderate in severity. At least one treatment-related adverse event was

reported by 48.2% of adolescents receiving long-term treatment with aripiprazole. Influenza, vomiting and headache were the only treatment-related adverse events reported by 5% or more of adolescents. Serious adverse events occurred in 5.9% of adolescents. The manufacturer's submission stated that data were insufficient to make conclusions about the impact of aripiprazole treatment on clinical chemistry parameters (such as prolactin levels). At 6 weeks, the percentage of adolescents who experienced a clinically significant weight gain (defined as weight gain of 7% or more compared to baseline) was 12.7%, whereas 7% of adolescents experienced a weight loss of 7% or more relative to baseline. There were no clinically meaningful changes in mean QTc intervals.

The results of the second open-label study (31-03-241) showed that the majority of treatment-related adverse events were mild or moderate in severity. At least one treatment-related adverse event was reported by 69% of adolescents in the schizophrenia subpopulation, and serious adverse events occurred in 5.9% of this population.

[redacted]

[redacted]

[redacted]At 6 weeks, the percentage of adolescents who experienced a clinically significant weight gain (defined as weight gain of 7% or more compared to baseline) was 24.5%, whereas 4.6% of adolescents experienced a weight loss of 7% or more relative to baseline. There were no clinically meaningful changes in mean QT or QTc intervals or other ECG abnormalities observed.

For further details on adverse events please refer to tables 32 to 34 (pages 66 to 69) in the manufacturer's submission.

Results of the manufacturer's indirect comparison

Results for the six outcome measures considered in the indirect comparison are presented in Table 6 (for details of the outcomes from the two studies included in the indirect comparison please see table 10 on page 35 of the

ERG report). These results suggest that aripiprazole was not favoured over olanzapine for the six outcomes considered (for three outcomes the odds ratios/relative risks were better for aripiprazole than olanzapine, however the 95% confidence intervals included 1.0, that is, they were not statistically significant).

Table 6 Results of the manufacturer's indirect comparison (olanzapine compared with aripiprazole 10 mg)

Outcome	Odds Ratio (95% CI)	Relative Risk (95% CI)
Withdrawals due to adverse events	1.57 (0.06, 43.87)	1.55 (0.06, 40.30)
Withdrawals due to lack of efficacy	0.03 (0.00, 0.31)	0.05 (0.01, 0.50)
Withdrawals for other reasons	3.73 (0.48, 28.70)	3.40 (0.50, 23.11)
Significant weight increase from baseline ≥ 7%	0.51 (0.02, 11.50)	0.34 (0.02, 6.96)
Somnolence	5.34 (0.54, 53.01)	4.44 (0.50, 39.34)
Participants receiving benzodiazipines	0.39 (0.14, 1.08)	0.57 (0.30, 1.06)

2.2 Evidence Review Group comments

The ERG reviewed the literature search strategy included in the manufacturer's submission and noted that clozapine was not included as a possible comparator on the basis that it is not routinely used in UK clinical practice for the treatment of adolescents with schizophrenia. The ERG also commented that a search was not carried out for adverse events data. Overall the ERG was of the opinion that the manufacturer's approach to evidence synthesis did not meet all of the quality criteria for a systematic review, as the manufacturer's submission did not fully assess the quality of all included studies and no reference was made to study quality in the synthesis and interpretation of study findings. The ERG stated that possible sources of systematic error might include: imbalances in the baseline characteristics of populations, ambiguity about whether all relevant evidence was included (such as how the manufacturer's own studies were identified and selected, and whether information on adverse events was missed), lack of confounding

in single-arm trials, differences in attrition between groups, ambiguity in how the LOCF imputation was applied in statistical analyses, and possible selective reporting.

The ERG stated that the evidence of clinical effectiveness presented in the manufacturer's submission was derived from one main randomised clinical trial (study 31-03-239). The group stated that the trial was relevant to the decision problem and that it provided evidence which is generalisable to the UK population. Overall the ERG stated that the 31-03-239 trial provided an unbiased estimate of the efficacy of aripiprazole at 6 weeks follow-up and that adverse events were moderate in severity.

The ERG noted that data on adverse events was from two open-label extension studies (31-03-241 and 31-05-243) identified from manufacturer sources. However, the ERG noted that these studies were less relevant to the decision problem as they included a mixed study population of children, adolescents and adults with schizophrenia or with bipolar I disorder, and as such they could be considered to be a single cohort extension study.

The ERG highlighted several areas of concern about the clinical evidence submitted by the manufacturer. They noted that in terms of the 31-03-239 study population, adolescents were aged 13–17 years which was broader than the population defined in the final scope (adolescents aged 15–17 years, in accordance with the UK marketing authorisation). Furthermore, although the manufacturer's submission reported that the three study arms were demographically similar and had similar baseline characteristics, there were a number of differences between groups. The ERG noted that there were differences between the 10 mg aripiprazole group compared with the 30 mg aripiprazole and placebo groups in terms of there being a higher percentage of female participants, a higher proportion of White people, and a higher proportion of adolescents who had previously received antipsychotic treatment.

The ERG also expressed doubt about whether appropriate methods were used to account for missing data in the 31-03-239 study. The manufacturer's submission stated that all participants were included in an intention-to-treat analysis and OC and LOCF datasets were derived and used for the efficacy analyses. However they noted that in the data tables (tables 12 to 19 in the manufacturer's submission on pages 41-50) different numbers were analysed for different groups and different outcomes and therefore do not reflect the ITT population. The ERG stated that it is unclear why the numbers of LOCF vary between the different outcomes (such as CGAS and P-QLES-Q) because these assessments were undertaken at the same time, and particularly because there are differences between subscales of the P-QLES-Q. During clarification the manufacturer justified using the LOCF approach but did not explain how many data were carried forward at each week.

The ERG noted that the effectiveness outcomes presented in the manufacturer's submission are widely used in the literature for assessing the effects of antipsychotic drugs; however they received clinical advice that suggested that questionnaire-based outcomes are rarely used in UK clinical practice in the adolescent population. Furthermore, although the manufacturer's submission stated that the degree of change in the outcomes is equivalent to the median of the mean difference seen in aripiprazole studies with adults, the ERG noted that it was unclear whether this was the case for adolescents. The manufacturer stated 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 and how they link with each other. The ERG stated that the PANSS total and overall scores and the clinical significance of the differences observed were uncertain and the manufacturer's submission did not provide a threshold to define treatment response, particularly given the placebo effect observed.

The ERG also highlighted that there was evidence from a journal publication of the 31-03-239 study to suggest that the manufacturer measured more outcomes than were reported in the manufacturer's submission. Data from the

following three rating scales for assessing clinical effects of antipsychotic drugs were reported in the 31-03-239 study and clinical study report, but these were not included in the manufacturer's submission: Simpson-Angus scale, the Barnes rating scale, and the abnormal involuntary movement scale (AIMS) for monitoring and classifying extrapyramidal side effects (antipsychotic induced parkinsonism, drug induced akathisia and drug induced dyskinesias).

The ERG noted that the manufacturer's submission reported that given that there were no head-to-head RCTs of aripiprazole and any other atypical antipsychotics in adolescents, it was necessary to undertake an indirect comparison to fulfil the decision problem. The ERG noted that for an indirect comparison to be carried out appropriately, the individual studies should be as similar as possible in terms of their study characteristics. However they highlighted that in the study of olanzapine, adolescents randomised to receive placebo had a higher prior use of antipsychotics than those randomised to receive aripiprazole. The participants were also recruited from a larger number of countries. The ERG stated that these aspects of trial characteristics are important for assisting the interpretation of indirect comparisons and these were not considered in the manufacturer's submission; furthermore no formal assessment of heterogeneity was carried out.

The ERG was mindful that the manufacturer's adjusted indirect comparison included a restricted set of outcomes for aripiprazole and olanzapine (adverse events, withdrawals due to lack of efficacy and other reasons, significant weight increase, somnolence, and benzodiazepine use). They noted that the manufacturer provided no discussion about whether there were other outcomes available to carry out a more detailed adjusted indirect comparison to support the clinical effectiveness assessment when comparing aripiprazole with olanzapine (the manufacturer's chosen comparator for the health economic evaluation). The ERG noted that the results for the outcomes included from each study showed that there were a large number of withdrawals due to lack of efficacy in adolescents randomised to receive placebo in the olanzapine study (51%). Also, the overall proportions of

adolescents withdrawing from the study were higher in the olanzapine study (32% olanzapine compared with 57% placebo) than the aripiprazole study [redacted]The ERG also highlighted that the number of participants experiencing weight increase were fewer than the total sample size and there was no explanation of this in the manufacturer's submission. The ERG also 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. They stated that the results suggested that aripiprazole was not favoured over olanzapine for the six outcomes included.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer's submission conducted a literature search of economic evaluations of pharmacological treatments for adolescent schizophrenia in the UK, however no studies were identified. An additional search was carried out to identify studies in adults and four economic evaluations were found, which were described in the submission.

Economic model structure

The manufacturer developed 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 adolescent schizophrenia. The model incorporated first-line and second-line treatments (both first-line aripiprazole and second-line olanzapine or vice versa) and clozapine as third-line treatment. Patients could switch to the next treatment when they discontinued or relapsed. The model had a time horizon of 3 years and a cycle length of 6 weeks, with no half-cycle correction applied.

The decision tree was used to determine whether adolescents remain on current treatment or discontinue (due to lack of efficacy, adverse events or

other causes) and was evaluated over two 6-week cycles. Adolescents then entered the Markov model in which they either experienced relapse (switching from their current treatment to the next available line, unless they are already on the rescue treatment [clozapine]) or remained with stable schizophrenia. The model was intended to reflect the progression of schizophrenia in adolescents after an acute schizophrenic episode and the clinical management of discontinuation and relapse in order to capture the impact of first-line treatment on costs and patient outcomes until the age of 18 years is reached (when other treatments may become available to them). Disease progression was measured for both treatment strategies through the risk of relapse, adverse events and of treatment discontinuation due to lack of efficacy, adverse events or other reasons.

In the first two cycles, adolescents undergoing treatment could discontinue and switch to another antipsychotic drug. These were represented in the decision tree using the following health states: stable schizophrenia and withdrawal (due to lack of efficacy adverse events or other reasons). In the second cycle, adolescents could relapse from treatment. Adolescents who did not relapse or discontinue treatment were assumed to continue on treatment in the stable schizophrenia state. Discontinuation was assumed to occur only in these first two cycles. From the third cycle onwards, adolescents were assumed to either continue in a stable condition with a given antipsychotic or to relapse and subsequently switch antipsychotic treatment. A Markov model was then used with only two states – maintenance on treatment and relapse for the three lines of therapy. Adolescents who discontinued or relapsed on the second treatment were assumed to receive clozapine as a last line treatment and to continue receiving clozapine after relapse. The manufacturer's submission stated that death was not modelled due to the short time horizon and the lack of efficacy data on death rates.

The manufacturer's base-case analysis compared first-line aripiprazole with the alternative treatment strategy of first-line olanzapine in adolescents with schizophrenia aged 13–17 years. Results were presented in terms of total and

incremental costs and quality-adjusted life years and incremental cost-effectiveness ratios between the two strategies.

Clinical evidence

Effectiveness evidence used in the model was taken from a variety of sources. The clinical parameters included in the model were: withdrawals (due to lack of efficacy, adverse events or other reasons), rates of adverse events (weight gain and somnolence) and longer-term rates of relapse. Treatment effectiveness was measured by the ability of each drug to maintain adolescents in the stable schizophrenia state (by avoiding discontinuation or relapse). The probability of withdrawals and adverse events (weight gain and somnolence) was calculated directly from study 31-03-239 for aripiprazole and the probability for olanzapine was taken from the manufacturer's adjusted indirect comparison and applied to the odds of the event with aripiprazole. The manufacturer stated that extrapyramidal symptoms were not consistently reported in the two studies of aripiprazole and olanzapine and therefore relative rates of this adverse event could not be determined using the indirect comparison. The manufacturer was also of the opinion that benzodiazepine use is a poor surrogate for extrapyramidal symptoms and this was therefore not included in the base-case analysis.

The manufacturer stated that no long-term data on treatment effects, including relapse rates for aripiprazole and olanzapine, were identified in the literature for the adolescent population, and therefore data on relapse were taken from a published study in adults with schizophrenia receiving aripiprazole compared with other atypical antipsychotics. The manufacturer stated that this study reported a 6-month rate of relapse with aripiprazole of 20% and 19.4% for all other antipsychotics (clozapine, olanzapine, risperidone and quetiapine). The relative risk of relapse between aripiprazole and other atypical antipsychotics was 0.92 (95% confidence interval 0.67 to 1.26). However the manufacturer stated that this value is an error, as it does not equal the ratio of the proportion of people whose condition has relapsed after

using other atypical antipsychotics divided by the proportion of people whose condition has relapsed after using aripiprazole. The manufacturer's submission therefore uses an adjusted relative risk of [redacted] in the economic model (assuming 89 of 444 patients receiving aripiprazole relapsed, and 101 of 521 people receiving other atypical antipsychotics relapsed) together with a relapse rate of 20% for aripiprazole.

Clozapine was considered as a rescue treatment in the model, however the manufacturer's submission did not include this treatment in the systematic review. Adverse event rates for clozapine were assumed to be equal to the rates of adverse events for aripiprazole, and rates of relapse were derived from the same published study as that for aripiprazole and olanzapine.

The population in the manufacturer's economic evaluation was based on the 31-03-239 study of aripiprazole and the study of olanzapine included in the indirect comparison, which comprised adolescents aged 13–17 years with schizophrenia, which is broader than the UK marketing authorisation for aripiprazole (adolescents with schizophrenia aged 15–17 years). The manufacturer's submission stated that a post-hoc analysis of the 31-03-239 study examined differences in patients with schizophrenia across outcomes (long-term symptom improvement, remission and maintained remission) and age groups (13–17, 15–17, and adults 18 years and over) and showed that outcomes were similar for all age groups. Therefore the manufacturer was of the opinion that this supported the use of the full clinical trial populations as a proxy for the subgroup (adolescents aged 15-17yrs) in the marketing authorisation. The manufacturer stated that sensitivity analyses were carried out on the efficacy parameters (that is, outcomes included in the model such as discontinuations and adverse events) to establish the effect of the younger cohort (adolescents aged 13-15 years) on the model results. The comparator in the economic evaluation was limited to olanzapine (which does not have a UK marketing authorisation for the treatment of adolescent schizophrenia). The manufacturer stated that the only comparators outlined in the decision problem which have a UK marketing authorisation for the adolescent

population are amisulpride (for which no clinical trials were identified) and clozapine (which was included in the model as third-line rescue treatment).

Table 7 provides a summary of the values applied in the manufacturer's economic model.

Table 7 Values used in the manufacturer's model for discontinuation and adverse events

Variable	Value	CI (distribution)	Reference to section in submission
Probability of discontinuation due to adverse events with aripiprazole	[redacted]	[redacted]	Indirect comparison section 5.7
Probability of discontinuation due to LOE with aripiprazole	[redacted]	[redacted]	Indirect comparison section 5.7
Probability of discontinuation due to other reasons with aripiprazole	[redacted]	[redacted]	Indirect comparison section 5.7
Probability of improved symptoms with aripiprazole	[redacted]	[redacted]	Section 6.3.2
Probability of weight gain with aripiprazole	[redacted]	[redacted]	Indirect comparison section 5.7
Probability of somnolence with aripiprazole	[redacted]	[redacted]	Indirect comparison section 5.7
Probability of relapse with aripiprazole	[redacted]	[redacted]	Relapse rates section 0
Odds ratio for discontinuation due to adverse events with olanzapine vs. aripiprazole	[redacted]	[redacted]	Final probability calculated using odds ratios from indirect comparison section 5.7
Odds ratio for discontinuation due to LOE with olanzapine vs. aripiprazole	[redacted]	[redacted]	Indirect comparison section 5.7
Odds ratio for discontinuation due to other reasons with olanzapine vs. aripiprazole	[redacted]	[redacted]	Indirect comparison section 5.7
Probability of improved symptoms with olanzapine	[redacted]	[redacted]	Section 6.3.2
Odds ratio for weight gain with olanzapine vs. aripiprazole	[redacted]	[redacted]	Indirect comparison section 5.7
Odds ratio for somnolence with olanzapine vs.	[redacted]	[redacted]	Indirect comparison section 5.7

aripiprazole			
Relative risk of relapse with olanzapine and clozapine vs. aripiprazole	[redacted]	[redacted]	Relapse rates section 6.3.2
CI, confidence interval; LOE, loss of efficacy *Adjusted to match publication			

Utility

The manufacturer's submission stated that health-related quality of life data was collected in the 31-03-239 study, but that it was not used in the model because it did not meet the NICE reference case (that is EQ-5D was not used). A systematic review of the literature was carried out to identify alternative utility values. Due to the paucity of studies in the adolescent population, a search was carried out for studies in adults which resulted in one study by Briggs et al (2008) being identified as relevant to the decision problem. The manufacturer stated that the study considered the impact of schizophrenia on health-related quality of life and the impact of some treatment-related adverse events in a UK setting. The study recruited 49 people with stable schizophrenia and 75 lay people who each completed a utility interview in which they were asked to rate seven health states. Two of these were associated with the underlying condition (stable schizophrenia and relapse) and the remaining five related to treatment-related adverse events (weight gain, diabetes, hyperprolactinemia [male], hyperprolactinemia [female], and extrapyramidal symptoms). In addition the 49 people with stable schizophrenia completed the EQ-5D questionnaire which was rated using a standard UK population tariff. The utility interview consisted of rating the health states using a visual analogue scale and then using time trade-off. The health state utility values derived from the study by Briggs et al (2008) are outlined in Table 8.

The impact of adverse events associated with antipsychotic treatment on quality of life was also modelled (which was consistent with previous economic evaluations).

Table 8 Health state utility values derived from Briggs et al (2008)

Health state	Mean utility (SE)		t-test for difference[a]
	Patient	Lay person	
Stable schizophrenia	0.919 (0.023)	0.865 (0.021)	p = 0.087
Weight gain	0.825 (0.028)	0.779 (0.024)	p = 0.216
Diabetes	0.769 (0.036)	0.712 (0.028)	p = 0.215
Hyperprolactinemia	0.815 (0.030)	0.783 (0.025)	p = 0.415
Relapse	0.604 (0.042)	0.479 (0.033)	p = 0.022
EPS	0.722 (0.037)	0.574 (0.032)	p = 0.003
Notes [a] Unequal variance t-test			

Costs and resource use

The manufacturer's submission calculated the cost of four types of resource use: drug acquisition, on-treatment monitoring and switching of medication, management of adverse events, and health state costs (associated with relapse requiring either hospital inpatient admission or community support from child and adolescent mental health services). Limited data specific to adolescent populations were found in the literature. Therefore resource use data for adults derived from NICE clinical guideline 82 on adult schizophrenia were adjusted to reflect the use of child and adolescent services in line with recommendations from clinical experts.

As several formulations are available for the antipsychotic drugs included in the manufacturer's economic model, a UK prescription cost analysis (2008) was used to establish the most prescribed formulation of each agent and this was then used to calculate the daily cost of the antipsychotic drugs based on dosing data from the relevant randomised controlled studies for aripiprazole and olanzapine and the Monthly Index of Medical Specialities (MIMS). For further details please refer to table 34 on page 62 of the manufacturer's submission. The range of costs was examined in a sensitivity analysis based on the lowest and highest calculated costs per day. Only clozapine requires patient monitoring and the resources used and costs associated with this service were assumed to be 1 hour of a mental health nurse's time at a cost of

£28 per hour. The daily dose and monitoring-related resource use were estimated according to the Summary of Product Characteristics for clozapine.

The unit costs for the antipsychotic drugs included in the economic model are presented in Table 9.

Table 9 Unit costs for the antipsychotic drugs included in the manufacturer's economic model

Items	Aripiprazole (10mgs) (range)	Olanzapine (12,5mgs) (range)	Clozapine (325mgs) (range)
Technology cost per day	£3.42 (£2.28, £6.84)	£3.55 (£3.55, £4.29)	£2.86 (£1.28, £2.86)
Monitoring cost per 6 week cycle	£0	£0	£24.17
Total cost per 6 week cycle	£144	£149	£120+£24.17

Two adverse events were included in the manufacturer's base case analysis (weight gain and somnolence). The resource use and costs associated with theses are outlined in Table 10.

Table 10 Adverse events and associated costs included in the manufacturer's economic model

Adverse events	Items	% of patients	Unit cost	No. of units	Cost per 6-week time period
Weight gain	GP	100%	£35.00	2	£70.00
	Dietician	20%	£34.00	2	£68.00
Somnolence	Psychiatrist	100%	£322.00	1	£107.33

Adolescents moving to the next line of treatment (because of intolerable side effects or relapse) were assumed to incur additional costs (associated with three visits to a consultant psychiatrist lasting 20 minutes each at a total cost of £322).

The list of health states and costs associated with relapse in the model are outlined in Table 11. Unit costs were taken from the Personal Social Services Research Unit 2009 report, and the NHS 2008–2009 Reference Costs.

Table 11 List of health states and costs associated with relapse in the manufacturer's economic model

Health states	Items	Value	Duration (days)	Total cost	% people treated	Reference in submission
Relapse	Acute hospital stay (HRG PA52)	£534.00/day*	42	£22,428	77.3%	NICE guideline model (6) and expert advice, section 6.5.3
	Child and adolescent mental health services	£19.34/day**	42	£812.28	22.7%	NICE guideline model (6) and expert advice, section 6.5.3
	Olanzapine 15 mg per day	£4.26	42	£179	100.0%	NICE guideline model (6) and expert advice, section 6.5.3
	Average cost per patient	£17,700				

*Acute hospital stay, £534 per day (national average unit cost of £24,581/46 days) using ref costs (HRG code PA52, mapped from ICD10 code F200).
** CAMHS taken from the PSSRU 2009 (49). Average cost per case per team (£3384) divided by weighted average length of episode (25 weeks).

Results

The deterministic and probabilistic results of the manufacturer's base case analyses are presented in Table 12 and Table 13.

Table 12 Deterministic results for the manufacturer's base case analysis

Treatment strategy	Total cost (£)	Total QALYs	Incremental cost	Incremental QALY	ICER (£/QALY)
First-line	23,723	2.597	-69.21	0.004	Dominant

aripiprazole					
First-line olanzapine	23,792	2.593			

Table 13 Probabilistic results for the manufacturer's base case analysis

Treatment strategy	Total cost (£)	Total QALYs	Incremental cost	Incremental QALY	ICER (£/QALY)
First-line aripiprazole	23,763	2.596	-1,016	0.008	Dominant
First-line olanzapine	24,778	2.589			

The manufacturer carried out one-way deterministic sensitivity analyses to test each model variable individually. The results of these analyses showed that the model was most sensitive to changes in the relative risk of relapse and the daily cost of aripiprazole.

Probabilistic sensitivity analyses were also carried out to characterise the uncertainty associated with the mean parameter values in the model. The results of these analyses are outlined in Table 14.

Table 14 Results of the manufacturer's probabilistic sensitivity analysis

Technologies	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
Aripiprazole - olanzapine - clozapine	£23,763	2.596	-£1,016	0.008	Dominant
Olanzapine - aripiprazole - clozapine	£24,778	2.589	-	-	-
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

The manufacturer carried out four scenario analyses to test structural assumptions in the model concerning:

- the use of relative risk of relapse from adult populations (that is, the impact of using annual probabilities from the mixed treatment comparison in the NICE clinical guideline on adult schizophrenia).

- the inclusion of extrapyramidal symptoms (that is, the impact of including extrapyramidal symptoms) also using the associated costs of a psychiatrist visit and prescription of benzodiazepines, as well as the disutility associated with extrapyramidal symptoms.
- the disutility from treatment with clozapine (that is, the impact of including the highest and lowest utility decrements used for other adverse events in the model in order to capture patient awareness of clozapine's potential serious adverse events).
- the methodological decision of electing to use odds ratios of the trial outcomes instead of relative risks.

The scenario analyses demonstrated that the model is sensitive to the relative risk of relapse assumed. The inclusion of patients receiving benzodiazepines, as a proxy for extrapyramidal symptoms, also had a substantial effect on the model results. The inclusion of an additional disutility associated with clozapine did not change the base case result. The use of relative risks or odds ratios from the indirect comparison for use in the model also did not appear to greatly influence the base case results.

For further details of the results of the other scenario analyses please refer to tables 47 to 51 on pages 113 to 122 in the manufacturer's submission.

3.2 Evidence Review Group comments

The ERG noted that the manufacturer's approach to economic modelling followed examples of previous models and was generally considered to be appropriate. They noted that the manufacturer's approach to separate the model into a decision tree followed by a Markov model introduced unnecessary complexity. The ERG noted that data on relapse, health state utility, disutility associated with treatment-related adverse events and resource use assumptions were all derived from studies of adults rather than

adolescent populations. Although this approach can be justified in the absence of data specific to the population, the ERG said this should be acknowledged as a limitation and a source of uncertainty when interpreting the results of the economic evaluation.

The ERG expressed concern with the manufacturer's approach to compare sequential treatment strategies (covering three lines of treatment) rather than individual drug regimens. They noted that this approach requires information on the breakdown of cost and effect by line of treatment, and the relevance of each complete treatment strategy to current clinical practice to be interpreted properly.

The ERG noted there are comparatively small differences between costs and QALYs for the two treatment strategies included in the manufacturer's submission, and the major contribution of costs of managing relapse to total costs for both treatment strategies.

The ERG noted that the manufacturer's economic evaluation was based on a more limited comparison than outlined in the final scope. The manufacturer's submission justified the exclusion of other comparators due to the lack of data in adolescents but did not discuss the relevance of the comparator to clinical practice in England and Wales. The ERG received clinical advice suggesting that risperidone would be the most common first-line treatment for schizophrenia in adolescent populations currently used in the UK. Furthermore, risperidone has been shown in a previous study (in adults with schizophrenia) to be a component of cost-effective treatment strategies.

The ERG noted that the model accounts for the health-related quality of life impact of adverse events, but that it does not consider any other aspect of health-related quality of life (for example, the stable schizophrenia health state in the model did not account for symptomatology other than that associated with relapse).The ERG was mindful that not all potentially relevant adverse events were included in the model, such as the extrapyramidal adverse events (which could only be included by using benzodiazepine use as a proxy

measure), and sexual dysfunction. Clinical advice received by the ERG suggested that sexual dysfunction may be an important adverse event for some adolescents.

The ERG commented that the utility values adopted in the manufacturer's submission appeared to have been derived appropriately, however they were unclear whether these values accurately reflected the impact of schizophrenia or treatment-related adverse events on adolescents. Clinical advice received by the ERG suggested that weight gain may be a more significant factor in adolescents than in adults. Overall the ERG was of the opinion that more consideration could have been given to including health-related quality of life data from the included trials in the model, either through mapping or based on expert opinion.

There was limited discussion about the data sources used to populate the manufacturer's economic model, and in many cases there was no evidence of systematic targeted searches. As a consequence, the ERG noted that there is uncertainty around the appropriateness of applying some of the data derived from adult populations to adolescents (for example, if the relapse risk observed in an adult population is assumed to be applicable to an adolescent population). The ERG commented that the manufacturer's submission has not used the relative risk of relapse reported from the original publication, but uses a re-established value based on crude risks reported in the paper. The ERG noted that the appropriateness of adopting a relative risk based on the crude risks appears questionable given the baseline differences in populations reported in the paper. The ERG added that the manufacturer did not report the methods used to identify this reference and there was no critical appraisal of this study or any discussion of the generalisability of evidence from treatment of adults with schizophrenia in the US to the UK context included in the submission.

The ERG identified several errors in the manufacturer's model that were corrected where possible, and an estimate of the extent to which these may

have systematically biased the results was provided. These included a discrepancy where the utility effect of relapse in patients on first-line medication (in the second cycle) was included but no cost was applied. The ERG's correction of this error led to the results shown in Table 15.

Table 15 ERG's correction of base case results for exclusion of the cost of relapse in cycle 2

Treatment strategy	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)
First-line aripiprazole	£24,483	2.597	£27.15	0.004	£6,231
First-line olanzapine	£24,456	2.593			

The ERG stated that the acute hospital cost per day used in the economic model was based on the national average unit cost for Health Resource Group (HRG) code PA53B (eating disorders with length of stay 8 days or more) rather than the national average unit cost for HRG code PA52C (behavioural disorders with length of stay 8 days or more). The revised base-case result with the updated costs supplied by the manufacturer is shown in Table 16.

Table 16 Revised base case result (with updated cost)

Technologies	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)
Aripiprazole - olanzapine - clozapine	£22,981	2.597	-£72.63	0.004	Dominant
Olanzapine - aripiprazole - clozapine	£23,054	2.593	-	-	-

The ERG also identified an error in the probabilistic sensitivity analyses (PSA) presented in the manufacturer's submission. Correct values for total discounted cost and total discounted QALYs for first-line aripiprazole and total discounted QALYs for first-line olanzapine were included, where total

undiscounted cost for first-line olanzapine had been included previously. The ERG carried out corrections to the model and re-ran the probabilistic sensitivity analysis. In addition corrections to the parameterisation of distributions for variables expressed as percentages, alternative estimates for variation in relative risk of relapse and in risk of relapse on aripiprazole were also applied. An ICER of £22,182 per QALY gained was reported for the PSA conducted on the corrected base case and with additional changes to the manufacturer's model to correct errors in sampling. When the ERG repeated the analysis and included a relative risk of relapse (olanzapine versus aripiprazole) estimated using the values reported by Moeller and colleagues rather than the value assumed by the manufacturer, an ICER of £47,103 per QALY gained was reported (see section 4.3.4.6 of ERG report).

There were also methodological uncertainties arising from the way in which zero value cell counts in two-by-two tables were used in the adjusted indirect comparison. The ERG stated that although the results of the cost-effectiveness analysis appear to be reasonably robust to this uncertainty for one of the input variables, the results were more sensitive for another.

The cost-effectiveness results for combinations of scenarios undertaken by the ERG in their scenario analyses are shown in Table 17.

Table 17 Scenario analysis with cumulative changes to base case assumptions

		Total		Incremental		ICER (£/QALY)
		Cost (£)	QALYs	Cost (£)	QALYs	
Corrected base case	First line aripiprazole	24,483	2.597	27	0.004	6,231
	First line olanzapine	24,456	2.593			
Adjust medication costs for patients who experience relapse	First line aripiprazole	24,322	2.597	60	0.004	13,763
	First line olanzapine	24,262	2.593			
As above plus: disutility associated	First line aripiprazole	24,322	2.588	60	0.004	15,663

with weight gain continues while patients remain on a given treatment	First line olanzapine	24,262	2.584			
As above plus: utility for patients discontinuing in the first treatment cycle is 20% lower than for stable schizophrenia	First line aripiprazole	24,322	2.591	60	0.003	23,144
	First line olanzapine	24,262	2.588			
As above plus: 50% of relapsed patients are admitted as inpatients	First line aripiprazole	17,677	2.591	-1	0.003	Dominant
	First line olanzapine	17,678	2.588			
As above plus: length of stay for relapsed patients admitted as inpatients = 107.7 days	First line aripiprazole	37,429	2.591	180	0.003	69,638
	First line olanzapine	37,248	2.588			
As above plus: Relative risk of relapse = 0.92	First line aripiprazole	36,593	2.592	514	0.002	232,981
	First line olanzapine	36,079	2.590			

Table 17 shows that adjusting medication costs for people who experience relapse approximately doubles incremental costs, without affecting incremental QALYs, leading to an increase in the ICER. Reducing disutility for people discounting due to adverse events, lack of efficacy or other reasons in the first treatment cycle has a larger effect (ICER increases from £15,663 to £23,144 per QALY gained) when this assumption is applied to those already considered. Reducing the proportion of relapsed patients who are admitted as inpatients leads to first-line aripiprazole becoming dominant. However, if the length of stay for admitted patients increases to 107.7 days, the ICER increases significantly to £56,972 and further increases to £218,853 if the relative risk of relapse reported by Moeller and colleagues is used.

3.3 Further considerations following premeeting briefing teleconference

Following the premeeting briefing teleconference, the ERG was requested to under the following exploratory analyses as an addendum to the ERG report:

1. Calculate the ICER for aripiprazole versus risperidone (based solely on price of risperidone)

    a. This will require replacing unit costs and dosage for olanzapine with appropriate costs and dosage for risperidone; re-running base case analyses and deterministic sensitivity analyses (as for manufacturer's submission) to compare results directly with manufacturer's submission; providing commentary and explanatory text around analyses, noting all caveats

2. Calculate the ICER for aripiprazole versus risperidone (based on the price of risperidone and including the efficacy of risperidone, where feasible)

    a. This will require replacing the odds ratios for withdrawal in the first cycle of treatment (due to intolerable adverse effects, lack of efficacy and other causes) and for treatment-related adverse events with olanzapine versus aripiprazole (which will be proxy-ing for odds ratios for risperidone in results reported for task 1 above) with the odds ratios for risperidone derived from an adjusted indirect comparison using data from an RCT reported by Haas and colleagues (for risperidone) and the aripiprazole RCT.

4 Equalities issues

No equalities issues were raised during the scoping process for this appraisal.

The manufacturer's submission noted that the diagnosis of schizophrenia

requires a definitive methodological approach using precise diagnostic criteria detailed in a number of different tools, including DSM-IV and K-SADS-PL (a child specific tool). While some individuals with learning difficulties may exhibit psychoses, unless they fulfil the DSM-IV and K-SADS-PL criteria for schizophrenia, they are (by definition) not schizophrenic, and therefore not appropriate for inclusion in this appraisal. Both the DSM-IV and K-SADS-PL are used in clinical practice, as well as in the studies of aripiprazole.

The ERG stated that clinical opinion suggests that this population is relevant.

5 Authors

Fay McCracken, Scott Goulden (Technical leads) and Fiona Rinaldi (Technical Adviser), with input from the Lead Team (Neil Myers, Rachel Elliott and Judith Wardle).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

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

- Jones J et al, Aripiprazole for the treatment of schizophrenia in adolescents ages 15-17 years, July 2010.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Bristol-Myers Squibb and Otsuka Pharmaceuticals

II Professional/specialist, patient/carer and other groups:

- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- North Wales Adolescent Service