# Aripiprazole (Abilify®) for the treatment of schizophrenia in adolescents (15-17 years)

## Single Technology Appraisal (STA)

## Submission to the National Institute for Health and Clinical Excellence (NICE)

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# List of Abbreviations

| | |
|---|---|
| AE | Adverse event |
| ANOVA | One way analysis of variance |
| BMI | Body mass index |
| BMS | Bristol-Myers Squibb |
| BPRS | Brief Psychotic Rating Scale |
| CBT | Cognitive behaviour therapy |
| CDRS | Children's Depression Rating Scale |
| CDRS-R | Children's Depression Rating Scale, Revised |
| CE | Cost effective |
| CEAC | Cost-effectiveness acceptability curve |
| CGAS | Children's Global Assessment Scale |
| CGI | Clinical Global Impression |
| CGI-I | Clinical Global Impression improvement scale |
| CGI-S | Clinical Global Impression severity scale |
| CHD | Coronary heart disease |
| CHMP | Committee for Medicinal Products for Human use |
| CI | Confidence interval |
| CMH | Cochran-Mantel-Haenszel |
| CPK | Creatine phosphokinase |
| DMS-IV | Diagnostic and Statistical Manual of Mental Disorders, 4$^{th}$ edition |
| EC | European Commission |
| ECG | Electrocardiogram |
| ECT | Electroconvulsive therapy |
| EPAR | European Public Assessment Report |
| EPS | Extrapyramidal symptoms |
| EU | European Union |
| GAS | Global Assessment Scale |
| GPRD | General Practice Research Database |
| $HbA_{1c}$ | Haemaglobin $A_{1c}$ |
| HDL | High-density lipoprotein |
| HDL-C | High-density lipoprotein cholesterol |
| HRQL | Health related quality of life |
| ICER | Incremental cost-effectiveness ratio |
| ITT | Intent-to-treat |
| IVRS | Interactive voice response system |
| K-SADS-PL | Kiddie-Sads-Present and Lifetime version |
| LDH | Lactic dehydrogenase |
| LOCF | Last observation carried forward |
| LS | Least squares |
| MAH | Marketing Authorisation Holder |
| MTC | Mixed treatment comparison |
| NCCMH | National Collaborating Centre for Mental Health |

| | |
|---|---|
| NHS | National Health Service |
| NICE | National Institute for Health and Clinical Excellence |
| OC | Observed cases |
| OR | Odds ratio |
| PANSS | Positive And Negative Syndrome Scale |
| P-QLES-Q | Paediatric Quality of Life and Enjoyment and Satisfaction Questionnaire |
| PSA | Probabilistic sensitivity analysis |
| PSS | Personal Social Services |
| QALY | Quality adjusted life year |
| QoL | Quality of life |
| RCT | Randomised controlled trial |
| RR | Relative risk |
| SAE | Serious adverse event |
| SC | Standard of Care |
| SD | Standard deviation |
| SMC | Scottish Medicines Consortium |
| SOC | System organ class |
| SPC | Summary of Product Characteristics |
| TEAE | Treatment emergent adverse event |

# Executive summary

## Burden of disease

Schizophrenia is a devastating chronic psychiatric disorder characterised by abnormalities in the perception or expression of reality. Symptoms are generally divided into three clusters:

- Positive symptoms: hallucinations, paranoid or bizarre delusions, thought disorders.
- Negative symptoms: lack of motivation, paucity of speech and thought, self neglect, social withdrawal.
- Disorganised behaviours: chaotic speech, bizarre behaviour, poor attention, illogical thinking, impaired discourse skills.

The onset of psychotic symptoms before 13 years of age is very rare, however after the start of puberty the incidence of schizophrenia rises sharply. Approximately 1% of the population will experience at least one episode of schizophrenia, with the onset of symptoms starting before 18 years of age in 12-33% of patients (1, 2).

Adolescent schizophrenia is associated with a severe clinical course and a generally poor outcome (3): approximately 25% of sufferers recover within 5 years; 65% experience fluctuating symptoms over many years and 10-15% experience severe long term incapacity (4). Features include high levels of depression and anxiety, emerging cognitive and social deficits, unusual thought content and failure at school (5). In addition, adolescent schizophrenia is associated with more prominent negative symptoms, and relatively fewer delusions and auditory hallucinations, compared with adult schizophrenia, (3).

## Current management and unmet need

Early diagnosis and treatment of adolescent schizophrenia is extremely important as early, appropriate, treatment can prevent the progressive damage that may occur if the disease remains untreated and uncontrolled (3).

There are currently no NICE guidelines or guidance for the treatment of schizophrenia in adolescents. A clinical guideline is planned and appears on the NICE work program. While treatment generally is with atypical (second-generation) antipsychotics (3) (based on the NICE clinical guidelines for schizophrenia in adults (6), most antipsychotics are not licensed in adolescents.

It is important to recognise that adolescent schizophrenia is a different illness to that experienced by adults. Adolescents are more vulnerable than adults to the side effects associated with atypical antipsychotics, some of which may be more pronounced in post-pubertal adolescents. Consequently the side effect profile of any medication is particularly relevant for adolescents as it may guide the choice of treatment.

## Aripiprazole

Abilify® (aripiprazole) is an atypical antipsychotic drug with a novel pharmacologic profile. It is thought that its beneficial effect in both schizophrenia and bipolar disorder is due to its different effects on the dopamine and serotonin receptors.

On 21st August 2009 approval for aripiprazole was granted from the European Commission and it is currently marketed in the UK. Aripiprazole is indicated for the treatment of schizophrenia in adults; the treatment of schizophrenia in adolescents aged 15 years and older; and the treatment of adults with moderate to severe manic episodes and for the

prevention of a new manic episode in patients who have responded to aripiprazole treatment.

The licensed dose for adolescents is 10 mg/day. Treatment should be initiated at 2 mg (using aripiprazole oral solution 1 mg/ml) for 2 days and titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg. Aripiprazole is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents, although individual patients may benefit from a higher dose.

Aripiprazole is supplied in formulations detailed below:

| Formulation | Size | Supply | Acquisition costs |
|---|---|---|---|
| Tablet | 5 mg<br>10 mg<br>15 mg, | 28 per pack | £95.74 |
| Tablet | 30 mg | 28 per pack | £191.47 |
| Orodispersable tablet | 10 mg<br>15 mg | 28 per pack | £95.74 |
| Oral solution | 1 mg/ml | 150 ml | £102.57 |

The average cost of treatment with aripiprazole is £1,248.04/year based on the average daily dose 10 mg tablet x 365 days. Patients typically remain on treatment once stabilised in order to prevent a relapse.

Aripiprazole is the only commonly prescribed antipsychotic licensed for adolescent schizophrenia. Amisulpride, although licensed for use in adolescents, is infrequently prescribed due to its effect of significantly increasing prolactin levels. Other drugs that may be prescribed in this patient group include quetiapine, risperidone, olanzapine and clozapine. Clozapine is prescribed only when patients are refractory to at least two other antipsychotic treatments. Results from a systematic literature review conducted as part of this appraisal highlighted the paucity of appropriate clinical data for quetiapine and risperidone in the adolescent population, making comparisons impossible. Therefore, the comparator used in this appraisal is olanzapine.

## Aripiprazole in clinical practice

Aripiprazole, which is licensed for use in adolescents, offers a treatment of proven efficacy which supports the quality of life of patients.

### *Early effective control of core symptoms with sustained improvements over the long term*

- Early appropriate treatment of schizophrenia is critical in preventing progressive illness.
- Aripiprazole significantly improved the core symptoms of schizophrenia as early as week 1.
- Negative symptoms of schizophrenia, such as lack of motivation, self neglect and social withdrawal, have been identified as distinctive features of adolescent schizophrenia. Aripiprazole significantly improved these negative symptoms within 6 weeks.
- Positive symptoms, such as hallucinations and delusions, can be particularly devastating for patients. Significant improvements were seen in these from week 1 through to week 6 of aripiprazole treatment.

- Effective control of these core symptoms of schizophrenia were maintained in patients receiving aripiprazole over 6 months.

***Significant benefits in general functioning and quality of life***

- Significant improvements with both 10mg and 30mg doses of aripiprazole were seen in patients' overall social and psychological functioning. These improvements showed that patients' well being benefited from treatment with aripiprazole.
- Treatment effectiveness involves evaluation of both symptom severity and quality of life (QoL).
- Both aripiprazole groups demonstrated significant improvements in QoL over 6 weeks on the Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) overall score compared to placebo, with numerical improvements on the P-QLES-Q total score.
- The improvements in QoL of aripiprazole patients were maintained for up to 1 year providing support for the adolescent's longer-term independent functioning and social inclusion.

***Well tolerated safety profile***

- Aripiprazole is generally well tolerated in the adolescent population, with most Adverse Events (AEs) being mild or moderate in severity.
- Few patients dropped out of the studies because of side effects associated with their treatment.
- Stopping medication is recognised as a frequent occurrence in this patient population, which can be a major problem in treating schizophrenia (7).
- If a patient stops taking their medication, this is captured by 'Time to discontinuation'. Importantly, there were no significant differences seen in 'Time to discontinuation', between either aripiprazole doses or placebo.

***Differential advantages of aripiprazole***

- Unlike the majority of other antisychotics, aripiprazole offers the advantage of being licensed for the treatment of adolescent schizophrenia.
- Cardiac monitoring is not required, as no clinically significant impact has been seen on cardiac conduction.
- The long half-life of aripiprazole allows once daily dosing.
- Aripiprazole is associated with a lower impact on certain metabolic parameters compared to other atypical antipsychotics (8), with minimal weight changes and no significant changes in glucose or lipid levels. These factors support a lower long term risk of adult obesity, coronary heart disease and diabetes.
- Hyperprolactinaemia is not usually associated with aripiprazole treatment, unlike some other atypical antipsychotics, when used in adolescents (8).

**Cost-effectiveness**

- Aripiprazole is backed by robust clinical evidence, supporting a position of first line treatment in adolescents aged 15-17 years with schizophrenia.
- The clinical profile makes a compelling value proposition for aripiprazole, which is supported by the health economic evidence in this submission, showing that aripiprazole is cost-effective as a first line treatment in comparison to olanzapine.

The cost-effectiveness of aripiprazole in adolescents with schizophrenia was compared with olanzapine. Comparisons with other atypical antipsychotics (e.g. risperidone, quetiapine, amisulpride) were not possible as adolescent population data were not available from clinical trials. Clozapine and typical antipsychotics were not considered by expert opinion to be appropriate first line options.

For the purposes of this submission a de novo economic evaluation was conducted with the aim of investigating the impact of the first line antipsychotic on costs and patient outcomes. The chosen structure of the economic analysis was a decision tree model followed by a Markov model.

The population included in this economic evaluation was adolescents aged 13-17 with schizophrenia, to incorporate as much adolescent data as possible. The licensed adolescent age range for aripiprazole, (15-17 years) represented 76% of the aripiprazole evidence base included in the evaluation. The Markov section of the modelling allows patients to be followed up to 18 years of age, when other treatments may then become available to them.

The results of this cost-utility model show that in adolescents with schizophrenia aripiprazole, as a first line antipsychotic, was dominant; (i.e. it is less costly and more effective) in the base case analysis when compared with olanzapine. The base case results are shown in Table 1.

**Table 1: Base-case cost-effectiveness results**

| Treatments | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Aripiprazole - olanzapine – clozapine | £23,723 | 2.597 | -£69.21 | 0.004 | Dominant |
| Olanzapine - aripiprazole - clozapine | £23,792 | 2.593 | - | - | - |

The results were tested in one-way sensitivity analyses and showed a high uncertainty around a number of parameters largely due to a lack of data availability. However, this same uncertainty has also been demonstrated in previous economic analyses conducted by NICE (6) when modeling schizophrenia as a disease.

Cost effective acceptability analyses demonstrated that at a threshold value of £20,000 aripiprazole has approximately a 95% probability of being cost effective.

Regarding the budgetary impact, it is estimated that considering drug cost alone, positive NICE guidance for aripiprazole would result in a minimal net cost to the NHS in England and Wales estimated to be between [redacted] in year 1 rising to [redacted] in year 5

## Conclusion

1. The successful treatment of adolescent schizophrenia represents a high unmet medical need.
2. Aripiprazole is the only licensed antipsychotic that is commonly prescribed for adolescent schizophrenia.

3. Aripiprazole offers early effective control of symptoms, benefits to quality of life and a low impact on weight, lipid and prolactin parameters.
4. Economic analyses demonstrate that aripiprazole is cost-effective and dominant compared with olanzapine.
5. It is estimated that the incremental cost to the NHS of NICE recommending aripiprazole would be minimal.

Aripiprazole, within its licensed indication, should be recommended as a first line treatment for adolescents (aged 15-17 years) with schizophrenia. A positive NICE recommendation would allow this small patient population to benefit from an effective, well tolerated and cost effective treatment, addressing their specific clinical and social needs.

# Section A – Decision problem

## 1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Abilify; Approved name: Aripiprazole; Therapeutic class: Atypical antipsychotic drugs.

1.2 What is the principal mechanism of action of the technology?

The efficacy of aripiprazole is mediated through a combination of partial agonism (agonism/antagonism) at dopamine $D_2$ and serotonin 5-$HT_{1A}$ receptors and antagonism at serotonin 5-$HT_{2A}$ receptor.

It is thought that the beneficial effects of aripiprazole are due to its effects on dopamine and serotonin receptors.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The Committee for Medicinal Products for Human Use (CHMP) positive opinion adopted: 27th July 2009 via a written procedure.
EC decision, final approval granted: 21st August 2009.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

It was considered that the lack of active comparator and the open label design of the extension studies made the results difficult to interpret in the longer-term. Acute and long-term efficacy data were presented that supported the similarity between adolescents (15-17 years) and adults for aripiprazole. Although the safety profile of aripiprazole in children appeared to be similar to the one observed in the adult population, the CHMP considered that further proactive safety data should be collected (e.g. extrapyramidal symptoms (EPS), weight gain, suicidality, growth and sexual maturation) and recommended that the prospective safety data should cover a minimum period of 2 years. This followed the Paediatric Committee conclusion that efficacy and safety data for antipsychotics cannot safely be extrapolated between different age groups (adult vs different paediatric subgroups).

The Marketing Authorisation Holder (MAH) agreed to conduct a number of pooled analyses from paediatric placebo-controlled completed studies and from ongoing studies, and to

collect prospective safety data over 2-years' exposure in adolescent schizophrenia patients, as post-authorisation commitments. To specifically address the concern over suicidality, the MAH agreed to conduct an epidemiologic cohort study to assess suicide in adolescent patients using aripiprazole, as a post-authorisation commitment.

The CHMP considered the proposed indication approvable provided that:

- The paediatric population was restricted to adolescents older than 15 years.
- Long-term efficacy and safety studies to further support the maintenance of the effect, and to better characterise the safety profile in the adolescent population, were performed by the MAH, as part of post-authorisation commitments.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The current indications for aripiprazole are:

- Treatment of schizophrenia in adults.
- Treatment of schizophrenia in adolescents 15-17 years.
- Treatment of moderate to severe manic episodes in Bipolar I Disorder.
- The prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

This submission is for the appraisal of aripiprazole for the treatment of schizophrenia in adolescents15-17 years of age.

Application for a licence for adolescent bipolar disorder is underway with an anticipated CHMP response, Q3, 2011.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There are currently no ongoing studies related to aripiprazole for the treatment of schizophrenia in adolescents (15-17 years). The post marketing authorisation study commitments are in the planning stage and will not report within 12 months.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Aripiprazole has been launched in the UK for the treatment of schizophrenia in adolescents 15-17 years of age.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Aripiprazole has regulatory approval for the treatment of schizophrenia in the adolescent population (15-17 years) in the following countries outside the UK:

EU (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden), Indonesia, Switzerland, Turkey and United States of America.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

An abbreviated submission was made to the Scottish Medicines Consortium (SMC) on the 2nd of February 2010. An update on the status of this submission is due but timelines have not yet been provided to the company.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

**Table 2: Unit costs of technology being appraised**

| | |
|---|---|
| Pharmaceutical formulation | Tablets: 5 mg, 10 mg, 15 mg and 30 mg.<br>Orodispersible tablets: 10 mg and 15 mg.<br>Oral solution: 150 ml (aripiprazole 1 mg/ml). |
| Acquisition cost (excluding VAT) | Tablets: 5 mg, 10 mg, 15 mg (£95.74 x 28 tablets), 30 mg (£191.47 x 28 tablets).<br>Orodispersible tablets: 10 mg and 15 mg (£95.74 x 28 tablets).<br>Oral solution: (£102.57 – 150 ml). |
| Method of administration | Tablets, orodispersible tablets and oral solution are for oral use. |
| Doses | 10 mg/day. 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.<br>When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg. Aripiprazole is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents although individual patients may benefit from a higher dose. |
| Dosing frequency | Once a day. |
| Average length of a course of treatment | 365 days a year. |
| Average cost of a course of treatment | Average cost/year £1,248.04 (based on average daily dose, 10 mg tablet x 365 days). |
| Anticipated average interval between courses of treatments | None. |
| Anticipated number of repeat courses of treatments | Once stabilised, patients typically remain on treatment in order to prevent relapse. |
| Dose adjustments | **Dose adjustments due to interactions:** When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.<br><br>When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose. |

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A; aripiprazole is not a device.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

As per treatment with other atypical antipsychotics, sedation medication (benzodiazepine) can be added if necessary.

# 2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Schizophrenia is a devastating chronic psychiatric disorder, or cluster of disorders, characterised by abnormalities in the perception or expression of reality. Schizophrenia symptoms are generally divided into three clusters:

| | |
|---|---|
| Positive symptoms | Hallucinations, paranoid or bizarre delusions, thought disorders |
| Negative symptoms | Lack of motivation, paucity of speech and thought, self neglect, social withdrawal |
| Disorganised behaviours | Chaotic speech, bizarre behaviour, poor attention, illogical thinking, impaired discourse skills |

**Typically the course of schizophrenia can be divided into several phases**; pre-onset, acute, stabilisation and maintenance. The prodromal (pre-onset) phase is characterised by early signs of deterioration in personal functioning, including memory and concentration problems, unusual behaviour and ideas, social withdrawal and apathy. In the acute phase, the patient has an overt loss of contact with reality (psychotic episode) that requires intervention and treatment. In the stabilisation phase, the acute episode has been brought under control but the patient is at risk of relapse if treatment is interrupted. In the maintenance phase, the patient is relatively stable and can be kept indefinitely on antipsychotic medications. Even in the maintenance phase, however, relapses are not unusual and patients do not always return to full functioning.

**The pathophysiology of schizophrenia is unclear**. However, increased dopamine activity in the mesolimbic pathway of the brain has been consistently found in people with schizophrenia. It is thought that antipsychotic medications work by blocking dopamine D2 receptors, thus diminishing psychotic symptoms. Genetic (hereditary), social, neurobiological and psychological factors may also contribute to the onset of schizophrenia.

**The onset of psychotic symptoms before the age of 13 years is very rare**, however after the start of puberty the incidence of schizophrenia rises sharply. Approximately one in a hundred (1%) people will experience at least one episode of schizophrenia during their lifetime, and in 12-33% of these patients the onset of their illness occurs before they reach 18 years of age (1, 2).

**Adolescent schizophrenia is associated with a severe clinical course and a generally poor outcome** (3). Of those who develop schizophrenia, approximately 25% recover within 5 years, 65% experience fluctuating symptoms over many years and 10-15% experience severe long term incapacity (4).

**Poor premorbid functioning and early developmental delays have been associated with adolescent schizophrenia.** However, early recognition of adolescent schizophrenia can be difficult as the disorder frequently presents with an insidious rather than acute onset, and the premorbid cognitive and social impairments gradually merge into prodromal symptoms (3). In adolescents, prodromal symptoms include high levels of depression and anxiety, emerging cognitive and social deficits, unusual thought content and failure at school (5). Compared with adult schizophrenia, adolescent schizophrenia is associated with more

prominent negative symptoms and relatively fewer delusions and auditory hallucinations (3). This highlights the fact the illness as experienced by adolescents is symptomatically different to that experienced by adults.

**Early diagnosis and treatment of adolescent schizophrenia are extremely important.** There are indications that early, appropriate treatment can prevent some of the progressive damage that may occur if the disease remains untreated and the patient continues to experience uncontrolled schizophrenic episodes (3). Adolescents are generally treated with atypical (second-generation) antipsychotics due to their improved action against negative symptoms, and lower risk of extrapyramidal side effects, compared with typical (first-generation) antipsychotics (3). The use of atypical antipsychotics in adolescent schizophrenia is markedly different to that in adult schizophrenia. Medication is usually titrated rather than initiated at a recognised therapeutic dose. Doses used in adolescents tend to be lower than in adults.

**Adolescents are more vulnerable than adults to the adverse events associated with atypical antipsychotics.** Endocrine and metabolic side effects are of particular concern. Weight gain and related metabolic abnormalities (hyperglycaemia and dyslipidemia) are particularly problematic during development, as they predict adult obesity and metabolic syndrome that put patients at high risk for coronary heart disease (CHD) and diabetes in the longer term.

The effects of hyperprolactinaemia (abnormally high levels of prolactin), such as amenorrhea, (the absence or suppression of normal menstrual flow), decreased libido, orgasmic dysfunction and breast engorgement, can be disruptive and may be more pronounced in post-pubertal adolescents. Hyperprolactinaemia associated with antipsychotic use may be more prevalent in adolescents, because the density of dopamine receptors in the central nervous system is higher in adolescents than in adults (9).

**Adolescent schizophrenia is a different illness to that experienced by adults**. The most prominent symptoms vary between the two groups, the use of antipsychotics to treat the illness is different, particularly in relation to dosing, and certain treatment associated side effects may be of more concern or problematic in adolescents than in adults. This highlights the requirement for adolescent specific research in this area, in order to guide clinical practice and balance symptom improvements with the different risks of adverse events associated with specific antipsychotics.

**Aripiprazole offers advantages in the treatment of adolescent schizophrenia.** Cardiac monitoring is not required as no impact has been seen on cardiac conduction. The long half-life facilitates once daily dosing. The impact on metabolic parameters including weight and prolactin levels appears to be less than some other atypical antipsychotics when used in adolescents (8). Along with proven efficacy, these specific advantages support the quality of life of these adolescent patients suffering from a devastating, chronic disorder.

## 2.2 How many patients are assumed to be eligible? How is this figure derived?

Country specific estimates from epidemiology studies vary greatly. The variation is related to differences in study design making it difficult to estimate the prevalence of this condition in the adolescent age group.

A General Practice Research Database (GPRD)[1] study was undertaken in order to estimate the prevalence of schizophrenia in the 15-17 age group. Data were taken for 2001-2006, and the estimated numbers of subjects eligible for treatment with aripiprazole are outlined in Table 3.

The annual prevalence rate is calculated as the number of cases in a calendar year divided by the estimated patient population for that calendar year, from which a normal approximation of binominal confidence interval was calculated (CI: P±1.96*sqrt(P*(1-P)/N). This was applied to mid-2008 population estimated for 15-17 years in England and Wales (males = 1,077,800 and females = 1,016,800) taken from the Office of National Statistics. Thus, the overall prevalence rate for males and females is estimated at 16.68 (95% CI, 9.25-24.12) and 7.49 (95% CI, 2.73-12.26)/100,000 population respectively.

**Table 3: Number of patients assumed to be eligible for treatment**

| Prevalence/100,000 | Point estimate | Lower estimate | Higher estimate |
|---|---|---|---|
| **Males** | 180 | 100 | 260 |
| **Females** | 76 | 28 | 125 |
| **Total** | 256 | 128 | 385 |

Patients with schizophrenia were identified using Oxford Medical Information Systems (OXMIS) codes and Read codes. The patient population was estimated based on the patient population in GPRD who born between (YR-17) and (YR-15), and who did not die or move out before the first day of the year for the calendar year (YR). For example, the 2001 population will be all patients born between 1984 and 1986 who did not die or move out before 01/01/2001.

The GPRD is the best source available to estimate patient numbers. However, there are some limitations, as those patients seeing a specialist only maybe missed. However, we can argue that GPRD is representative of those who are seeking medical care (i.e. those who are more likely to be on medication such as aripiprazole).

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

There are no specific NICE guidance/guidelines, or indeed any other published European guidelines, for the treatment of schizophrenia in adolescents. The NICE website indicates plans to develop a clinical guideline in this area, something UK clinicians have identified as critical to guiding their practice. NICE published a guideline on the core interventions in the treatment and management of schizophrenia in adults in primary and secondary care in March 2009 and recommended oral antipsychotics, including aripiprazole, as first-line treatment (6).

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

[1] GPRD is a database of patient records from general practices that cover England and Wales. The current updated database has approximately 6.5 million members from 487 primary care practices

There are currently no published UK guidelines for the treatment of adolescents with schizophrenia. Most of the antipsychotics included in the adult guidelines are not licensed in adolescents (e.g. clozapine). General information in the adult guideline that may be of relevance to adolescent treatment is detailed below.

It is considered that oral antipsychotic medication should be offered to those newly diagnosed with schizophrenia. In addition clinicians should:

- provide information on the benefits and side effects of each antipsychotic and discuss these with the service user.
- decide which antipsychotic to use in partnership with the service user, and their carer if appropriate.
- consider the relative potential of individual antipsychotics to cause extrapyramidal side effects (such as akathisia), metabolic side effects (such as weight gain), and other side effects (including unpleasant subjective experiences), as these are important when deciding on the most suitable medication.
- not start regular combined antipsychotic medication, except for short periods (for example, when changing medication).

For patients whose symptoms have not responded adequately to treatment, clinicians should:

- review the diagnosis.
- check that there has been compliance with antipsychotic medication, and that it is prescribed at an adequate dose and for the correct duration.
- check that psychological treatments have been offered and review patient engagement with these.
- offer cognitive behaviour therapy (CBT) if family intervention has been undertaken; if CBT has been undertaken, suggest family intervention for those in close contact with their family.
- consider other causes of non-response, for example comorbid substance or alcohol misuse, concurrent use of other prescribed medication, or physical illness.
- offer clozapine if symptoms have not responded adequately despite sequential use of at least two different antipsychotics, one of which should be a non-clozapine second-generation antipsychotic.
- if symptoms have not responded adequately to an optimised dose of clozapine, review the diagnosis, adherence to treatment, engagement with and use of psychological treatments, other possible causes of non-response and measure therapeutic drug levels before offering a second antipsychotic to augment clozapine.
- check that the second drug does not compound the common side effects of clozapine.
- consider that an adequate trial of such augmented therapies may need to be up to 8–10 weeks.

The introduction of licensed aripiprazole for the treatment of schizophrenia in adolescents is unlikely to change the current clinical pathway of care, as adolescent patients will continue to be offered antipsychotic treatment. However, the recommendations from this appraisal will fill the protocol gap in adolescent treatment.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

NICE has issued clear guidelines for healthcare professionals on the treatment of adults with schizophrenia, but there are no current guidelines or protocols relating to the treatment of adolescents with schizophrenia. Healthcare professionals are therefore uncertain as to what constitutes best practice in treatment of adolescent schizophrenia.

This appraisal confirms the clinical and cost-effectiveness of aripiprazole use in the adolescent schizophrenia population. Once issued, the recommendations will bring clarity and provide guidance to healthcare professionals, filling an existing protocol gap.

With the exception of amisulpride, aripiprazole is the only atypical antipsychotic licensed for use in the adolescent population in England and Wales. Amisulpride is infrequently prescribed to adolescents due to an increased effect on prolactin levels. The choice of drug in this group of patients is usually guided by the administration regimen (once daily is preferred for adolescents for adherence reasons) and the side-effect profile. However, the side-effect profiles differ markedly between atypical antipsychotics.

Important considerations regarding the treatment of the adolescent schizophrenic population are weight gain, metabolic factors and impact on prolactin levels. Treatment with aripiprazole is associated with a lower risk of weight gain relative to other atypical antipsychotics, while no clinically meaningful changes were observed in the other physical health parameters implicated in metabolic syndrome. Furthermore, incidences of hyperprolactinaemia with aripiprazole treatment were minimal.

The introduction of licensed aripiprazole in the adolescent population will reduce the risks associated with prescribing unlicensed atypical antipsychotics (olanzapine, risperidone and quetiapine) to this patient group.

2.6 Please identify the main comparator(s) and justify their selection.

The main comparator antipsychotic drug in this submission is olanzapine.

Other drugs that may be prescribed in this patient group include quetiapine, risperidone and amisulpride. Clozapine is prescribed only when patients are refractory to initial antipsychotic treatment. Quetiapine and risperidone are not licensed for use in England and Wales. Amisulpride, although licensed for use in adolescents, is infrequently prescribed due to the increased effect on prolactin levels.

The historical licensed indication for risperidone for the treatment of schizophrenia was for patients aged 15 years and above. However, in 2008 the CHMP harmonised the SPC as divergences across EU member states were identified. This resulted in revisions in October 2008 to the licensed indication for adolescent prescribing and reflects the current indication status for adolescents (10):

- CHMP revised the wording stating that risperidone should not be recommended for use in children/adolescents under 18 years of age, due to a lack of systematic efficacy, safety and clinical data for this age group.

- Clinicians are recommended to monitor sedative effects of the drug because of possible consequences on learning ability.

- Endocrine status should also be regularly evaluated because of the potential effects of prolonged hyperprolactinaemia on growth and sexual maturation in adolescents.

- The association between risperidone and mean increases in weight and BMI remain in the SPC.

A systematic literature review was undertaken to identify randomised, placebo-controlled trials for olanzapine, quetiapine, risperidone and amisulpride in the adolescent schizophrenia population. No randomised placebo-controlled trial data were identified for quetiapine, risperidone and amisulpride. Although one conference abstract was available for risperidone which indicated that a randomised placebo-controlled trial had been conducted, there was insufficient data presented for model parameters (11). As such, the clinical and cost effectiveness of aripiprazole versus quetiapine, risperidone and amisulpride (as outlined in the final scope for this appraisal) was not evaluated. It would be inappropriate to substitute adult schizophrenia clinical data parameters into the model for these comparators in light of the fact that we are using specific adolescent data for the aripiprazole group. In the model, adult utility data was only used where adolescent data was missing and the same input parameters were applied to both treatment groups (aripiprazole and olanzapine).

Only one randomised placebo-controlled trial was identified for olanzapine in the adolescent schizophrenia population (12) and the data from this trial was indirectly compared with the adolescent data in the randomised placebo-controlled aripiprazole trial in order to determine model parameters.

Clozapine is prescribed when patients are refractory to initial treatment (i.e. failed on at least two atypical antipsychotics). Clozapine is not licensed for use in adolescents under the age of 16 years. Clozapine is therefore considered in the economic analysis as a refractory treatment, and as such is not a main comparator to aripiprazole.

Typical antipsychotics were not included in the scope. Their exclusion was confirmed by clinical experts as appropriate, since they are rarely prescribed in adolescent schizophrenia due mainly to their adverse event profile.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Adverse events are typically managed by reducing the atypical antipsychotic dose, changing the time of administration or by switching patients to another atypical antipsychotic treatment. As with all atypical antipsychotic treatment, sedatives (benzodiazepine) can be added if necessary.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Adolescent patients with a diagnosis of schizophrenia are typically managed by secondary care mental health services (6). In-patient care is the most costly healthcare component and is needed in the most uncontrolled and severe cases of schizophrenia. The opportunity to effectively manage adolescents with schizophrenia using aripiprazole would hopefully reduce the need for in-patient admissions.

Aripiprazole is not normally associated with any monitoring tests.

2.9 Does the technology require additional infrastructure to be put in place?

No.

# 3 Equity and equality

## *3.1 Identification of equity and equalities issues*

**3.1.1** Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

NICE has issued clear guidelines for healthcare professionals on the treatment of adults with schizophrenia whilst guidelines for the adolescent population are currently not available. This appraisal confirms the clinical and cost-effectiveness of aripiprazole use in the adolescent schizophrenia population and therefore will provide clarity and guidance to healthcare professionals, fulfilling the existing protocol gap.

The diagnosis of schizophrenia is a very definitive one. Clinicians are guided by diagnostic criteria, detailed in a number of different tools, including DSM-IV and K-SADS-PL (a child specific tool). These are used in clinical practice, as well as in the studies of aripiprazole. For this reason, other areas of mental health disorders such as learning disabilities are not appropriate for review in this appraisal.

**3.1.2** Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No.

**3.1.3** How have the clinical and cost-effectiveness analyses addressed these issues?

N/A.

# 4 Statement of the decision problem

| | Final scope issued by NICE | Decision problem addressed in the submission | Rationale if different from the scope |
|---|---|---|---|
| Population | People with schizophrenia, aged 15-17 | People with schizophrenia, aged 15-17 | |
| Intervention | Aripiprazole | Aripiprazole | |
| Comparator(s) | • Olanzapine<br>• Risperidone<br>• Quetiapine<br>• Amisulpride<br>• Clozapine | • Olanzapine | Adolescent data were not available from randomised placebo-controlled trials for quetiapine, risperidone and amisulpride. Therefore these treatments are not considered as comparators in the submission.<br>Clozapine is typically reserved for refractory patients and has therefore been included in the economic analysis but has not been considered as a main comparator to aripiprazole. |
| Outcomes | • Treatment response<br>• Positive symptoms<br>• Negative symptoms<br>• Recurrence of psychosis<br>• Mortality<br>• Adverse effects of treatment<br>• Health-related quality of life | • Treatment response<br>• Positive symptoms<br>• Negative symptoms<br>• Mortality<br>• Adverse effects of treatment<br>• Health-related quality of life | There are no data regarding the recurrence of psychosis for aripiprazole, and so this aspect has not been considered. |
| Economic analysis | The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). | The cost effectiveness of treatments is expressed in terms of an incremental cost per QALY. | |
| | The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes being compared | The model time horizon is 3 years, as this reflects the maximum time period before adolescents (15-17 years) are considered adults.<br>The time horizon takes into account the main differences in the | |

| | Final scope issued by NICE | Decision problem addressed in the submission | Rationale if different from the scope |
|---|---|---|---|
| | | technologies before adulthood. A lifetime model is currently available which has examined all evidence surrounding antipsychotics for adults. According to the NICE methods guide, a lifetime horizon should normally be adopted if a treatment affects survival at a differential rate when compared with the relevant comparator. There is currently no evidence that survival differs between the two treatments included in the model.<br>In addition, there is a lack of data on long-term treatment outcomes, therefore extrapolation of this data over a lifetime horizon would introduce significant bias into the model. | |
| | Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective. | Costs are considered from an NHS and PSS perspective. | |
| Other considerations | Guidance will only be issued in accordance with the marketing authorisation | 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. | |
| | If evidence allows, the appraisal will seek to identify subgroups of individuals for whom the technology is particularly clinically and cost-effective | | No subgroups of individuals for whom the technology is particularly clinically and cost-effective have been identified. |

# Section B – Clinical and cost effectiveness

# 5 Clinical evidence

## *5.1 Identification of studies*

A systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of aripiprazole, amisulpride, olanzapine, quetiapine and risperidone for the treatment of schizophrenia in adolescents. This was supplemented by hand searching the bibliographies of relevant review articles.

Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for 1) Schizophrenia, 2) Interventions, 3) RCT design, and 4) Child/Adolescent. The RCT filter used was based on that used in the recent NICE guideline on schizophrenia (6) and is sensitive enough to capture randomised as well as non-randomised evidence such as open label studies, observational data, and retrospective analyses. For this reason, during first pass exclusion (Figure 1:e1), relevant non-RCT studies were identified and labelled for subsequent interrogation (see Table 4). Child filters/MeSH headings were used to ensure all relevant studies were captured; studies only examining child populations (<13 years of age) were excluded by eye. (See Section 9.2, Appendix 2 for further details of actual search strings used).

## *5.2 Study selection*

### 5.2.1 Eligibility criteria

The eligibility criteria used in the search strategy are described in Table 4.

**Table 4: Eligibility criteria used in search strategy**

| | Description | Justification |
|---|---|---|
| ***Inclusion criteria*** | | |
| Population | People with schizophrenia, aged 15-17 years. | As specified by the Final Scope |
| Interventions | Olanzapine, risperidone, quetiapine, placebo, haloperidol, amisulpride, aripiprazole | • Aripiprazole included as it is the technology under appraisal<br>• Placebo included (not in isolation) to facilitate indirect comparisons with other interventions<br>• All other interventions are included as they are specified in the Final Scope (with the exception of haloperidol)<br>• Evidence supporting clozapine was excluded from the comparative clinical review as it is was not considered as a main comparator |

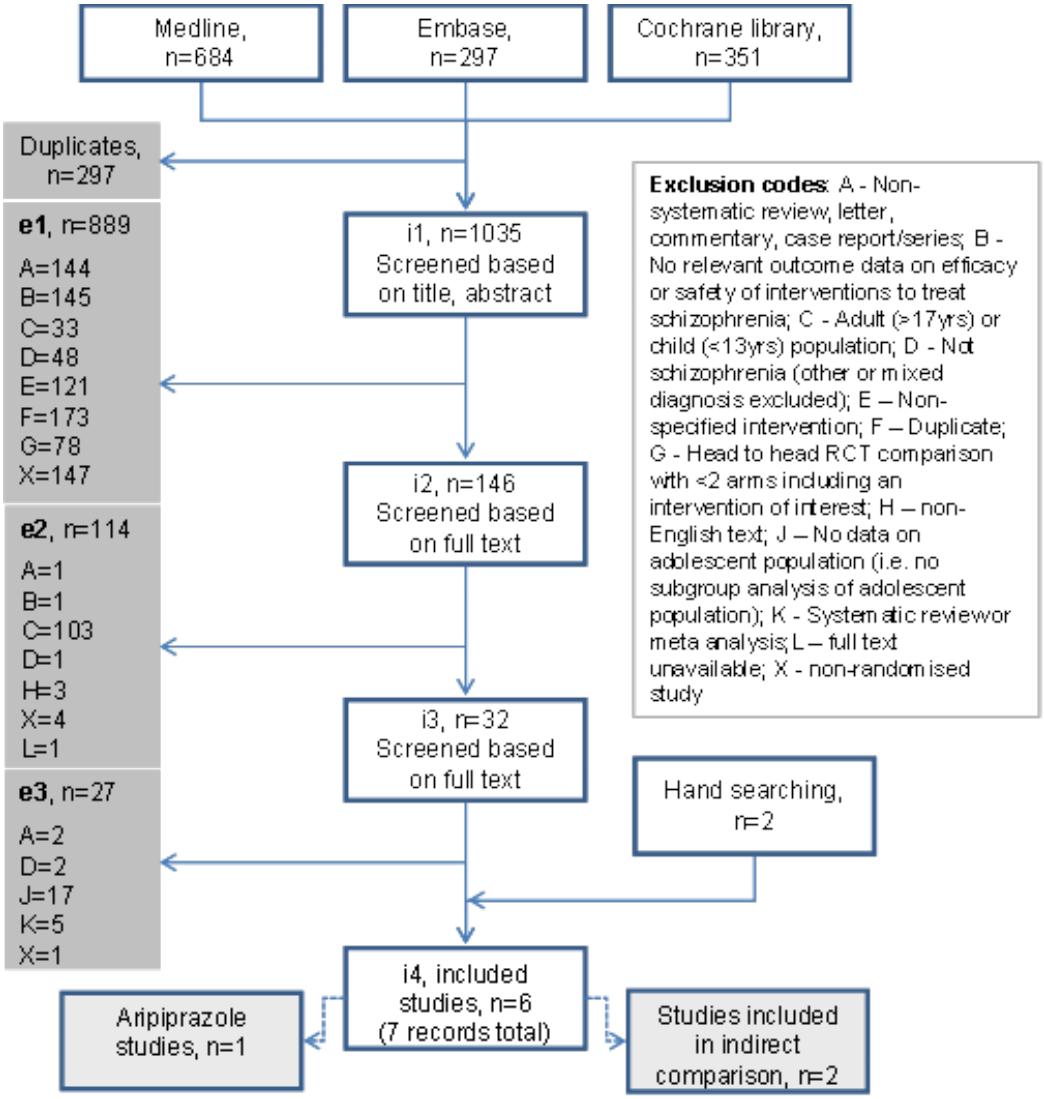
| | | |
|---|---|---|
| Outcomes | PANSS<br>BPRS<br>CGI<br>Discontinuations<br>Discontinuations due to AEs<br>Treatment response (e.g. time to relapse)<br>AEs<br>Mortality (suicide)<br>Mental state (total symptoms, depression)<br>Social functioning<br>Recurrence<br>HRQoL | As specified by the Final Scope.<br><br>Discontinuations included as a possible outcome to be used in economic modelling. |
| Study design | Randomised controlled trials | Randomised evidence prioritised as per specification.<br><br>Non-randomised evidence (e.g. observational data, open label clinical trial) were also identified by the search. During first round of exclusion, these studies were labelled for subsequent interrogation (see Figure 1). |
| ***Exclusion criteria*** | | |
| Population | • Adult (>17 years) or child (<13 years) other or mixed diagnosis, i.e. not schizophrenia alone | As specified by Final Scope.<br>Other diagnoses were not included in order to allow a meaningful comparison across interventions and to limit sources of potential bias. |
| Interventions | • Clozapine<br>• Other antipsychotics<br>• ECT<br>• Behavioural interventions | Clozapine and other antipsychotics are not routinely used in clinical practice to treat adolescents with schizophrenia and are therefore not considered as main comparators in this submission. |
| Study design | • Non-systematic reviews, letters, commentaries, case report/series, surveys<br>• Head to head studies with <2 arms including interventions of interest (as detailed in inclusion criteria) | • These types of records represent lower levels of evidence and were excluded to minimise potential sources of bias.<br>• These types of head-to-head studies would not contribute to any potential indirect comparison or mixed treatment comparison network, and so were excluded from the review. |
| Language restrictions | None | |

Abbreviations: AE, adverse event; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; ECT, electroconvulsive therapy; HRQoL, health-related quality of life; PANSS, Positive and Negative Syndrome Scale

**Study selection:** Studies were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded (e1), and allocated a "reason code" to document the rationale for exclusion. Papers included after this stage (i2) were then assessed based on the full text. The majority of papers excluded at this point (e2) were based on age of study populations (as many abstracts do not state the age of study participants, a high percentage of studies were excluded at this stage). A further round of exclusions was conducted (e3) before an (i4) included data set was identified. The full text of these studies was screened and those suitable for indirect comparison were selected.

### 5.2.2 Consort flow diagram of included and excluded studies

**Figure 1: Systematic review schematic: "Master" clinical search**




Following assessment and exclusion of studies based on title, abstract and full text, 6 studies were included in the final data set (i4) (11-16). Seven records were identified in total, but Pandina et al (2007) (17) was a child record of Haas et al (2009) (14). Of the 6 included studies, a single trial examined the intervention of interest (aripiprazole) in the population of interest (adolescents with schizophrenia) (13).

For the purposes of indirect comparison with comparator interventions, 2/6 studies were eligible for analysis (one study comparing aripiprazole versus placebo and one study comparing olanzapine versus placebo (12, 13) (see also Section 5.7). All the other studies (4/6) were unsuitable for indirect comparison as they either did not include a placebo group (14-16) or did not contain sufficient data for comparison (e.g. abstract by Haas (2007) (11)).

### 5.2.3 Data sources of identified RCTs

The systematic review identified a single Phase III randomised study comparing aripiprazole with placebo (13). In describing this study (Study No. 31-03-239), data were drawn from the following additional sources available to the manufacturer:

- Clinical study report for Study 31-03-239: A Multicenter, Randomized, Double-blind, Placebo-controlled Study of Two Fixed Oral Doses of Aripiprazole (10 mg or 30 mg) in the Treatment of Adolescent Patients with Schizophrenia (18)
- Poster: Efficacy of Aripiprazole in the Treatment of Adolescents with Schizophrenia – presented at the American Psychiatric Association 160th Annual Meeting in San Diego (US) by Robb A et al., 2007 (19)

Two non-RCTs are described in this submission (Study 31-03-241 and Study 31-05-243). Both are open-label extension studies;

- Study 31-03-241 included subjects who completed the Phase III RCT 31-03-239
- Study 31-05-243 included subjects who completed Study 31-03-241

### 5.2.4 Complete list of relevant RCTs

The systematic review identified a single Phase III randomised study comparing aripiprazole with placebo (Table 5). No RCTs were identified that compared aripiprazole with the appropriate comparators. No identified studies were excluded from further discussion.

**Table 5: List of relevant RCTs**

| Study no. (acronym) | Intervention | Comparator | Population | Primary study ref. |
|---|---|---|---|---|
| 31-03-239 | Aripiprazole: two fixed oral doses of 10 mg or 30 mg administered daily | Placebo | Adolescents with DSM-IV diagnosis of schizophrenia and confirmed by the KSADS-PL | Clinical study report (18) |

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition; KSADS-PL, Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children - Present and Lifetime Version

### 5.2.5 List of relevant non-RCTs

Non-RCTs considered relevant to the decision problem are summarised in Table 6.

**Table 6: List of relevant non-RCTs**

| Trial no. (acronym) | Intervention | Population | Objectives | Primary study ref. | Justification for inclusion |
|---|---|---|---|---|---|
| 31-03-241 | Aripiprazole: oral doses of 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg and 30 mg daily | Adolescent subjects with schizophrenia, and children and adolescent subjects with bipolar I disorder, manic or mixed episode, with or without psychotic features. | To determine the long-term safety and tolerability of aripiprazole tablets (5 mg to 30 mg/day) in adolescent subjects completing Study 31-03-239 | Clinical study report (20) | Provides long-term safety and tolerability data on aripiprazole (over a treatment period of 6 months) |
| 31-05-243 | Aripiprazole: oral doses of 5 mg to 30 mg daily | Patients with a DSM-IV diagnosis of schizophrenia who had completed study 31-03-241 | To continue to provide flexible doses (between 5 mg and 30 mg) of aripiprazole therapy to subjects with schizophrenia completing Study 31-03-241 | Clinical study report (21) | Provides additional long-term safety data on aripiprazole (over a treatment period of 60 months) |

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition

## *5.3 Summary of methodology of relevant RCTs*

### 5.3.1 Methods

The methodology of Study 31-03-239 is summarised in Table 7.

**Table 7: Summary of methodology of Study 31-03-239 (13, 18)**

| | |
|---|---|
| Location | Multicentre at 141 global sites (Argentina, Bulgaria, Croatia, India, Jamaica, Mexico, Romania, Russia, Serbia, South Africa, South Korea, Ukraine, and the US) |
| Design | Randomised, double-blind, placebo-controlled study |
| Duration of study | Up to 10 weeks (including a 28 day screening period and a 42 day treatment period) |
| Method of randomisation | Subjects were randomised 1:1:1 via IVRS to receive aripiprazole 10 mg, aripiprazole 30 mg, or placebo following computer-generated randomisation codes prepared by the sponsor's<br>Biostatistics Department. The randomisation was stratified by region ( US, European region, and all other regions) |
| Method of blinding (care provider, patient and outcome assessor) | The study was double-blind. Blinding was maintained by the use of blister cards from which subjects took the same number of tablets per dose, regardless of treatment arm assigned. All tablets were identical in appearance.<br>Blinded study medication disclosure panels were supplied for each subject in the event of an emergency. The investigator could break the blinding only if knowledge of the investigational product was essential for the clinical management or welfare of the subject. |
| Intervention(s) (n) and comparator(s) (n) | Aripiprazole 10 mg (n = 100)<br>Aripiprazole 30 mg (n = 102)<br>Placebo (n = 100) |
| Primary outcomes (including scoring methods and timings of assessments) | Mean change from Baseline to Endpoint (Day 42) in the PANSS Total Score |
| Secondary outcomes (including scoring methods and timings of assessments) | Mean changes in scores from Baseline to Endpoint (Day 42) in the CGAS, CGI-Severity, CGI−Improvement, and PANSS Positive and PANSS Negative Subscales. Time to discontinuation due to all reasons |
| Duration of follow-up | Subjects who completed this study were eligible for an open-label safety study of aripiprazole (Study 31-03-241) for an additional 6 months. For any subject who did not continue on in the open-label study, a follow-up telephone call was made 30 days after the last dose of study medication to assess for any AEs |

Abbreviations: AE; Adverse event; CGAS, Children's Global Assessment Scale; CGI, Clinical Global Impression; IVRS, Interactive voice response system; PANSS, Positive and Negative Syndrome Scale

### 5.3.2 Participants

The inclusion and exclusion criteria for Study 31-03-239 are summarised Table 8.

**Table 8: Eligibility criteria in Study 31-03-239 (13, 18)**

| Inclusion criteria | Exculsion criteria |
|---|---|
| 1) Aged 13-17 years, with a K-SADS-PL confirmed DSM-IV diagnosis of schizophrenia[†]<br>2) PANSS score ≥ 70 at baseline (Day 1)<br>3) Written informed consent from a legally acceptable representative and informed assent at screening from the subject (with the understanding that he/she could withdraw at any time)<br>4) The subject and the designated representative comprehend and can satisfactorily comply with the protocol requirements | 1) Axis I (DSM-IV) diagnosis for schizoaffective disorder, or a current diagnosis of major depressive episode<br>2) Delirium, amnestic or other cognitive disorder, or bipolar disorder; psychotic symptoms better accounted for by another general medical condition or direct psychological effect of a substance (i.e. medication)<br>3) Hospitalised for a current acute episode of schizophrenia ≤ 14 days prior to screening visit<br>4) Mental retardation<br>5) Any neurological disorder (excluding Tourette's Syndrome)<br>6) Unable to comply with the washout of psychotropic medications for their specified period.<br>7) Sexually active males or females who did not agree to abstinence or birth control<br>8) Breast-feeding and/or pregnant<br>9) Subjects who were previously involved in a clinical study involving aripiprazole or were currently being treat with aripiprazole<br>10) Allergy or hypersensitivity to aripiprazole<br>11) Resistant to antipsychotic medication based on prior trials of two different antipsychotics that were of adequate dose and duration<br>12) History of neuroleptic malignant syndrome<br>13) Evidence of suicide risk<br>14) Psychoactive substance use or alcohol use disorder (abuse, dependence, and/or withdrawal) within the past 3 months or use of illegal drugs (excluding marijuana)<br>15) A clinically significant abnormal laboratory test result, vital sign, or ECG finding<br>16) History of uncontrolled diabetes, labile or unstable diabetes (brittle diabetes), newly diagnosed diabetes, clinically significant abnormal blood glucose level at screening, or clinically significant abnormal fasting blood glucose level at baseline<br>17) Epilepsy, history of seizure, severe head trauma or stroke, or any unstable medical conditions; current comorbid systemic illness requiring pharmacotherapy<br>18) The subject participated in any clinical trial with an investigational product within the past month |

[†]Schizophrenia must have been the primary DSM-IV Axis I diagnosis
Abbreviations: ECG, Electrocardiogram; KSADS-PL, Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version; PANSS, Positive and Negative Syndrome Scale

### 5.3.3 Patient characteristics at baseline

Patient characteristics at baseline are summarised in Table 9. The three treatment arms were demographically similar and had similar baseline disease characteristics.

**Table 9: Characteristics of participants in Study 31-03-239 (13, 18)**

| Baseline characteristic | Aripiprazole 10 mg (n = 100) | Aripiprazole 30 mg (n = 102) | Placebo (n = 100) |
|---|---|---|---|
| **Age in years, mean (SD)** | 15.6 (1.3) | 15.4 (1.4) | 15.4 (1.4) |
| **Male, n (%)** | 45/100 (45.0%) | 65/102 (63.7%) | 61/100 (61.0%) |
| **Height in cm, mean (SD)** | 164.0 (10.8) | 167.1 (11.4) | 166.0 (10.0) |
| **Weight in kg, mean (SD)** | 63.5 (19.1) | 64.5 (16.0) | 63.4 (15.6) |
| **Body mass index (BMI), mean (SD)** | 23.5 (6.0) | 23.0 (4.9) | 22.9 (5.3) |
| **Race, n (%)** | | | |
| **Caucasian** | 54 (54.0) | 62 (61.0) | 64 (64.0) |
| **Black** | 17 (17.0) | 11 (11.0) | 6 (6.0) |
| **Asian** | 16 (16.0) | 12 (12.0) | 15 (15.0) |
| **American Indian or Alaska Native** | 0 (0.0) | 0 (0.0) | 1 (1.0) |
| **Other** | 13 (13.0) | 17 (17.0) | 14 (14.0) |
| **PANSS total score, mean (SD)** | 93.6 (15.7) | 94.0 (16.1) | 94.6 (15.6) |
| **CDRS-R suicidal ideations score, mean (SD)** | 1.3 (0.6) | 1.3 (0.6) | 1.3 (0.5) |
| **Treatment given for previous episodes, n (%)** | Yes = 75 (75.0)<br>No = 25 (25.0) | Yes = 75 (74.0)<br>No = 27 (26.0) | Yes = 73 (73.0)<br>No = 27 (27.0) |
| **Used anti-psychotic before study, n (%)** | 53 (53.0) | 47 (46.1) | 46 (46.0) |
| **Atypical anti-psychotic, n (%)** | 44 (44.0) | 36 (35.3) | 43 (43.0) |
| **Typical antipsychotic, n (%)** | 13 (13.0) | 17 (16.7) | 8 (8.0) |

Abbreviations: CDRS-R, Children's Depression Rating Scale – Revised; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation

### 5.3.4 Outcomes

The outcomes investigated in Study 31-03-239 and their relevance to the decision problem are presented in Table 10.

**Table 10: Primary and secondary outcomes of Study 31-03-239 (13, 18)**

| Primary outcome(s) and measures | Secondary outcome(s) and measures | Other outcomes and measures | Reliability/validity/ current use in clinical practice |
|---|---|---|---|
| Mean change from baseline to endpoint (Day 42) in the PANSS total score | • PANSS total score at all visits other than week 6<br>• Mean changes from baseline to endpoint (Day 42) in CGAS score<br>• Changes from baseline score in CGI severity score<br>• CGI-improvement score<br>• Changes from baseline in PANSS positive subscale score<br>• Changes from baseline in PANSS negative subscale score<br>• Time to discontinuation due to all reasons | • The number of hospitalisations for each subject<br>• P-QLES-Q (screening and Day 42) | • PANSS is one of the most common standardised methods used for assessing the effectiveness of schizophrenia medication, and its use in paediatric and adolescent trials is well-documented (22-25)<br>• The CGAS was developed from the Adult Global Assessment Scale to provide global measurement of severity of disturbance in children and adolescents and is a valid and reliable tool for rating a child's general level of functioning. (26)<br>• The CGI is a classic instrument for making global assessments (27) and has been extensively used in clinical trials for schizophrenia (28, 29)<br>• The P-QLES-Q is a reliable and valid instrument for the assessment of quality of life in children and adolescents (30) |

Abbreviations: CGAS, Children's Global Assessment Scale; CGI, Clinical Global Impression; PANSS, Positive and Negative Syndrome Scale; P-QLES-Q, Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire

### 5.3.5 Statistical analysis and definition of study groups

**Table 11: Summary of statistical analyses in Study 31-03-239 (13, 18)**

| Trial no. (acronym) | Hypothesis objective | Statistical analysis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|---|
| **Study 31-03-239** | Null hypothesis for the primary efficacy analysis: no difference between aripiprazole treatment (at either dose) and placebo based on change from baseline to study end point in the PANSS Total Score. | The change from baseline PANSS scores (LOCF) were analysed using an ANCOVA model with treatment and region as factors, and baseline PANSS total score as covariate.<br>For the baseline PANSS total score, only treatment and region were included in the ANOVA model.<br>The LS means obtained from the type III analysis using Statistical Analysis System were used for the treatment comparisons.<br>Two-tailed student's t-tests were used to test the difference between LS means within the ANCOVA or ANOVA model.<br>A nominal overall significance level of 0.05 (two-tailed) was used in testing statistical significance of these two comparisons. Hochberg's procedure was used to account for multiplicity, as follows: If both p-values < 0.05 (two-tailed) = statistical significant for both doses. If the larger of the two p-values was > 0.05, the smaller p-value was compared with 0.025 (two-tailed) and the corresponding treatment comparison was declared statistically significant if this p-value was < 0.025.<br>All secondary efficacy variables were analysed similarly to the primary efficacy analysis with the exception of;<br>Assessment of CGI-improvement score - analysed for Weeks 1 through 6 using the CMH method stratified by region based on raw mean score statistics.<br>Time to discontinuation due to all reasons - analysed by plotting the Kaplan-Meier curves and testing for significance of the differences in survival curves using the log-rank test. | The study was designed to have a 85% statistical power to detect a difference of -11.4 between aripiprazole and placebo for the change from baseline in PANSS total score (which was equivalent to the median of the mean differences seen in the adult aripiprazole studies for schizophrenia).<br>A total of 255 randomised subjects (85 subjects per treatment arm) were required for 85% power using a two-sided alpha of 0.025. The study involved 302 patients, all of whom were analysed for efficacy and safety. | In order to handle missing data and restrictions imposed by different types of analyses, other ITT-derived data sets were used for the efficacy analyses (e.g. OC and LOCF datasets). For change from baseline analysis, only subjects who had both baseline and post-baseline values were included in the OC and LOCF data sets. LOCF data sets were the primary analysis data sets. |

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CMH, Cochran-Mantel-Haenszel; LOCF, last observation carried forward (missing data at a post-baseline visit was imputed with the value obtained at the nearest preceding visit, except that baseline values were not carried forward to impute missing values at a post-baseline visit); LS, least squares; OC, observed cases (all subjects who were evaluated at that visit on the efficacy variable under analysis, subjects with missing data due to dropout or other reasons were not included).

**5.3.6** Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

A post-hoc subgroup analysis of adolescents aged 15-17 years in study 31-03-239 was performed to assess the similarity between this group and adults with schizophrenia treated with aripiprazole as part of the marketing authorisation process. A cut-off age of 15 years was used to segment the 15-17 year old cohort from the younger adolescent cohort (aged 13-14) in the aripiprazole clinical study.

The key points to emerge from this analysis were:

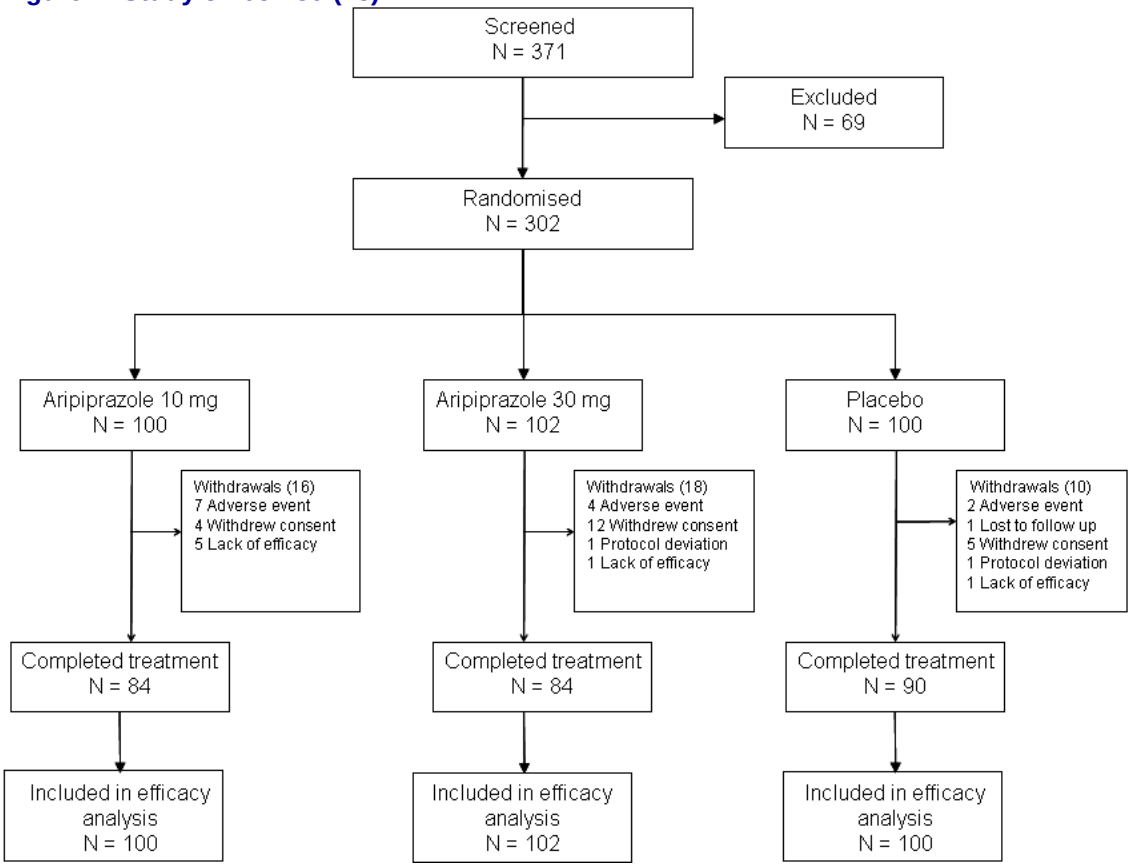
- Comparable efficacy improvements were demonstrated in the adolescent 15-17 year subgroup and in the overall adolescent dataset for aripiprazole.
- Maintenance of effect was observed in adolescent patients with schizophrenia aged 15-17 years.
- Similar safety and tolerability was observed in adolescent and adult patients.

No similar analyses have been done for other antipsychotics. Therefore certain similarities between adolescents and adults found in relation to treatment of schizophrenia with aripiprazole cannot be assumed to apply across the class.

### 5.3.7 Participant flow

A CONSORT flow chart showing the number of patients who were eligible to enter Study 31-03-239, (13, 18) and were randomised and allocated to each treatment is presented below in Fig 2.

**Figure 2: Study 31-03-239 (18)**




## *5.4 Critical appraisal of relevant RCTs*

A critical appraisal of study 31-03-239 is provided in Section 9.3, Appendix 3

## *5.5 Results of the relevant RCTs*

### Study 31-03-239 Efficacy Results (13, 18)

**Summary**

- Aripiprazole significantly improved the core symptoms of schizophrenia as early as week 1, as measured by the PANSS total score.
- Significant improvements were seen with both 10 mg and 30 mg doses of aripiprazole in overall social and psychological functioning, as shown by the assessment scales CGI and CGAS.
- Aripiprazole significantly improved the negative symptoms of schizophrenia, such as lack of motivation, self neglect and social withdrawal; such symptoms have been identified as distinctive features of adolescent schizophrenia.

**Datasets analysed**

All subjects having a baseline and a post-baseline efficacy measurement were included in a "change from baseline" analysis, and all subjects having a post-baseline measurement were included in CGI-I analysis based only on post-baseline measurements. Subjects were included in the safety analysis if they received at least one dose of study medication.

**Primary Efficacy Results**

**PANSS total score at week 6 (Day 42) (LOCF) (13, 18)**

**Key Findings**

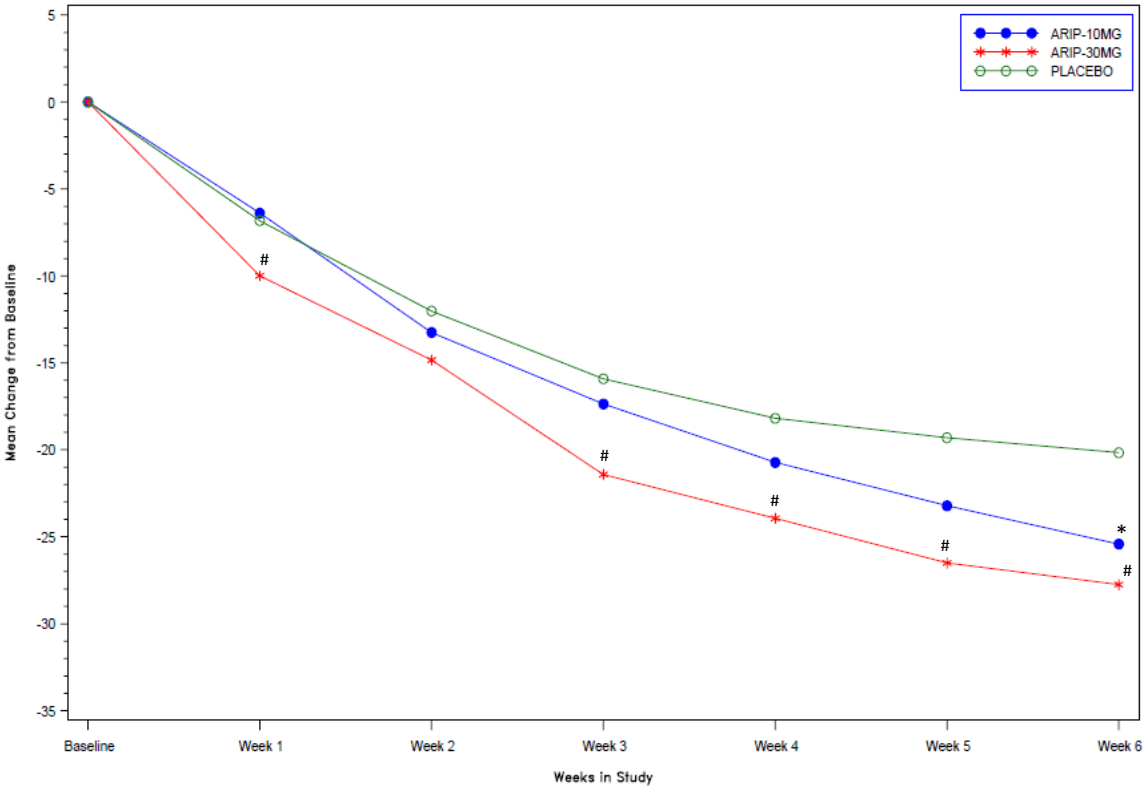
- Early appropriate treatment of schizophrenia is vital to prevent progressive illness.
- Core symptoms, including both positive and negative symptoms of schizophrenia are measured using the PANSS total score with reductions in score indicating improvement of symptoms.
- Patients on both the 10mg and 30mg doses of aripiprazole showed significant improvements in PANSS total score over 6 weeks of treatment.

**Table 12: Mean change from baseline in PANSS total score by week (LOCF) in study 31-03-239 (18)**

| Visit/ week | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Placebo | | Aripiprazole 10 mg versus placebo | Aripiprazole 30 mg versus placebo |
|---|---|---|---|---|---|---|---|---|
| | n | LS mean[†] | n | LS mean[†] | n | LS mean† | P-value[‡] | P-value[‡] |
| Baseline[§] | 99 | 93.7 | 97 | 94.9 | 98 | 95.0 | 0.5375 | 0.9372 |
| Week 1 | 98 | [redacted] | 95 | -10.4 | 97 | -7.2 | [redacted] | 0.0465 |
| Week 2 | 99 | [redacted] | 97 | [redacted] | 98 | -12.5 | [redacted] | [redacted] |
| Week 3 | 99 | [redacted] | 97 | -22.1 | 98 | -16.7 | [redacted] | 0.0269 |
| Week 4 | 99 | [redacted] | 97 | -24.6 | 98 | -19.0 | [redacted] | 0.0181 |
| Week 5 | 99 | [redacted] | 97 | -27.3 | 98 | -20.3 | [redacted] | 0.0057 |
| **Week 6 (Primary endpoint)** | **99** | **-26.7** | **97** | **-28.6** | **98** | **-21.2** | **0.0414** | **0.0061** |

[†]Adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata, a negative LS mean indicated improvement; [‡]Derived from Student's t tests on estimates of treatment comparisons which were based on LS means; [§]For baseline N and mean are provided

**Figure 3: Mean change from baseline in PANSS total score by week (LOCF) in study 31-03-239 (18)**




* P < 0.05 for aripiprazole 10 mg vs placebo; # P < 0.05 for 30 mg aripiprazole vs placebo

Treatment with both doses of aripiprazole resulted in significantly greater improvements than placebo between baseline and the end of treatment on the PANSS total score, with significance shown as early as week 1.

## Secondary Efficacy Results

**Key Findings**

- Significant improvements in the core symptoms of schizophrenia were seen as early as week 1 of aripiprazole treatment, as measured by the PANSS total score.
- Positive symptoms, such as hallucinations and delusions, can be particularly devastating for patients. Significant improvements were seen in these positive symptoms from week 1 through to week 6 of aripiprazole treatment, as measured by the PANSS positive score.
- Negative symptoms, such as lack of motivation, self neglect and social withdrawal are distinctive features of adolescent schizophrenia. Treatment with aripiprazole showed significant improvement in these negative symptoms within 6 weeks of aripiprazole treatment, as measured by the PANSS negative score.
- Holistic assessments of patients' social and psychological functioning are measured using CGAS and CGI. Improvements in these assessments are likely to support successful independence in society. Aripiprazole demonstrated significant improvements in both the CGAS and CGI scales demonstrating that a patients' wellbeing improved with aripiprazole treatment.
- Importantly, there were no significant differences in the 'time to discontinuation', between aripiprazole doses and placebo. Treatment discontinuation is recognised as a frequent occurrence in this patient population, which can be a major problem in treating schizophrenia (7).

### PANSS total score at all visits (18)

Improvements in the change from baseline in PANSS total score were reported for the aripiprazole 10 mg group versus the placebo arm at all visits; the improvements were only statistically significant compared with placebo at Week 6 (as shown previously in Table 12 and Figure 3) (18).

However, a statistically significant improvement was observed with aripiprazole 30 mg versus placebo in the change from baseline in PANSS total score at Weeks 1, 3, 4, 5 and 6 (see Table 12) (18).

### Mean changes in scores from baseline to endpoint (Day 42) in the Children's Global Assessment Scale (CGAS) (LOCF) (18)

For the change from baseline in CGAS score, a positive LS mean indicated improvement.

A statistically significant improvement in change from baseline in CGAS score was reported for both doses of aripiprazole versus placebo at the study endpoint (Week 6/Day 42) (Table 13) (18).

**Table 13: Mean change from baseline in CGAS score (LOCF) in study 31-03-239 (18)**

| Visit/ week | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Placebo | | Aripiprazole 10 mg versus placebo | Aripiprazole 30 mg versus placebo |
|---|---|---|---|---|---|---|---|---|
| | n | LS mean[†] | n | LS mean[†] | n | LS mean[†] | P-value[‡] | P-value[‡] |
| Baseline[§] | 97 | 46.7 | 94 | 45.6 | 98 | 45.4 | 0.4278 | 0.8667 |
| **Week 6 (Primary endpoint)** | **97** | **14.7** | **94** | **14.8** | **98** | **9.8** | **0.0054** | **0.0044** |

[†]Adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata, a positive LS mean indicated improvement; [‡]Derived from Student's t tests on estimates of treatment comparisons which were based on LS means; [§]For baseline N and mean are provided

## Change from baseline in Clinical Global Impression (CGI) severity score (LOCF) (13, 18)

For the change from baseline in CGI-severity score, a negative LS mean indicated improvement (18).

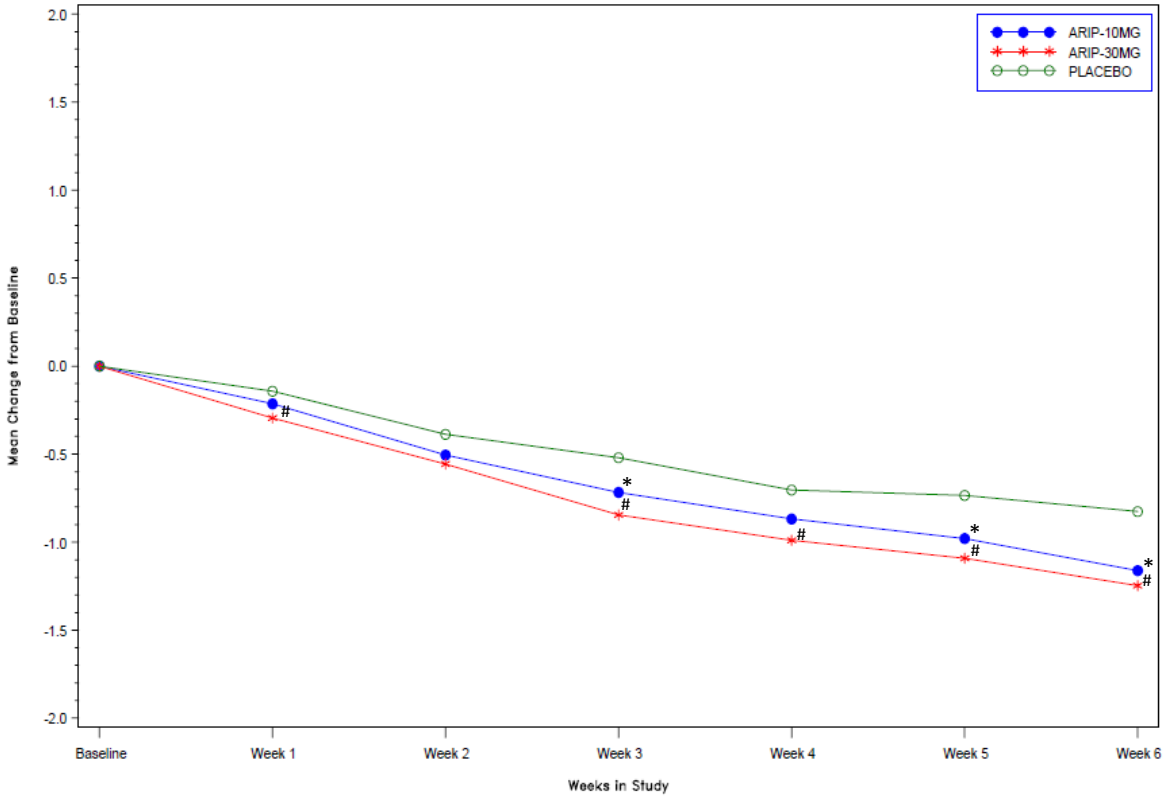
The CGI severity score improved from "moderately"/"markedly" ill at baseline to "mildly"/moderately" ill at the primary endpoint in all treatment groups (13). Statistically significant improvements from baseline in CGI severity score were reported in the aripiprazole 10 mg group versus placebo arm at Weeks 3, 5 and 6. (Table 14) (14) Similarly, a statistically significant improvement in the CGI severity score was reported with aripiprazole 30 mg versus placebo at Weeks 1, 3, 4, 5 and 6. (Table 14) (18).

**Table 14: Mean change from baseline in CGI severity score by week (LOCF) in study 31-03-239 (18)**

| Visit/ Week | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Placebo | | Aripiprazole 10 mg versus placebo | Aripiprazole 30 mg versus placebo |
|---|---|---|---|---|---|---|---|---|
| | n | LS mean[†] | n | LS mean[†] | n | LS mean[†] | P-value[‡] | P-value[‡] |
| Baseline[§] | 99 | 4.5 | 97 | 4.6 | 98 | 4.6 | 0.2381 | 0.5990 |
| Week 1 | 98 | [redacted] | 95 | -0.3 | 98 | -0.2 | [redacted] | 0.0210 |
| Week 2 | 99 | [redacted] | 97 | [redacted] | 98 | -0.4 | [redacted] | [redacted] |
| Week 3 | 99 | -0.8 | 97 | -0.9 | 98 | -0.6 | 0.0399 | 0.0023 |
| Week 4 | 99 | [redacted] | 97 | -1.0 | 98 | -0.8 | [redacted] | 0.0158 |
| Week 5 | 99 | -1.1 | 97 | -1.1 | 98 | -0.8 | 0.0252 | 0.0031 |
| **Week 6 (Primary endpoint)** | **99** | **-1.2** | **97** | **-1.3** | **98** | **-0.9** | **0.0071** | **0.0016** |

[†]Adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata, a negative LS mean indicated improvement; [‡]Derived from Student's t tests on estimates of treatment comparisons which were based on LS means; [§]For baseline N and mean are provided

**Figure 4: Mean change from baseline in CGI-severity score by week (LOCF) in study 31-03-239 (18)**




* P < 0.05 for aripiprazole 10 mg vs placebo; # P < 0.05 for 30 mg aripiprazole vs placebo

## Change from baseline in CGI improvement score (13, 18)

For the CGI-improvement, a lesser mean score indicated improvement (18).

During the course of the study, CGI improvement scores progressively improved from baseline (13) with statistically significant improvements reported for aripiprazole 10 mg versus placebo at Weeks 1, 5 and 6. (18) (Table 15).

The CGI-improvement score was significantly improved compared with placebo for the aripiprazole 30 mg arm at Weeks 1,3,4,5 and 6 (18).

**Table 15: Mean change from baseline in CGI improvement score by week (LOCF) in study 31-03-239 (18)**

| Visit/ week | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Placebo | | Aripiprazole 10 mg versus placebo | Aripiprazole 30 mg versus placebo |
|---|---|---|---|---|---|---|---|---|
| | n | Mean† | n | Mean† | n | Mean† | P-value‡ | P-value‡ |
| Week 1 | 98 | 3.6 | 95 | 3.4 | 98 | 3.8 | 0.0175 | 0.0013 |
| Week 2 | 99 | [redacted] | 97 | [redacted] | 98 | 3.4 | [redacted] | [redacted] |
| Week 3 | 99 | [redacted] | 97 | 2.8 | 98 | 3.2 | [redacted] | 0.0044 |
| Week 4 | 99 | [redacted] | 97 | 2.7 | 98 | 3.2 | [redacted] | 0.0033 |
| Week 5 | 99 | 2.8 | 97 | 2.6 | 98 | 3.2 | 0.0239 | 0.0002 |
| **Week 6 (Primary endpoint)** | **99** | **2.7** | **97** | **2.5** | **98** | **3.1** | **0.0167** | **0.0004** |

†A lesser mean indicated improvement; ‡Derived from CMH method stratified by region

## Change from baseline in PANSS positive subscale score (13, 18)

For the change from baseline in PANSS positive subscale score, a negative LS mean indicated improvement.

The PANSS positive subscale score was improved from baseline in both aripiprazole treatment arms when compared with the placebo group at all time points (Table 16 and Figure 5) (13, 18).

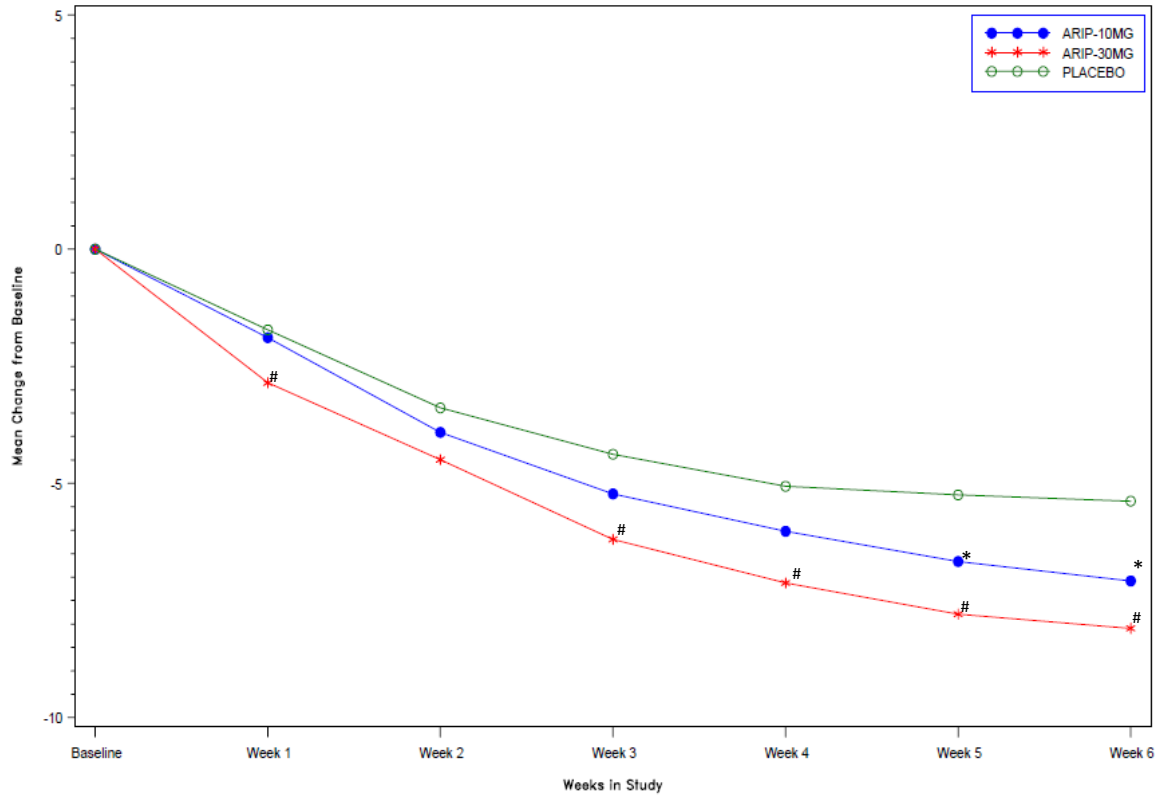
The improvements were statistically significant versus placebo for the aripiprazole 10 mg group at Weeks 5 and 6 and for the aripiprazole 30 mg arm at Weeks 1,3,4,5 and 6 (Table 16 and Figure 5).

**Table 16: Mean change from baseline in PANSS positive subscale score by week (LOCF) in study 31-03-239 (18)**

| Visit/ week | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Placebo | | Aripiprazole 10 mg versus placebo | Aripiprazole 30 mg versus placebo |
|---|---|---|---|---|---|---|---|---|
| | n | LS mean[†] | n | LS mean[†] | n | LS mean[†] | P-value[‡] | P-value[‡] |
| Baseline[§] | 99 | 22.1 | 97 | 23.5 | 98 | 22.9 | 0.2548 | 0.4602 |
| Week 1 | 98 | [redacted] | 95 | -2.9 | 97 | -1.8 | [redacted] | 0.0256 |
| Week 2 | 99 | [redacted] | 97 | [redacted] | 98 | -3.6 | [redacted] | [redacted] |
| Week 3 | 99 | [redacted] | 97 | -6.2 | 98 | -4.6 | [redacted] | 0.0270 |
| Week 4 | 99 | [redacted] | 97 | -7.1 | 98 | -5.3 | [redacted] | 0.0118 |
| Week 5 | 99 | -7.2 | 97 | -7.8 | 98 | -5.6 | 0.0276 | 0.0029 |
| **Week 6 (Primary endpoint)** | **99** | **-7.6** | **97** | **-8.1** | **98** | **-5.6** | **0.0134** | **0.0018** |

[†]Adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata, a negative LS mean indicated improvement; [‡]Derived from Student's t tests on estimates of treatment comparisons which were based on LS means; [§]For baseline N and mean are provided. Maximum positive score = 49

**Figure 5: Mean change from baseline in PANSS positive subscale score by week (LOCF) in study 31-03-239 (18)**




* P < 0.05 for aripiprazole 10 mg vs placebo; # P < 0.05 for 30 mg aripiprazole vs placebo

### Change from baseline in PANSS negative subscale score (13, 18)

For the change from baseline in PANSS negative subscale score, a negative LS mean indicated improvement.

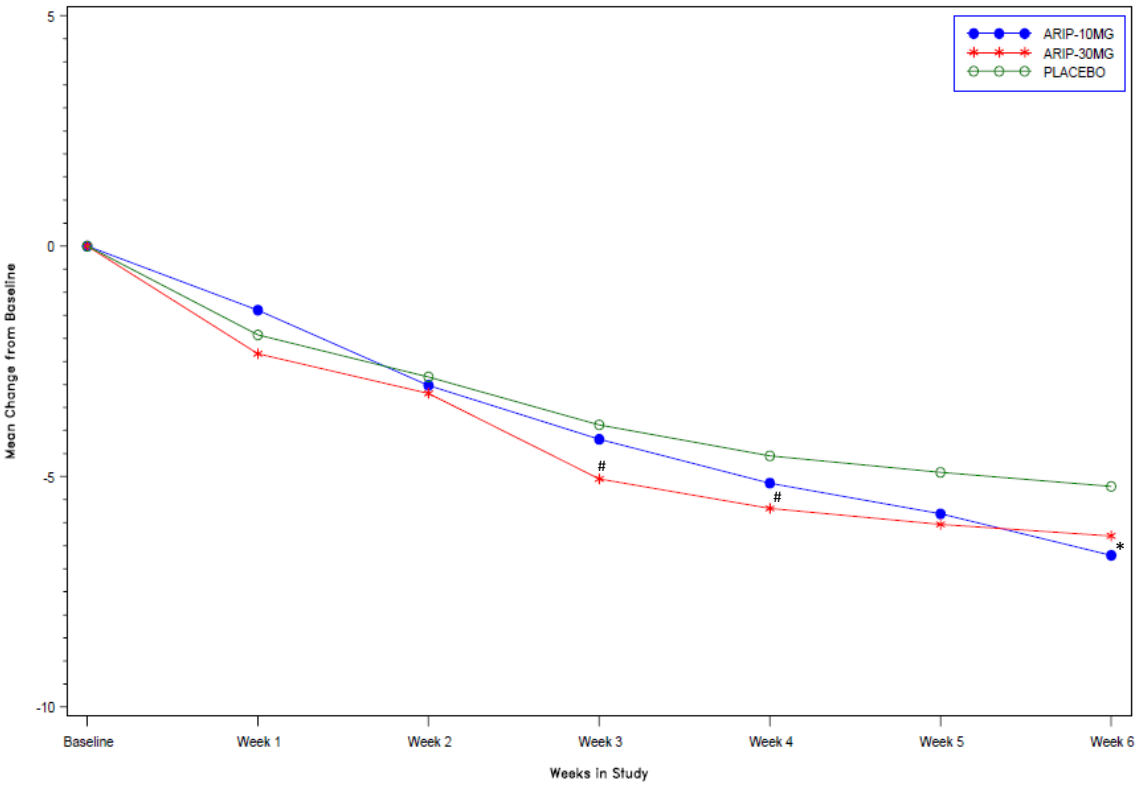
Statistically significant improvements in the mean change from baseline in PANSS negative subscale score versus placebo were demonstrated for aripiprazole 10 mg at the study endpoint (Week 6): and for aripiprazole 30 mg at Weeks 3 and 4 (Table 17 and Figure 6) (18).

**Table 17: Mean change from baseline in PANSS negative subscale score by week (LOCF) in study 31-03-239 (18)**

| Visit/ week | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Placebo | | Aripiprazole 10 mg versus placebo | Aripiprazole 30 mg versus placebo |
|---|---|---|---|---|---|---|---|---|
| | n | LS mean[†] | n | LS mean[†] | n | LS mean[†] | P-value[‡] | P-value[‡] |
| Baseline[§] | 99 | 25.4 | 97 | 24.9 | 98 | 25.6 | 0.7881 | 0.3984 |
| Week 1 | 98 | [redacted] | 95 | [redacted] | 97 | -2.0 | [redacted] | [redacted] |
| Week 2 | 99 | [redacted] | 97 | [redacted] | 98 | -2.9 | [redacted] | [redacted] |
| Week 3 | 99 | [redacted] | 97 | -5.4 | 98 | -4.0 | [redacted] | 0.0410 |
| Week 4 | 99 | [redacted] | 97 | -6.0 | 98 | -4.6 | [redacted] | 0.0427 |
| Week 5 | 99 | [redacted] | 97 | [redacted] | 98 | -5.0 | [redacted] | [redacted] |
| **Week 6 (Primary endpoint)** | **99** | **-6.9** | **97** | **-6.6** | **98** | **-5.4** | **0.0462** | **0.0972** |

[†]Adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata, a negative LS mean indicated improvement; [‡]Derived from Student's t tests on estimates of treatment comparisons which were based on LS means; [§]For baseline N and mean are provided. Maximum positive score = 49

**Figure 6: Mean change from baseline in PANSS negative subscale score by week (LOCF) in study 31-03-239 (18)**




* P < 0.05 for aripiprazole 10 mg vs placebo; # P < 0.05 for 30 mg aripiprazole vs placebo

**Time to discontinuation due to all reasons (18)**

There were no statistically significant differences between any of the treatment groups for time to discontinuation due to all reasons.

## Further Efficacy Results

**Summary**

- It is important to evaluate QoL alongside measures of symptom severity when determining treatment effectiveness. The Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) is a paediatric specific assessment of QoL.
- Both aripiprazole groups demonstrated significant improvements at the end of the study on the P-QLES-Q overall score. The overall score is a combined value for all the aripiprazole patients compared with all of those treated with placebo.
- Numerical improvements were seen in both aripiprazole groups compared with placebo on the P-QLES-Q total score.

### Change from baseline in Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q) total score (LOCF) (13, 18)

Improvements were observed in all three treatment arms, however no statistically significant improvements from baseline were observed between either of the aripiprazole treatment arms and the placebo group for the P-QLES-Q total score (Table 18) (13, 18).

**Table 18: Mean change from baseline to week 6 in P-QLES-Q total score (LOCF) in Study 31-03-239 (18)**

| Visit/ week | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Placebo | | Aripiprazole 10 mg versus placebo | Aripiprazole 30 mg versus placebo |
|---|---|---|---|---|---|---|---|---|
| | n | LS mean[†] | n | LS mean[†] | n | LS mean[†] | P-value[‡] | P-value[‡] |
| Baseline[§] | 95 | 43.9 | 87 | 44.3 | 89 | 44.3 | 0.9068 | 0.8115 |
| **Week 6 (Primary endpoint)** | **95** | **5.2** | **87** | **5.9** | **89** | **4.5** | **0.5466** | **0.2522** |

[†]Adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata, a positive LS mean indicated improvement; [‡]Derived from Student's t tests on estimates of treatment comparisons which were based on LS means; [§]For baseline N and mean are provided

### Change from baseline in P-QLES-Q overall score (LOCF)

Baseline scores were statistically significantly higher in the placebo arm when compared with the aripiprazole 10 mg arm (p = 0.0477). At the study endpoint (Week 6/Day 42), statistically significant improvements compared with placebo were observed in both aripiprazole dose groups (Table 19).

**Table 19: Mean change from baseline to Week 6 in P-QLES-Q overall score (LOCF) in Study 31-03-239 (18)**

| Visit/ week | Aripiprazole 10 mg | | Aripiprazole 30 mg | | Placebo | | Aripiprazole 10 mg versus placebo | Aripiprazole 30 mg versus placebo |
|---|---|---|---|---|---|---|---|---|
| | n | LS mean[†] | n | LS mean[†] | n | LS mean[†] | P-value[‡] | P-value[‡] |
| Baseline[§] | 96 | 3.2 | 91 | 3.3 | 92 | 3.4 | 0.0477 | 0.2617 |
| **Week 6 (Primary endpoint)** | **96** | **0.6** | **91** | **0.6** | **92** | **0.1** | **0.0045** | **0.0030** |

[†]A positive mean change indicated improvement; [‡]derived from CMH method stratified by region

## Hospitalisations due to worsening of schizophrenia (18)

The design of the study allowed patients to start the study as either inpatients or outpatients. /**********(18).

## *5.6 Meta-analysis*

**5.6.1** The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

A meta-analysis was inappropriate as only one aripiprazole RCT was identified (13, 18).

**5.6.2** If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

N/A.

**5.6.3** If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

N/A.

## *5.7 Indirect and mixed treatment comparisons*

**5.7.1** Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

Please see section 5.2 for the methods used to identify trials for use in the indirect comparison.

The search strategies detailed in Section 5.2 were designed to identify trials (either head to head or those that could be used in indirect comparisons if no head to head trials were identified). Sections 5.2.1 and 5.2.2 have outlined the criteria used to identify studies in adolescent patients with schizophrenia.

The systematic review did not identify any head to head RCTs of aripiprazole and other treatments for adolescent schizophrenia. Therefore, an indirect comparison was necessary.

For the purposes of indirect comparison with comparator interventions, two studies were eligible for analysis (one study comparing aripiprazole versus placebo and one study comparing olanzapine versus placebo in adolescent patients with schizophrenia (12, 13). The clinical study report for aripiprazole was also used to extract data for the indirect comparison (18).

Studies were excluded if they were not suitable for indirect comparison as they either did not include a placebo group (14-16) or did not contain sufficient data for comparison (e.g. an abstract (11)).

**5.7.2** Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Please see section 5.2 for the methods used to identify trials for use in the indirect comparison.

**5.7.3** Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

**Table 20: Summary of the trials used to conduct the indirect comparison**

| No. trials | References of trials | Aripiprazole 10mg | Olanzapine flexible dose | Placebo |
|---|---|---|---|---|
| 1 | Findling et al (2008) (13)<br><br>Study 31-03-239 (18) | ✓ | | ✓ |
| 1 | Kryzhanovskaya et al (2009) (12) | | ✓ | ✓ |
| Adapted from Caldwell et al. (2005) Simultaneous comparison of multiple treatments combining direct and indirect evidence. BMJ 331: 897–900 | | | | |

**5.7.4** For the selected trials, provide a summary of the data used in the analysis.

Indirect comparisons were conducted to estimate the relative effect of aripiprazole and olanzapine versus placebo for use in the economic model (either for use in base case or sensitivity analysis) for a total of six outcome measures. The outcome measures investigated were:

1. Withdrawals due to adverse events (base case)
2. Withdrawals due to lack of efficacy (base case)
3. Withdrawals due to other reasons (base case)
4. Significant weight increase from baseline of ≥ 7% (base case)

5. Somnolence (base case)
6. Participants received benzodiazepines (sensitivity analysis)

A summary of the data used from Findling et al (2008) (13) and Study 31-03-239 (18) for aripiprazole and Kryzhanovskaya et al (2009) (12) for olanzapine are provided in Table 21 and Table 22. For patients receiving benzodiazepines, the CSR for aripiprazole lists the psycholeptic treatments that patients received during the trial. From this list, the number of patients receiving treatments classed as benzodiazepines were extracted and used in the indirect comparison to provide a proxy for extrapyrimidal symptoms which could be compared with olanzapine in sensitivity analyses.

**Table 21: Data used in the analyses for aripiprazole (10mgs)**

| | **Aripiprazole (10mg) (N=100*)** | **Placebo (N=100*)** |
|---|---|---|
| **Dichotomous outcome measures** | Number of patients with event n (%) | Number of patients with event n (%) |
| Withdrawals due to adverse events | 7 (7%) | 2 (2%) |
| Withdrawals due to lack of efficacy | [redacted] | [redacted] |
| Withdrawals due to other reasons | [redacted] | [redacted] |
| Significant weight increase from baseline of ≥ 7%* | [redacted] | [redacted] |
| Somnolence | 11 (11%) | 6 (6%) |
| Participants received benzodiazepines | [redacted] | [redacted] |

* aripiprazole N=84, placebo N = 89

**Table 22: Data used in the analyses for olanzapine (flexible dosing)**

| | **Olanzapine (flexible dosing) (N=72)** | **Placebo (N=35)** |
|---|---|---|
| **Dichotomous outcome measures** | Number of patients with event n (%) | Number of patients with event n (%) |
| Withdrawals due to adverse events | 5 (7%) | 0 (0%) |
| Withdrawals due to lack of efficacy | 10 (14%) | 18 (51%) |
| Withdrawals due to other reasons | 8 (11%) | 2 (6%) |
| Significant weight increase from baseline of ≥ 7% | 33 (46%) | 5 (14%) |
| Somnolence | 17 (24%) | 1 (3%) |
| Participants received benzodiazepines | 21 (29%) | 18 (51%) |

**5.7.5** Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

## Dichotomous data

For dichotomous data, both odds ratios (ORs) and relative risks (RRs) can be used to compare outcomes between the treatments and were therefore estimated as a measure of

treatment effect. The results for dichotomous data can be presented in a 2x2 table (see Table 23). This table presents the numbers of participants who do or do not experience an event in each of the groups (here called experimental and control).

**Table 23: Study data**

| | Event | No Event | Total |
|---|---|---|---|
| Experimental group | $S_E$ | $F_E$ | $N_E$ |
| Control group | $S_C$ | $F_C$ | $N_C$ |

The OR can be calculated from the following equation (31) $OR = \frac{S_E/F_E}{S_C/F_C}$ with the standard error of the log odds ratio being: $\mathrm{SE}\{\ln(\mathrm{OR})\} = \sqrt{\frac{1}{S_E}+\frac{1}{F_E}+\frac{1}{S_C}+\frac{1}{F_C}}$

Similarly the RR can be calculated from (31) $RR = \frac{S_E/N_E}{S_C/N_C}$ with the standard error of the log risk ratio being $\mathrm{SE}\{\ln(\mathrm{RR})\} = \sqrt{\frac{1}{S_E}+\frac{1}{S_C}-\frac{1}{N_E}-\frac{1}{N_C}}$

In the case where there are no events in the control group ½ was added to each cell of the 2x2 table given above for the analysis (32).

**5.7.6** Please present the results of the analysis.

Results of the indirect comparisons for the six outcome measures considered are presented in Table 24 as ORs and RRs used in the base case economic analysis.

**Table 24: Results of indirect comparisons - olanzapine vs aripiprazole 10 mg**

| Comparison | OR (95% CI) | RR (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 due to other reasons | 3.73 (0.48, 28.70) | 3.40 (0.50, 23.11) |
| Significant weight increase from baseline of ≥ 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) |
| Patients received benzodiazepines | 0.39 (0.14, 1.08) | 0.57 (0.30, 1.06) |

**5.7.7** Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

The treatment groups in the aripiprazole study (13, 18) and the olanzapine study (12) were generally well matched for demographic and baseline characteristics. The average age of patients in Findling et al (2008) (13) was 15.4 in the placebo arm and 15.6 in the aripiprazole 10 mg arm, compared with an average age of 16.3 in the placebo arm and 16.1 in the olanzapine arm in the Kryzhanovskaya et al (2009) study (12). Both studies recorded outcomes at 6 weeks and measured outcomes in a similar way. We assumed that the

similarity of the trials included in the indirect comparison avoids bias in the estimates of the indirect comparison (33).

**5.7.8** If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

N/A.

**5.7.9** Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

No pairwise comparisons were conducted. In addition, inconsistency checks between direct and indirect evidence were not possible as direct evidence for aripiprazole compared with olanzapine was not available.

## *5.8 Non-RCT evidence*

Non-RCT evidence was identified through the “master” clinical search described previously (see Section 5.2). In total, 152 records were identified and further reviewed for aripiprazole studies using “aripiprazole” and “Abilify” keyword searches. After assessment of the title and abstract, 4 records were identified as being potentially relevant. Upon examination of the full text, 3/4 records were excluded as they included only adult patients. One study remained, a Phase II tolerability and pharmacokinetic study (34), which was conducted in adolescent patients. However, as this was a Phase II tolerability and pharmacokinetic study and included only 21 patients it was not considered relevant to this appraisal.

Further non-RCT evidence (two phase III trials) was identified from manufacturer sources. Studies 31-03-241 and 31-05-243 were designed primarily to assess safety outcomes; consequently the methodology and safety results are presented in Section 5.9. Secondary outcome measures in these trials included efficacy variables that are relevant to this appraisal and therefore the efficacy results from Studies 31-03-241 and 31-05-243 are presented within this section.

## Non-RCT efficacy results

**Summary**

- Patients on aripiprazole improved quickly, and this efficacy was maintained over 6 months of treatment.
- The greatest improvements in schizophrenia symptoms observed in the extension study were seen in patients who were switched from placebo to aripiprazole.
- In those patients receiving aripiprazole, improvements in QoL were maintained for up to 1 year. These improvements are likely to support an adolescent's independent functioning and social inclusion.

### Study 31-03-241

Study 31-03-241 included adolescent subjects with schizophrenia and child and adolescent subjects with bipolar I disorder. Results are presented only for the sub-population of patients with schizophrenia, as the bipolar I sub-population is not relevant to this appraisal.

Overall, the greatest improvement in efficacy parameters was seen in those subjects who received placebo in the parent study and were switched to aripiprazole. Efficacy was maintained in those subjects who received aripiprazole in the parent study and continued to receive aripiprazole in Study 31-03-241 (Table 25).

**Table 25: Efficacy results: study 31-03-241 (schizophrenia adolescent subpopulation)**

| Mean changes from baseline (or mean) in efficacy parameters at the last visit | | | | |
|---|---|---|---|---|
| | Treatment in parent study (31-03-239) | | | All patients |
| Parameter, time point | Aripiprazole 10mg | Aripiprazole 30mg | Placebo | |
| PANSS Total Score | | | | |
| N | 80 | 77 | 77 | 234 |
| Baseline | [redacted] | [redacted] | [redacted] | [redacted] |
| Change at Last visit | -5.23 | -6.21 | -10.71 | -7.35 |
| CGI Severity Score | | | | |
| N | 80 | 78 | 79 | 237 |
| Baseline | [redacted] | [redacted] | [redacted] | [redacted] |
| Change at Last visit | -0.38 | -0.45 | -0.70 | -0.51 |
| CGI Improvement Score (mean) | | | | |
| N | 80 | 78 | 79 | 237 |
| Last Visit | 2.26 | 2.38 | 2.53 | 2.39 |
| PANSS Positive Subscale Score | | | | |
| N | 80 | 77 | 77 | 234 |
| Baseline | [redacted] | [redacted] | [redacted] | [redacted] |
| Change at Last visit | -1.61 | -1.87 | -2.91 | -2.12 |
| PANSS Negative Subscale Score | | | | |
| N | 80 | 77 | 77 | 234 |
| Baseline | [redacted] | [redacted] | [redacted] | [redacted] |
| Change at Last visit | -1.33 | -1.70 | -3.03 | -2.01 |
| CGAS | | | | |
| N | 80 | 77 | 77 | 234 |
| Baseline | [redacted] | [redacted] | [redacted] | [redacted] |

| Mean changes from baseline (or mean) in efficacy parameters at the last visit | | | | |
|---|---|---|---|---|
| | Treatment in parent study (31-03-239) | | | All patients |
| Parameter, time point | Aripiprazole 10mg | Aripiprazole 30mg | Placebo | |
| Change at Last visit | 6.86 | 6.97 | 8.90 | 7.57 |
| CDRS-R | | | | |
| N | 63 | 65 | 65 | 193 |
| Baseline | [redacted] | [redacted] | [redacted] | [redacted] |
| Change at Last visit | -1.62 | -2.83 | -5.49 | -3.33 |

Abbreviations: CDRS-R, Children's Depression Rating Scale, Revised; CGAS, Children's Global Assessment Scale; CGI, Clinical Global Impression; PANSS, Positive and Negative Syndrome Scale

## Study 31-05-243 efficacy results

Mean scores for CGI-Severity ranged from 2.26 at Month 3 to 1.67 at Month 12. These values represented decreases from baseline at each time point evaluated indicating an improvement. Efficacy with aripiprazole treatment was maintained. The analysis of the last visit which included data from subjects who discontinued prematurely also showed maintenance of efficacy (Table 26).

Summary P-QLES-Q data from the last visit which included ongoing and withdrawn subjects showed little change from baseline. The overall rating of 3.82 on the P-QLES-Q indicated that, on average, the subjects' quality of life, enjoyment, and satisfaction were better than fair and approaching good at the last visit (Table 26).

**Table 26: Mean change in efficacy (CGI-S score) and other outcome variables (P-QLES-Q Total and Overall scores) between baseline and last study visit- observed cases**

| Parameter | N | Baseline mean | Last visit mean | Mean change from baseline | Standard deviation |
|---|---|---|---|---|---|
| CGI-S | 84 | [redacted] | [redacted] | [redacted] | [redacted] |
| P-QLES-Q Total | 68 | [redacted] | [redacted] | [redacted] | [redacted] |
| P-QLES-Q Overall | 71 | [redacted] | 3.82 | [redacted] | [redacted] |

Abbreviations: CGI, Clinical Global Impression; P-QLES-Q, Paediatric Quality of Life and Enjoyment and Satisfaction Questionnaire

## *5.9 Adverse events*

**Summary of clinical safety**

- Aripiprazole was generally well tolerated in the adolescent population, with most AEs being mild or moderate in severity.
- Few patients dropped out of the studies due to the side effects associated with their treatment.
- Aripiprazole was associated with a favourable physical health profile, with minimal weight changes, no significant changes in glucose or lipid levels and no overall clinically significant increases in prolactin levels. These factors support a lower long term risk of coronary heart disease and diabetes in patients.

### 5.9.1 Studies designed primarily to assess safety outcomes

#### Identification of studies

Two phase III, non randomised studies (Study 31-03-241 and Study 31-05-243) designed primarily to assess safety outcomes were identified from manufacturer sources (see section 5.8). The methodology and results of these studies are summarised below.

#### Summary of methodology of relevant safety studies

A summary of the methodology of studies 31-03-241 and 31-05-243 is presented in Table 27, inclusion/exclusion criteria are summarised in Table 28, baseline characteristics are summarised in Table 29, subject disposition in Table 30 and statistical analyses in Table 31.

**Table 27: Summary of methodology of relevant safety studies**

| | Study 31-03-241 | Study 31-05-243 |
|---|---|---|
| Objectives | To determine the long-term safety and tolerability of aripiprazole tablets in adolescent subjects with schizophrenia, and child and adolescent subjects with bipolar I disorder, manic or mixed episode with or without psychotic features | To continue to provide flexible dose of aripiprazole therapy to subjects with schizophrenia completing study 31-03-241 |
| Location | Multinational | Multinational |
| Design | Open-label, flexible dose study | Ongoing, open-label rollover study |
| Duration of study | 6 months | Ongoing (up to 6 months at cut-off date) |
| Participants | Adolescent subjects (13–17 years) with schizophrenia who had completed study 31-03-239 (n=239) and children and adolescent subjects (10–17 years) with bipolar I disorder, manic or mixed episode, with or without psychotic features, who had withdrawn from study 31-03-240 (n=86) | Adolescent (13–17 years) and adult (adolescents who reached 18 years during the parent studies) subjects with a DSM-IV diagnosis of schizophrenia who had completed study 31-03-241 |
| Intervention | Aripiprazole flexible dose (2mg–30mg) | Aripiprazole 5mg–30mg |
| Primary outcomes | Frequency and severity of AEs, SAEs, and discontinuation from the study due to AEs | Frequency and severity of AEs, SAEs, and discontinuation from the study due to AEs |
| Secondary outcomes | • Mean change from baseline on EPS symptom scales<br>• Mean change from baseline in vital sign parameters, ECG parameters, serum prolactin concentrations, CPK, $HbA_{1c}$<br>• Mean change from baseline in BMI, blood pressure, fasting insulin levels, triglycerides, high-density lipoproteins, fasting glucose<br>• Percentage of subjects showing significant weight gain or loss (≥ 7%) from baseline<br>• Mean change from baseline on the CDRS-R<br>• Mean change from baseline on the CGAS<br>• Time to discontinuation for all reasons<br>• Quality of life assessed by the P-QLES-Q<br>For subjects with schizophrenia:<br>• Mean change from baseline on the PANSS total score and on the Positive and Negative subscales<br>• Mean change from baseline on the CGI-S score and mean CGI-I score | • Mean change from baseline in vital sign parameters, BMI, ECG parameters, serum prolactin concentrations, fasting glucose and insulin levels, CPK, $HbA_{1c}$<br>• Percentage of subjects showing weight gain or loss from baseline<br>• Mean change from baseline on the CGI-S scale<br>• Mean change from baseline on the P-QLES-Q total and overall score |

Abbreviations: AE, adverse event, BMI, body mass index; CDRS-R, children's depression rating scale – revised; CGAS, children's global assessment scale; CGI-I, clinical global impression improvement; CGI-S, clinical global impression – severity; CPK, creatine phosphokinase; DSM-IV, diagnostic and statistical manual of mental disorders – fourth addition; ECG, electrocardiogram; EPS, extrapyramidal symptom; PANSS, Positive and Negative Syndrome Scale; P-QLES-Q, paediatric quality of life enjoyment and satisfaction questionnaire; SAE, serious adverse event.

**Table 28: Eligibility criteria in studies 31-03-241 and 31-05-243**

| Trial | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **31-03-241** | • Adolescent subjects aged 13–17 years with a DSM-IV diagnosis of schizophrenia who had completed study 31-03-239<br>• Children and adolescent subjects aged 10–17 years with bipolar I disorder, manic or mixed episode, with or without psychotic features, who had withdrawn from study 31-03-240<br>• Written informed consent from a legally acceptable representative and informed assent at screening from the subject (with the understanding that he/she could withdraw at any time)<br>• The subject and the designated representative comprehend and can satisfactorily comply with the protocol requirements | • Breast-feeding and/or pregnant<br>• Sexually active males or females who did not agree to abstinence or birth control<br>• Significant risk of suicide<br>• A clinically significant abnormal laboratory test result, vital sign, or ECG finding<br>• Newly diagnosed diabetes<br>• Epilepsy, or a history of seizure, severe head trauma, stroke, or other unstable medical condition<br>• Serious uncontrolled systemic illness<br>• Positive drug screen for cocaine or other drugs of abuse<br>• Inability to swallow oral tablets<br>• Hypersensitivity to aripiprazole<br>• Any subject who took antipsychotic medications during the course of the study |
| **31-05-243** | • Adolescent (aged 13-17 years) and adult (adolescents who reached 18 during participation in the parent studies) subjects with a DSM-IV diagnosis of schizophrenia who had completed the open-label safety and tolerability study 31-03-241 | • Breast-feeding and/or pregnant<br>• Sexually active males or females who did not agree to abstinence or birth control<br>• A clinically significant abnormal laboratory test result, vital sign, or ECG finding<br>• Newly diagnosed diabetes<br>• Hypersensitivity to aripiprazole<br>• Inability to swallow oral tablets<br>• Positive drug screen for cocaine or other drugs of abuse<br>• Significant risk of suicide<br>• Serious uncontrolled systemic illness<br>• Epilepsy, or a history of seizure, severe head trauma, stroke, or other unstable medical condition<br>• Subjects who required other antipsychotics during the study were to be discontinued |

Abbreviations: DSM-IV, diagnostic and statistical manual of mental disorders – fourth addition; ECG, electrocardiogram;

**Table 29: Patient characteristics at baseline in studies 31-03-241 and 31-05-243**

| Baseline characteristic | | **Study 31-03-241 Schizophrenia subpopulation** | Study 31-05-243 |
|---|---|---|---|
| | | N=239 | N=85 |
| Age (years) | N | 239 | 85 |
| | mean (SD) | [redacted] | [redacted] |
| Male, n (%) | | [redacted] | [redacted] |
| Height (cm) | N | [redacted] | [redacted] |
| | mean (SD) | [redacted] | [redacted] |
| Weight (kg) | N | [redacted] | [redacted] |
| | mean (SD) | [redacted] | [redacted] |
| BMI (kg/m$^2$) | N | [redacted] | [redacted] |
| | mean (SD) | [redacted] | [redacted] |
| Race, n (%) | | [redacted] | [redacted] |
| Caucasian | | [redacted] | [redacted] |
| Black | | [redacted] | [redacted] |
| Asian | | [redacted] | [redacted] |
| American Indian or Alaska Native | | [redacted] | [redacted] |
| Other | | [redacted] | [redacted] |

Abbreviations: BMI, body mass index; SD, standard deviation

**Table 30: Disposition of study subjects: Studies 31-03-241 and 31-05-243**

| | **Study 31-03-241 Schizophrenia subpopulation** n (%) | Study 31-05-243 n (%) |
|---|---|---|
| Enrolled | 239 (100) | 85 (100) |
| Completed | 181 (75.7) | 0 (0.0) |
| Ongoing | – | 75 (88.2) |
| Discontinued | 58 (24.3) | 10 (11.8) |
| Adverse event | 6 (2.5) | 4 (4.7) |
| Lost to follow up | 7 (2.9) | – |
| Subject met withdrawal criteria | [redacted] | 3 (3.5) |
| Investigator withdrew subject | [redacted] | – |
| Subject withdrew consent | 28 (11.7) | 2 (2.4) |
| Protocol deviation | [redacted] | – |
| Lack of efficacy as determined by investigator | [redacted] | 1 (1.2) |
| Dosed/analysed for safety | 239 (100) | 85 (100.0) |
| Analysed for efficacy | 239 (100) | 85 (100.0) |

**Table 31: Summary of statistical analyses in studies 31-03-241 and 31-05-243**

| Trial no. (acronym) | Hypothesis objective | Statistical analysis | Sample size, power calculation | Data management, patient withdrawals |
|---|---|---|---|---|
| **Study 31-03-241** | Long term safety and tolerability of aripiprazole tables in adolescent subjects with schizophrenia, and child and adolescent subjects with bipolar I disorder. | All data on safety and efficacy/outcome were summarised by descriptive statistics due to the open-label single-arm nature of the study.<br>No inferential statistical analyses were performed for any efficacy, safety or other outcome variable. | Sample size was not determined by a formal computation to achieve a target power. | The safety dataset included data from all patients who received at least one dose of aripiprazole. Baseline visit was defined as the last visit in the parent studies 31-03-239 and 31-03-240 (or the value at the last available visit with non-missing values). Subjects with missing baseline or post-baseline measurements were excluded from the descriptive statistics for those variables. No missing data were imputed for vital signs, clinical laboratory tests, or ECG data. The observed cases (OC) dataset was used for the EPS symptom rating scales. The OC dataset consisted of data from all subjects evaluated at a particular visit; subjects with missing data due to dropout or other reasons were excluded from the OC dataset. |
| **Study 31-05-243** | To continue to provide flexible doses of aripiprazole therapy to subjects with schizophrenia completing study 31-03-241 | All data on safety and efficacy/outcome were summarised by descriptive statistics due to the open-label single-arm nature of the study.<br>No inferential statistical analyses were performed for any efficacy, safety or other outcome variable. | Sample size was not determined by a formal computation to achieve a target power. | The safety dataset included data from all patients who received at least one dose of aripiprazole. Baseline visit was defined as the last visit in the parent study 31-03-214 (or the value at the last available visit with non-missing values). Subjects with missing baseline or post-baseline measurements were excluded from the descriptive statistics for those variables. No missing data were imputed for analyses by visit. |

Abbreviations: ECG, electrocardiogram; EPS, extrapyramidal symptoms; OC, observed cases

## Critical appraisal of relevant safety studies

See Appendix 7 (section 9.7).

## Results of relevant safety studies

## Study 31-03-241 adverse events

Study 31-03-241 included adolescent subjects with schizophrenia and child and adolescent subjects with bipolar I disorder. Results are presented only for the sub-population of patients with schizophrenia, as the bipolar I sub-population is not relevant to this appraisal.

Aripiprazole was generally well tolerated and the majority of Treatment-emergent adverse events (TEAEs) were mild or moderate in severity. At least one TEAE was reported by 69% of subjects in the schizophrenia subpopulation (Table 32). TEAEs occurring in ≥ 5% of patients (in any subpopulation or all patients in study 31-03-241) are shown in Table 32.

**Table 32: TEAEs occurring in ≥ 5% of patients: Study 31-03-241**

| **System organ class**<br>Adverse Event | **Schizophrenia subpopulation**<br>**(N=239)**<br>**n (%)** |
|---|---|
| Total subjects with at least one AE | 165 (69.0) |
| **Gastrointestinal disorders** | |
| Diarrhoea | [redacted] |
| Nausea | 16 (6.7) |
| Vomiting | 14 (5.9) |
| **General Disorders and Administration Site Conditions** | |
| Irritability | [redacted] |
| **Infections and infestations** | |
| Nasopharyngitis | 14 (5.9) |
| Upper respiratory tract infection | [redacted] |
| **Investigations** | |
| Weight increased | 19 (7.9) |
| **Metabolism and Nutrition Disorders** | |
| Increased appetite | 13 (5.4) |
| **Nervous system disorders** | |
| Akathisia | 20 (8.4) |
| Dizziness | [redacted] |
| Extrapyramidal disorder | 46 (19.2) |
| Headache | 17 (7.1) |
| Somnolence | 33 (13.8) |
| Tremor | 15 (6.3) |

| System organ class<br>Adverse Event | Schizophrenia subpopulation<br>(N=239)<br>n (%) |
|---|---|
| **Psychiatric disorders** | |
| Insomnia | 22 (9.2) |
| **Respiratory, Thoracic, and Mediastinal Disorders** | |
| Nasal congestion | [redacted] |

Abbreviations: AE, adverse event

There was one death in the study, in the subpopulation of adolescents with schizophrenia, which was an accidental electrocution and was considered not related to study drug. In the adolescent subpopulation of subjects with schizophrenia 14/239 (5.9%) experienced a serious adverse event (SAE) during the study.

The following SAEs were reported by one subject each; acute bronchitis, hepatitis A, electrocution, intentional overdose, acute psychosis, aggression, auditory hallucination, homicidal ideation, impulsive behaviour, intentional self-injury, and suicidal ideation. [redacted]

A total of 6/239 (2.5%) subjects with schizophrenia discontinued study medication due to a TEAE: psychotic disorder (2 subjects), leukopenia (1 subject), electrocution (1 subject), acute psychosis (1 subject), and auditory hallucination (1 subject).

### Other safety results

There were no clinically relevant transaminase elevations or changes in haematology parameters noted during the course of the study with aripiprazole in the subpopulation of adolescents with schizophrenia.

[redacted]

No clinically meaningful changes in mean QT or QTc intervals, or other ECG abnormalities, were observed.

[redacted]

At the last visit 58/237 (24.5%) of adolescent subjects with schizophrenia experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline), and 11/237 (4.6%) experienced a potentially clinically significant weight loss (≥ 7% weight loss compared to baseline). However, overall, the mean changes from baseline for weight and BMI z-scores for each visit were within 0.5 SD of the general population, which is considered within normal limits for this population.

## Study 31-05-243

At least one TEAE was reported by 48.2% of subjects receiving long-term treatment with aripiprazole (Table 33). Influenza and vomiting and headache were the only TEAEs reported by ≥ 5% of subjects.

TEAEs occurring in ≥ 2% of subjects are shown in Table 33. The majority of TEAEs were mild or moderate in intensity.

**Table 33: TEAEs occurring in ≥ 2% of patients: Study 31-05-243**

| System organ class<br>adverse events | Male<br>(N=43)<br>n (%) | Female<br>(N=42)<br>n (%) | Total<br>(N=85)<br>n (%) |
|---|---|---|---|
| Total subjects with at least one AE | [redacted] | [redacted] | 41 (48.2) |
| **Gastrointestinal disorders** | | [redacted] | |
| Nausea | [redacted] | [redacted] | [redacted] |
| Vomiting | [redacted] | [redacted] | 5 (5.9) |
| **General Disorders and Administration Site Conditions** | [redacted] | [redacted] | |
| Pyrexia | [redacted] | [redacted] | [redacted] |
| **Infections and infestations** | [redacted] | [redacted] | |
| Influenza | [redacted] | [redacted] | 6 (7.1) |
| Nasopharyngitis | [redacted] | [redacted] | [redacted] |
| **Investigations** | [redacted] | [redacted] | [redacted] |
| Weight increased | [redacted] | [redacted] | [redacted] |
| **Metabolism and Nutrition Disorders** | [redacted] | [redacted] | [redacted] |
| Anorexia | [redacted] | [redacted] | [redacted] |
| **Nervous system disorders** | [redacted] | [redacted] | [redacted] |
| Extrapyramidal disorder | [redacted] | [redacted] | [redacted] |
| Headache | [redacted] | [redacted] | [redacted] |
| Somnolence | [redacted] | [redacted] | [redacted] |
| Tremor | [redacted] | [redacted] | [redacted] |
| **Psychiatric disorders** | [redacted] | [redacted] | [redacted] |
| Aggression | [redacted] | [redacted] | [redacted] |
| Depression | [redacted] | [redacted] | [redacted] |
| Insomnia | [redacted] | [redacted] | [redacted] |
| Psychiatric disorder | [redacted] | [redacted] | [redacted] |
| Schizophrenia | [redacted] | [redacted] | [redacted] |
| Suicide attempt | [redacted] | [redacted] | [redacted] |
| **Respiratory, Thoracic, and Mediastinal Disorders** | [redacted] | [redacted] | [redacted] |
| Cough | [redacted] | [redacted] | [redacted] |
| Rhinorrhoea | [redacted] | [redacted] | [redacted] |

Abbreviations: AE, adverse event

No deaths occurred during the reporting period.

Overall, 5/85 (5.9%) subjects experienced SAEs during the study. One subject experienced severe psychomotor hyperactivity and aggression. Other SAEs reported by one subject each were ligament injury and worsening of schizophrenia. The only SAE reported by more than one subject was suicide attempt, reported by 2 subjects.

The suicide attempts were considered unrelated or not likely to be related to aripiprazole treatment.

Four of the SAEs resulted in discontinuation of study medication: suicide attempt (2 subjects), aggression (1 subject), and worsening of schizophrenia (1 subject). No other subjects discontinued study medication due to TEAEs.

**Other safety results**
The first scheduled post-baseline evaluation of clinical laboratory parameters in Study 31-05-243 was Month 12. Paired data were available for very few subjects and included the 3 subjects who completed Month 12 and the end of treatment evaluations for withdrawn subjects. Therefore data were insufficient to draw conclusions regarding the potential impact of long-term aripiprazole treatment on clinical chemistry parameters, including prolactin and insulin. There were no clinically meaningful changes in mean QTc intervals in the sample.

At the last visit, the percentage of subjects who experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline) was 12.7% (9 out of 71 patients with a weight result at the last visit) whereas 7.0% of subjects (5 of 71) experienced a weight loss of ≥ 7% relative to baseline. There was no signal of increased abdominal obesity associated with aripiprazole and no clinically meaningful changes were observed in z-scores for weight and BMI.

### 5.9.2 Safety Results from other relevant RCTs

**Study 31-03-239**

The percentage of subjects who experienced at least one TEAE was slightly higher in the aripiprazole arms than in the placebo arm. TEAEs were experienced by 71.0% of subjects in the aripiprazole 10 mg arm; 72.5% in the aripiprazole 30 mg arm and 57.0% in the placebo arm. The majority of TEAEs were mild or moderate in severity. Table 34 summarises the most commonly reported TEAEs (by ≥ 5% incidence in any treatment arm).

**Table 34: TEAEs in ≥ 5% of patients across randomised groups in Study 31-03-239 (13, 18)**

| System organ class<br>Adverse Events | Study endpoint (Day 42) | | |
|---|---|---|---|
| | Aripiprazole 10 mg (n = 100) | Aripiprazole 30 mg (n = 102) | Placebo (n = 100) |
| **Total subjects with ≥ 1 TEAE** | 71 (71.0) | 74 (72.5) | 57 (57.0) |
| **Gastrointestinal disorders, n (%)** | | | |
| Nausea | 9 (9.0) | 10 (9.8) | 6 (6.0) |
| Vomiting | 5 (5.0) | 3 (2.9) | 5 (5.0) |
| **Infections and infestations** | | | |
| Nasopharyngitis | 5 (5.0) | 5 (4.9) | 4 (4.0) |
| **Nervous system disorders** | | | |
| Akathisia | 5 (5.0) | 12 (11.8) | 5 (5.0) |
| Dizziness | 7 (7.0) | 4 (3.9) | 3 (3.0) |
| Extrapyramidal disorder | 13 (13.0) | 22 (21.6) | 5 (5.0) |
| Headache | 16 (16.0) | 11 (10.8) | 10 (10.0) |
| Somnolence | 11 (11.0) | 22 (21.6) | 6 (6.0) |
| Tremor | 2 (2.0) | 12 (11.8) | 2 (2.0) |
| **Psychiatric disorders** | | | |
| Agitation | 1 (1.0) | 3 (2.9) | 5 (5.0) |
| Insomnia | 11 (11.0) | 10 (9.8) | 15 (15.0) |

There were no deaths reported in the study. The most commonly reported SAEs were psychotic disorder (1 patient in each treatment arm) and worsening of schizophrenia (1 patient in each aripiprazole treatment arm).

The following SAEs were reported by 1 patient each in the aripiprazole 10 mg arm: extrapyramidal disorder; possible neuroleptic malignant syndrome; aggression; psychotic disorder; worsening of schizophrenia and thrombophlebitis.

[redacted]

In the aripiprazole 30 mg arm, the following SAEs were reported by 1 subject each: varicella; depression; psychotic disorder; worsening of schizophrenia and suicidal ideation.

[redacted]

In the placebo arm, intentional overdose, overdose, psychotic disorder, and suicide attempt were each reported by 1 subject.

[redacted] An additional non-serious TEAE of suicidal ideation was experienced by 1 subject in the placebo group.

A total of 13/302 (4.3%) subjects discontinued study medication due to a TEAE: 7/100 (7.0%) in the aripiprazole 10 mg arm, 4/102 (3.9%) in the aripiprazole 30 mg arm, and 2/100 (2.0%) in the placebo arm. The majority of the events were moderate to severe in intensity.
The most commonly reported TEAEs resulting in discontinuation of study medication were: psychotic disorder (1 subject in each treatment arm); schizophrenia (2 subjects in the aripiprazole 10 mg arm and 1 subject in the aripiprazole 30 mg arm).

[redacted]

The most commonly reported TEAEs associated with EPS-related symptoms (≥ 5% incidence in any treatment group) were: akathisia, extrapyramidal disorder and tremor.

[redacted]

The majority of EPS related events were mild or moderate in severity and only one event (dystonia, aripiprazole 30 mg arm) led to a subject's discontinuation from the study.

## Other safety results

No clinically relevant mean changes were observed in the results for the serum chemistry, insulin, haematology, or urinalysis laboratory tests, vital signs, or ECG parameters.

### *Prolactin levels*

A mean decrease in prolactin levels relative to baseline was observed overall across all treatment groups. The mean change from baseline to Day 42 in prolactin levels was -8.82 ng/mL, -11.94 ng/mL, and -16.74 ng/mL in the placebo, aripiprazole 10 mg, and aripiprazole 30 mg arms respectively.

[redacted]

The overall incidence of low prolactin levels (≤ 3 ng/dL in females and ≤ 2 ng/dL in males) was greatest in the aripiprazole 10 mg arm (33.7%), followed by the aripiprazole 30 mg arm (26.3%), and then by the placebo arm (8.3%).

Importantly, none of these events were reported as TEAEs or SAEs, or resulted in discontinuation of study medication.

### *Weight gain*

Overall, the mean weight and BMI z-scores for each visit were within 0.5 standard deviations (SD) of the general population for all 3 treatment arms, which is considered within normal limits for this population and the changes from baseline were negligible.

At the last visit, the percentage of subjects who experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline) was 4.0% in the aripiprazole 10 mg arm, 5.2% in the aripiprazole 30 mg arm and 1.0% in the placebo arm. The percentage of subjects who experienced a potentially clinically significant weight loss (≥ 7% weight loss compared to baseline) at the last visit was 3.0% in the aripiprazole 10 mg arm, 2.1% in the aripiprazole 30 mg arm and 6.1% in the placebo arm.

In the parameters used to evaluate metabolic syndrome, including glucose, lipids, heart rate and blood pressure, there were no clinically meaningful changes from baseline.

### **5.9.3** Give a brief overview of the safety of the technology in relation to the decision problem.

Aripiprazole is generally well tolerated in the adolescent population, with the majority of reported TEAEs being mild or moderate in severity. Across the clinical studies (31-03-239, 31-03-241 and 31-05-243) the incidences of TEAEs and discontinuations due to AEs were low.

EPS was the most commonly reported TEAE. It is important to note that several studies with second-generation antipsychotics suggest that EPS-related side effects are more frequently observed in children and adolescents than in adults (35). Furthermore, EPS-related side effects with second generation antipsychotics do not appear to occur as frequently or with the same degree of severity as with first generation antipsychotics; for example EPS-related events have been reported in adolescents at an incidence of > 70% with haloperidol (36, 37).

Aripiprazole offers advantages in the treatment of adolescent schizophrenia. Cardiac monitoring is not required, as no impact has been seen on cardiac conduction. The impact on metabolic parameters and prolactin levels appears to be less than some other atypical antipsychotics when used in adolescence (8). Along with proven efficacy, these support the quality of life of these patients suffering with a devastating, chronic disorder.

## *5.10 Interpretation of clinical evidence*

**5.10.1** Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Aripiprazole is effective in the treatment of adolescent schizophrenia at daily doses of 10 mg and 30 mg, as demonstrated by clinically significant improvements compared with placebo in PANSS total score, CGAS score, CGI-severity score, and mean CGI-improvement score. Efficacy results continue to be seen in the long-term extension studies demonstrating efficacy was maintained in the long-term.

Aripiprazole is generally well tolerated in the adolescent population, with the majority of reported TEAEs being mild or moderate in severity. Across the clinical studies the incidences of TEAEs and discontinuations due to AEs were low.

Aripiprazole offers advantages in the treatment of adolescent schizophrenia over other unlicensed antipsychotics. Cardiac monitoring is not required, as no clinical impact has been seen on cardiac conduction. The long half-life facilitates once daily dosing. The impact on weight and other metabolic parameters, as well as prolactin levels appears to be less than some other atypical antipsychotics when used in adolescence (8).

Along with proven efficacy, aripiprazole offers a licensed treatment that supports the quality of life of these patients suffering with a devastating, chronic disorder.

**5.10.2** Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The clinical-evidence base is from one large, placebo-controlled RCT that has been published and two open-label extension studies. To our knowledge, Study 31-03-239 is the largest RCT conducted to date in adolescents with schizophrenia and a significant number of these patients were followed up via the two open-label follow-up studies.

Further data will be obtained from planned studies associated with post-marketing commitments.

**5.10.3** Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The clinical studies were conducted on patient populations that closely parallel the patient population seen in clinical practice and the subject of this appraisal.

PANSS is one of the most common standardised methods used for assessing the effectiveness of schizophrenia medication, and its use in paediatric and adolescent trials is well-documented (22-25). However, as this measure is less frequently used in clinical practice, the CGAS was developed from the Adult Global Assessment Scale to provide global measurement of severity of disturbance in children and

adolescents. The CGAS is a valid and reliable tool for rating a child's general level of functioning (26). The CGI is a classic assessment instrument (27) and has been used extensively in clinical trials for schizophrenia (28, 29).

**5.10.4** Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The use of aripiprazole in the clinical trial reflects the indicated license for the treatment of schizophrenia in adolescents 15 years and older.

The diagnosis of psychotic disorders in paediatric and adolescent patients is difficult and challenging due to the overlap between various psychiatric conditions and other emotional and developmental issues. The rate of misdiagnosis of paediatric psychotic illness, especially at the onset of the disorder, is high; consequently studies carefully select patients for inclusion.

In clinical practice, the choice of antipsychotic medication is decided by the healthcare professional. The older typical antipsychotics are used less commonly due to their more frequent dosing and greater frequency of less tolerable side effects. The newer, atypical antipsychotics are generally similar to each other in terms of efficacy, however their adverse-effect profiles are markedly different. Consequently, the physician's choice may be influenced by the side-effect profile.

Aripiprazole is generally well tolerated in the adolescent population, with the majority of reported TEAEs being mild or moderate in severity. Importantly, treatment with aripiprazole is not usually associated with weight gain, or clinical changes leading to metabolic syndrome. Furthermore, hyperprolactinaemia is not usually associated with aripiprazole treatment.

Finally, a very important consideration is that many of the alternative antipsychotic medications to aripiprazole are not licensed for use in the adolescent population.

The evidence base supports the use of the adolescent doses given in the Summary of Product Characteristics (SPC) for aripiprazole. Notably, the target dose recommended in the SPC for the treatment of adolescent schizophrenia is 10mg. Anecdotally, clinicians tend to use doses at the lower end of the recommended 10-30mg dosage range in this patient population. The higher dose of 30mg was proven to be generally well tolerated by these patients, but no significant additional efficacy benefit was seen in the RCT.

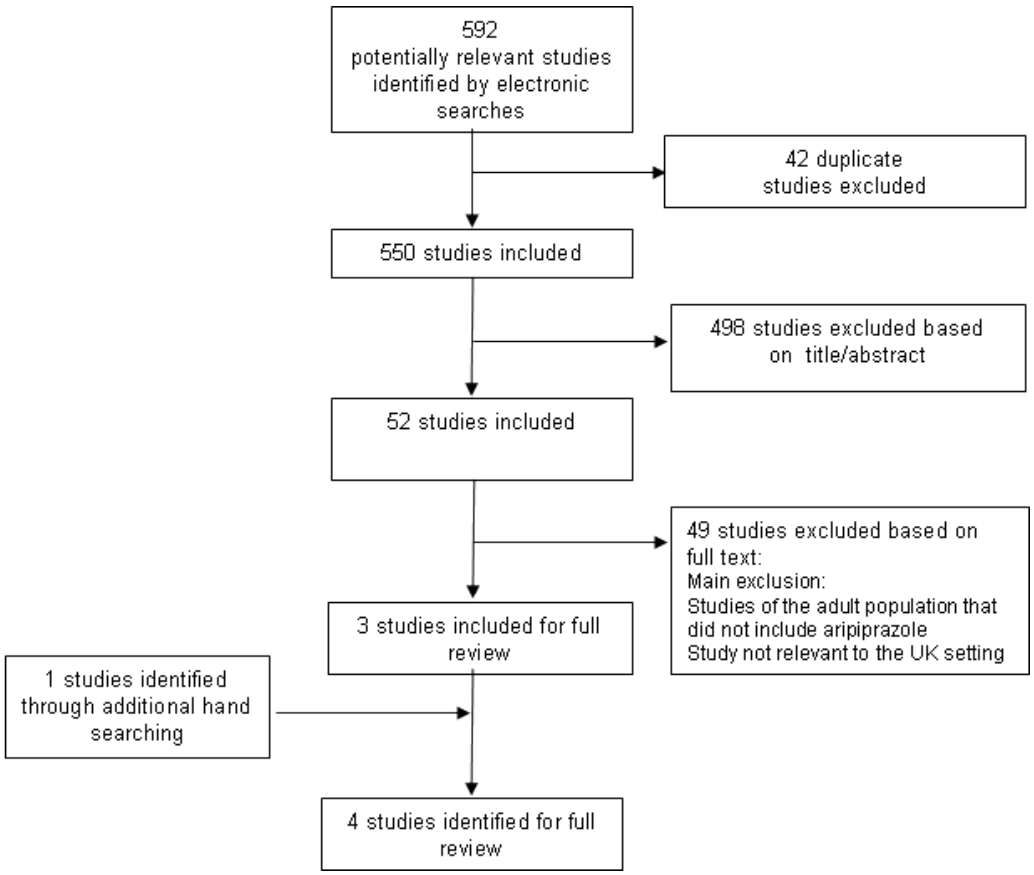
# 6 Cost-effectiveness

## *6.1 Published cost-effectiveness evaluations*

### 6.1.1 Identification of studies

A systematic review of the literature was carried out in order to identify existing cost-effectiveness studies of aripiprazole in the treatment of adolescent schizophrenia. Cost-effectiveness search terms were combined with terms for the disease area specified in Appendix 10 (Section 9.10). The inclusion and exclusion criteria were chosen to identify all economic evaluations assessing treatments for adolescent schizophrenia. The full review of papers was restricted to those addressing the UK health care setting to ensure the inclusion and review of the most relevant analyses. A priori, an additional search was proposed to include economic evaluations specifically including aripiprazole as a treatment for schizophrenia in the adult population due to the expected paucity of economic studies for adolescents with schizophrenia. The results of these searches are reported within this section. The methods used are reported in Appendix 10 (Section 9.10).

**Figure 7: Consort flow diagram for cost-effectiveness studies**



Five hundred and fifty potentially relevant publications were identified for inclusion in the systematic review, of which 498 were excluded on the basis of title and abstract. After review of the 52 full text papers, a further 49 were excluded. Three papers met the applied criteria. In addition, hand searching was carried out to identify any available economic evaluations carried out as part of national clinical guidelines/appraisals which would not have been picked up by the main review. This search identified an additional relevant study. The methods of the hand searching are outlined in section Appendix 10 (section 9.10).

### 6.1.2 Description of identified studies

No studies were identified that assessed the cost effectiveness of aripiprazole in the adolescent population. In total, four economic evaluations in the adult population that included aripiprazole as a treatment for schizophrenia were reviewed. All of the studies were conducted using UK cost data and were therefore assessed to be relevant to the UK setting. Three cost-utility analyses and one cost-consequence analysis was identified.

Barnett et al (2009) (38) used data from the STAR (schizophrenia trial of aripiprazole) study that compared aripiprazole with 'standard of care' which was the clinician's choice of olanzapine, quetiapine or risperidone. This study was conducted over 26 weeks and showed that the metabolic side-effects of aripiprazole were less than those for standard of care. A follow up study suggested that the projected risks for diabetes and coronary heart disease (CHD) were also lower in the aripiprazole treatment group. Using this data with direct and indirect costs, Barnett et al (38) conducted a cost-consequence analysis. The authors predicted the long-term risks of diabetes and CHD for patients receiving aripiprazole or standard of care. These data were then used to estimate the associated cost impact of diabetes and CHD. The authors concluded that aripiprazole was predicted to result in fewer onsets of diabetes over 7.5 years, and fewer incidences of CHD over 10 years compared with standard of care, resulting in cost savings (38).

Davies et al (2008) (39) is a cost effectiveness analysis of atypical antipsychotics (aripiprazole, olanzapine, risperidone, quetiapine) for the management of schizophrenia. The authors developed a Markov model and looked at treatment sequences for schizophrenia. Two antipsychotics were considered before clozapine was administered. The clinical data in this study came from the CATIE trial and from a separate trial comparing aripiprazole and olanzapine in adults. Utility values for stable schizophrenia and disutility due to side effects and diabetes were included. The study showed that at a willingness to pay threshold of £30,000 per QALY gained, the sequence of aripiprazole then risperidone was optimal in all but one scenario. Sensitivity analysis showed that results were robust to changes made in the model. Of note, the authors concluded that lower pricing for risperidone, which was tested due to generic availability, did not impact the results (39).

Heeg et al (2008) (40) carried out a discrete event simulation to evaluate the cost effectiveness of atypical antipsychotics compared with typical antipsychotics in the first-line treatment of schizophrenia. Clinical data on the efficacy of treatment and incidence of side effects came from a variety of published sources. Quality of life was derived from the patients' PANSS scores and disutility due to adverse events including EPS, tardive dyskinesia, somnolence and weight gain, was included. Utility data were taken from the published literature. The authors concluded that in the

base case analysis, atypical antipsychotics dominate typical antipsychotic treatments because they are more effective and less costly. Probabilistic analysis suggested that the results were robust. When the only difference between atypical antipsychotics and typical antipsychotics is indicated by side-effect profiles the cost effectiveness of atypical treatment is reduced (40).

The NICE guideline for adults with schizophrenia (6) included a cost effectiveness analysis which incorporated aripiprazole. The National Collaborating Centre for Mental Health (NCCMH) developed a Markov model to assess the relative cost-effectiveness of antipsychotic medications aimed at supporting the recovery of people with schizophrenia in remission by preventing relapse. The treatments included were olanzapine, amisulpride, zotepine, aripiprazole, paliperidone, risperidone and haloperidol. The clinical data in this study came from the systematic review conducted as part of the clinical guideline. An extensive mixed treatment comparison was conducted to estimate the transition probabilities of a range of input parameters. Utility values for stable schizophrenia and disutility due to side effects and diabetes were included in the model. The authors concluded that although zotepine was considered the most cost-effective treatment in deterministic sensitivity analysis, probabilistic analysis showed that all of the treatments included had a low chance of being considered cost-effective compared with the other treatments in the analysis. Due to the high level of uncertainty none of the antipsychotic medications could be considered clearly cost-effective compared to the other options (6).

NICE took into account all the available evidence on the effectiveness and cost effectiveness of pharmacological treatments of schizophrenia in various settings and also examined previous recommendations made in the original technology appraisal (TA43). NICE concluded that evidence from the systematic reviews of the clinical evidence presented "suggest that choosing the most appropriate drug and formulation for an individual may be more important than the drug group." (6)

The guideline states that "the evidence supports a specific recommendation for clozapine for people whose illness does not respond adequately to other antipsychotic medication." However, for other antipsychotics, the recommendations conclude that when examining all available clinical and economic evidence, taking into account the uncertainty characterising the results of economic modelling undertaken, *the evidence did not enable them to make a recommendation for one antipsychotic to be preferred over another.*

Therefore, the recommendation for initiation of treatment (first episode), acute treatment, and preventing relapse, is for other factors to be taken into consideration when deciding upon an appropriate oral antipsychotic medication – factors such as: the potential of the treatment to cause side effects; current treatment response; past side effect experience and the views of the carer if the service user agrees.

No economic evaluations assessing the cost-effectiveness of aripiprazole specifically in adolescents with schizophrenia were identified; consequently a de novo economic evaluation was conducted for the purposes of this submission.

**Table 35: Summary list of relevant UK cost-effectiveness evaluations**

| Study and year | Summary of model | Patient population (average age in years) | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|
| Barnett et al 2009 (38) | Cost consequence study using data from the STAR (schizophrenia trial of aripiprazole) study. Aripiprazole was compared with standard of care (SC - clinician choice from olanzapine, quetiapine or risperidone) | Patients were aged 18-65 with a diagnosis of schizophrenia (according to DSM-IV criteria) | QALYs were not reported. Outcomes presented included metabolic risk, diabetes risk and CHD risk predictions. | Accumulated avoided direct and indirect costs were provided for aripiprazole compared with SC.<br>A total of ~£37M may be saved on projected diabetes events over a 10 year period.<br>A total of ~£7.5M may be saved on projected CHD events over a 10 year period. | The authors concluded that aripiprazole treatment may result in fewer onsets of diabetes and fewer incidences of CHD compared with standards of care and as a result could be associated with long-term cost savings to the UK health care system. |
| Davies et al 2008 (39) | Probabilistic Markov model of sequences of two to four atypical antipsychotics followed by clozapine as an end of line therapy as outlined in the NICE guidelines. Treatments included were aripiprazole, risperidone, quetiapine, olanzapine. | Patients with stable (treatment refractory) schizophrenia. Average age not reported. Clinical studies used to inform the analysis showed that the patient population was 18-65 years. | ARI–RSP=6.618<br>RSP–ARI=6.612<br>ARI–QTP=6.601<br>QTP–RSP=6.599<br>QTP–ARI=6.598<br>ARI–OLZ=6.597<br>RSP–QTP=6.595<br>RSP–OLZ=6.591<br>OLZ–ARI=6.588<br>OLZ–RSP=6.584<br>QTP–OLZ=6.578<br>OLZ–QTP=6.573 | ARI–RSP=£44092<br>RSP–ARI=£44104<br>ARI–QTP=£45598<br>QTP–RSP=£44745<br>QTP–ARI=£45645<br>ARI–OLZ=£44717<br>RSP–QTP=£44703<br>RSP–OLZ=£43835<br>OLZ–ARI=£44757<br>OLZ–RSP=£43920<br>QTP–OLZ=£45367<br>OLZ–QTP=£45339 | ARI–RSP=£9440<br>RSP–ARI=Dominated<br>ARI–QTP=Dominated<br>QTP–RSP=Dominated<br>QTP–ARI=Dominated<br>ARI–OLZ=Dominated<br>RSP–QTP=Dominated<br>RSP–OLZ=N/A<br>OLZ–ARI=Dominated<br>OLZ–RSP=Dominated<br>QTP–OLZ=Dominated<br>OLZ–QTP=Dominated |
| Heeg et al 2008 (40) | Discrete event simulation model designed to analyse the cost- | Patients suffering an episode of psychosis. The average age of the | Conventional group=3.53<br>Atypical | Conventional group=£59,541<br>Atypical=£57,908 | Base case results showed that atypical treatment dominated the conventional group as it was cost saving and |

| Study and year | Summary of model | Patient population (average age in years) | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|
| | effectiveness of atypical antipsychotics compared with conventional antipsychotics for the first-line treatment of schizophrenia. Aripiprazole was included in the list of atypical antipsychotic treatments. | patient population was not reported. Examination of the source of aripiprazole clinical data appears to suggest that patients were over 18 years. | group=3.64<br><br>Incremental=0.10 | <br><br>Incremental=-£1,633 | resulted in more QALYs. |
| NICE guidelines-NCC mental health 2009 (6) | A decision-analytic model (Markov model) was developed to assess the relative cost-effectiveness of antipsychotic medications aimed at promoting recovery (preventing relapse) in people with schizophrenia in remission. The treatments included were olanzapine, amisulpride, zotepine, aripiprazole, paliperidone, risperidone and haloperidol based on availability of data. | Patients with schizophrenia in remission. The average age of the population was not reported. Examination of the source of clinical data appears to show that patients were over 18 years. | Zotepine 6.468<br>Paliperidone 6.427<br>Olanzapine 6.420<br>Risperidone 6.417<br>Haloperidol 6.413<br>Aripiprazole 6.400<br>Amisulpride 6.392 | Zotepine £139,170<br>Paliperidone £142,173<br>Olanzapine £141,212<br>Risperidone £149,112<br>Haloperidol £143,406<br>Aripiprazole £145,697<br>Amisulpride £147,920 | The incremental analysis "in steps" resulted in the following ranking of methods in terms of cost effectiveness:<br>(1) Zotepine<br>(2) Olanzapine<br>(3) Paliperidone<br>(4) Haloperidol<br>(5) Aripiprazole<br>(6) Amisulpride<br>(7) Risperidone.<br>Following extensive sensitivity analysis the authors concluded that results were characterised by high uncertainty and probabilistic analysis showed that no antipsychotic medication could be considered clearly cost-effective compared to the other options included in the assessment. |

Abbreviations: ARI, aripiprazole; ICER, incremental cost-effectiveness ratio; OLZ, olanzapine; QALY(s), quality-adjusted life year(s); QTP, quetiapine; RSP, risperidone; SC, standard of care; NCC, national collaborating centre

### 6.1.3 Quality assessment

A quality assessment was completed for each of the four studies included in the review. The completed checklists are available in Section 9.11, Appendix 11.

## *6.2 De novo analysis*

### 6.2.1 Patients

The patient population considered in the economic evaluation is adolescents with schizophrenia aged 13-17. The UK marketing authorisation restricts the licence for aripiprazole to patients with schizophrenia aged 15-17. However, the randomised controlled trial of aripiprazole included patients aged 13-17 as did the olanzapine trial. The data in the olanzapine trial was not presented for the subgroup of 15-17 year olds. In order to conduct an indirect comparison it was necessary to use data from both the aripiprazole and the olanzapine trials for the 13-17 year age group.

A post-hoc analysis of the aripiprazole clinical trial data examines the differences in patients with schizophrenia across outcomes between three age groups: 13-17, 15-17 and adults 18 years and over. This analysis has indicated that long term symptom improvement, remission and maintained remission outcomes are similar for all three groups (see section 5.3.6 for further details). This supports the use of the use of the full clinical trial population as a proxy for the licensed indication sub-group

### 6.2.2 Model structure

**Figure 8: Decision tree model schematic**

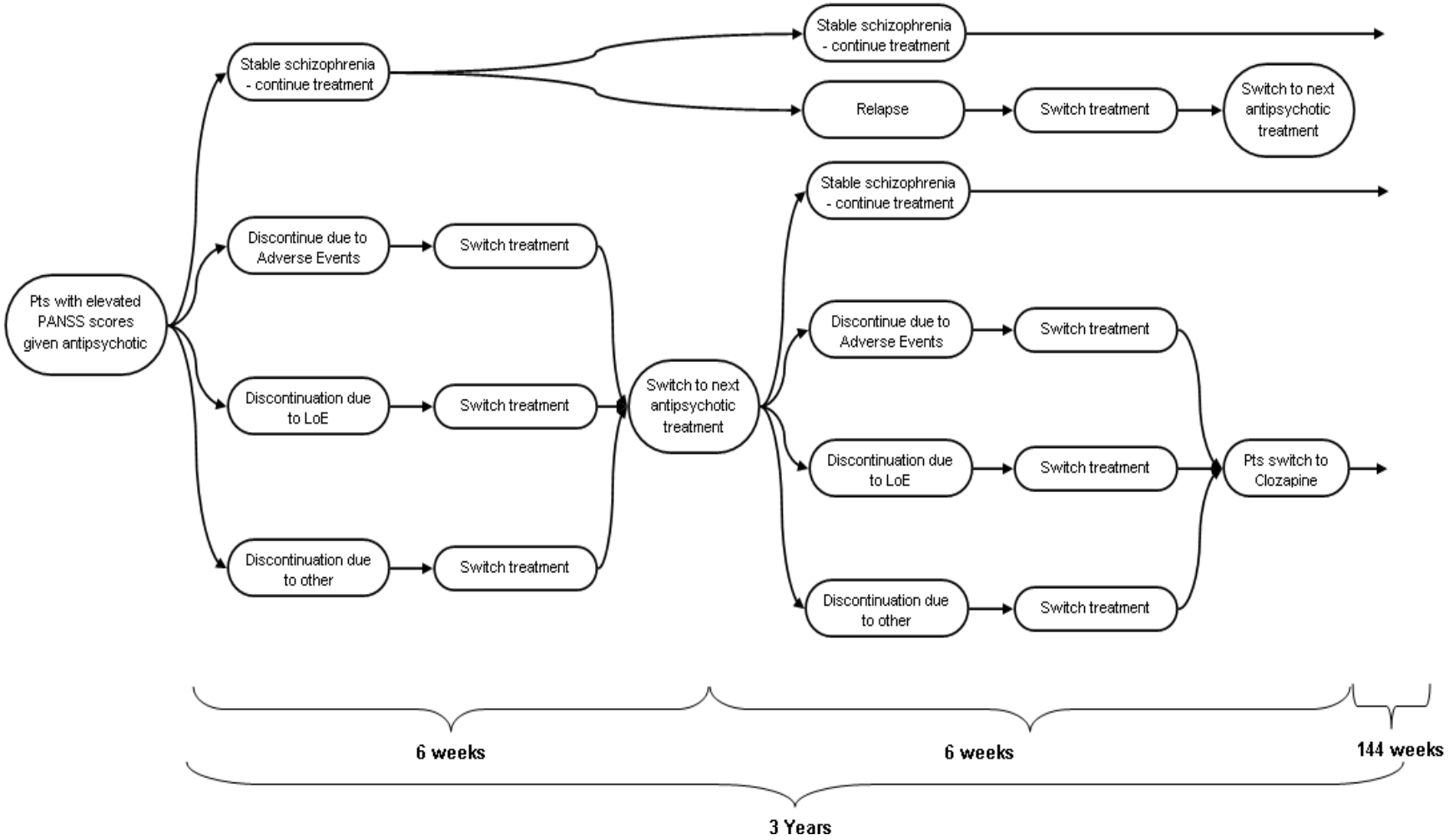
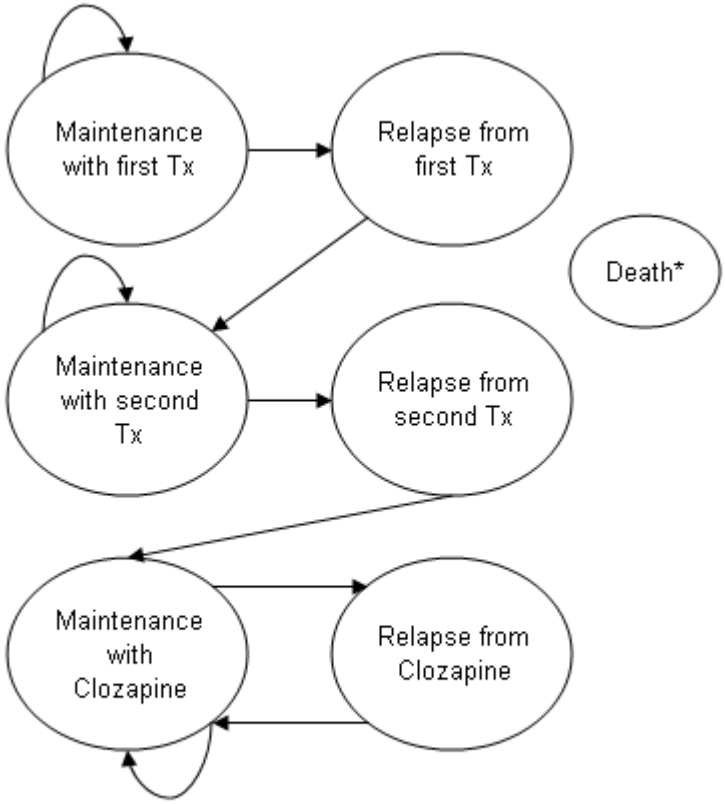


**Figure 9: Markov model schematic**




* Due to the short time horizon and no efficacy data related to death rates mortality has not been included within the model.

### 6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The chosen structure of the economic analysis is a decision tree model followed by a Markov model. The decision tree incorporates two 6-week time periods, allowing patients to switch treatments (i.e. aripiprazole – olanzapine – clozapine and olanzapine – aripiprazole – clozapine). These 6-week time periods, incorporate the length of the clinical trials and the likely length of time between patient visits to clinicians.

Patients who discontinue due to adverse events, lack of efficacy or other reasons, switch to either olanzapine or aripiprazole depending on their first-line treatment. Patients who discontinue due to the reasons outlined above on the second treatment receive clozapine. Clozapine is considered a rescue treatment in the context of this model in line with the SPC for clozapine (41). It is assumed that if a patient does not discontinue, they carry on receiving the first line or second line treatment for the remainder of the model or until they relapse. Patients may also experience adverse events that do not lead to discontinuation but will affect their quality of life whilst on treatment. Therefore 'stable schizophrenia' incorporates adverse events whilst on treatment. Patients who continue on treatment also have an ongoing probability of relapse throughout the model.

The Markov section of the model allows patients to be followed up until they are 18 years old when other treatments may then become available to them. A previous NICE clinical guideline has examined the clinical and cost effectiveness for treatments for adults with schizophrenia and therefore this guidance should be followed when adolescents reach adulthood (6).

The aim of the model is not to evaluate a sequence of treatments but to investigate the impact of the first line antipsychotic on costs and patient outcomes and to accurately reflect clinical practice when patients discontinue treatment or have a relapse.

**6.2.4** Please define what the health states in the model are meant to capture.

The health states in the model capture the discontinuations reported in the clinical trials and therefore the need to switch treatments in the clinical setting. Adverse events due to treatment are an important clinical aspect of these treatments and are included in the model to capture the reduced quality of life and costs due to side effects whilst on treatment (i.e. significant weight gain $\geq$ 7% and somnolence).

**6.2.5** How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The phases of the disease are described in section 2.1. This model reflects patients who are in the acute phase of the disease with elevated PANSS scores according to the clinical trials. Patients are given a choice of treatment as described in section 2.4 and will then enter the maintenance phase unless they discontinue within a six-week time period and switch treatment. As discussed in section 2.1, patients remain at risk of relapse throughout their treatment therefore this aspect of the underlying disease progression is included in the model. The model structure was externally validated by an expert in the field of health economics with an interest in mental health. As described in section 2.1, adolescents may be more vulnerable than adults to adverse events associated with atypical antipsychotics. Where possible the model takes into account the side effects associated with treatment.

**6.2.6** Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

**Table 36: Key features of analysis**

| Factor | Chosen values | Justification | Reference |
|---|---|---|---|
| Time horizon | 3 years | The overall time horizon is three years following patients into adulthood where treatment options may differ and further evidence is available on the cost effectiveness of treatments.<br>The time horizon takes into account the main differences in the technologies before adulthood. A lifetime model is currently available which has examined all evidence surrounding antipsychotics for adults. According to the NICE methods guide, a lifetime horizon should normally be adopted if a treatment affects survival at a differential rate when compared with the relevant comparator. There is currently no evidence that survival differs between the two treatments included in the model.<br>In addition, there is a lack of data on long-term treatment outcomes; therefore extrapolation of this data over a lifetime horizon would introduce significant bias into the model. | As per the licensed indication.<br>Validated by expert opinion.<br>NICE methods guide |
| Cycle length | 6 weeks | Average time between clinician visits.<br>Reflects the length of the RCTs available in adolescent schizophrenia | Clinical trial (13, 18) and expert opinion. |
| Half-cycle correction | None | The time horizon of the model is short and the length of the cycles in the Markov model are also short. As costs and benefits are applied over these short periods of time, no half cycle correction was added. | Not applicable. |
| Were health effects measured in QALYs; if not, what was used? | Yes | As stated in the decision problem | NICE methods guide |
| Discount of 3.5% for utilities and costs | Yes | As stated in the decision problem | NICE methods guide |
| Perspective (NHS/PSS) | NHS/PSS | As stated in the decision problem | NICE methods guide |
| NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years | | | |

**Technology**

**6.2.7** Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The intervention in the model is aripiprazole and the comparator is olanzapine. The intervention considered in this model uses data from the main clinical trial for aripiprazole. The marketing authorisation for aripiprazole is for adolescents with schizophrenia aged 15-17 years. However, the clinical trial contains data from a larger subgroup of patients aged 13-17 years. The total population from this trial is utilised within this model, therefore capturing data for a larger subgroup of patients than stated within the licence. The justification for using the clinical trial population within the model is this is the only clinical trial available for aripiprazole for the treatment of adolescents. Including a subgroup of patients, 15-17 years only, would decrease the patient numbers and may compromise a robust analysis against olanzapine. In addition, post-hoc analysis carried out on the aripiprazole patient group shows that data for the group containing all patients is comparable to that of a subgroup containing patients aged 15-17 years.

The comparator in the model is olanzapine, as stated in the manufacturer decision problem. The trial identified for olanzapine for use in the economic model also incorporated adolescents aged 13-17, and no post-hoc analysis is available for 15-17 years (12). Therefore due to this data gap it was not possible to conduct a subgroup analysis of aripiprazole versus olanzapine in patients aged 15-17 years.

Olanzapine does not have a marketing authorisation for adolescents. The only comparators listed in the scope with marketing authorisations were amisulpride (for which no clinical trials were identified) and clozapine. Clozapine has a marketing authorisation that covers adolescents aged 16 and over; however, clozapine would not be used as a first-line treatment option for patients with schizophrenia as per the SPC (41).

In order to ensure that inclusion of the younger patient population in the model would not bias the results, sensitivity analyses were carried out on the efficacy parameters taken from the clinical trials, that is, the ORs for clinical outcomes included in the model (such as discontinuations and adverse events) were varied to establish their effect on the model results. The results of the sensitivity analyses are presented in section 6.7.7.

**6.2.8** Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).

- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

In the base case analysis, patients are assumed to continue with the initial treatment if they have not discontinued within the first 6 weeks (based on the clinical trial data). This is also supported by expert opinion. Patients will subsequently continue on treatment until they relapse at which point they will discontinue and switch to the next therapy. Again this was validated with clinical expert opinion.

## *6.3 Clinical parameters and variables*

**6.3.1** Please demonstrate how the clinical data were implemented into the model.

Clinical data informed the following parameters in the model:

- Withdrawal due to lack of efficacy
- Withdrawal due to adverse events
- Withdrawal due to other reasons
- Rates of adverse events (weight gain and somnolence)
- Longer term rates of relapse

A probability of discontinuation was applied to patients on their first or second treatment during each 6-week period in the model from the indirect comparison results (see section 5.7 for further details). Patients who remained on treatment had a risk of relapse that was applied to each cycle of the model. No long-term data on treatment effects, including relapse rates of aripiprazole or olanzapine, were identified in the systematic review. Therefore data on relapse were sourced from a published study that estimated the rates of relapse in adults with schizophrenia (42). Expert opinion was consulted to validate the use of adult data in this context. Rates of relapse were not thought to differ significantly between adults and children.

The probability of having a treatment related adverse event was applied to patients on treatment. Probabilities of having weight gain $\geq$ 7% and rates of somnolence were taken from the indirect comparisons.

EPS is also considered to be an important adverse event for patients, affecting their quality-of-life whilst on treatment. However, EPS was not consistently reported in the trials and therefore the relative rates of this adverse event with olanzapine compared with aripiprazole could not be determined using indirect comparison. Patients receiving benzodiazepines were reported in both the aripiprazole and olanzapine clinical trials; however, this is thought to be a poor proxy for EPS and was therefore not included in the model in the base case analysis.

**6.3.2** Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

## Aripiprazole and olanzapine

### *Withdrawals and adverse events*

To estimate the probability of withdrawals and adverse events, the probability of an event occurring while receiving aripiprazole was calculated directly from the clinical trial, that is, the probability of having an event at 6 weeks (n/N). In order to calculate the probability of an event for olanzapine, the probabilities for aripiprazole were first converted into odds using the equation:

Odds = probability / (1-probability)

The OR of discontinuing (due to the reasons above) with olanzapine compared with aripiprazole was taken from the indirect comparison and applied to the odd of the event with aripiprazole. The adjusted odds were then converted back into probabilities using the following formula:

Probability = Odds / (1+odds)

Those who remain on treatment, that is, those who do not discontinue, are assumed to have improved symptoms and will carry on receiving treatment in the model.

Adverse events included in the model were also calculated using the method described above. The final probabilities used in the model for discontinuation and adverse events are presented in Table 37.

**Table 37: Table of probabilities used in the model for discontinuation and adverse events**

| Variable | Aripiprazole | Olanzapine |
|---|---|---|
| Discontinuation due to adverse events | [redacted] | 10.57% |
| Discontinuation due to lack of efficacy | [redacted] | 0.16% |
| Discontinuation due to other reasons | [redacted] | 13.45% |
| Improved symptoms (calculated) | [redacted] | 75.82% |
| Weight gain ≥ 7% | [redacted] | 2.49% |
| Somnolence | [redacted] | 39.76% |

### *Relative risk of relapse*

As there is limited long-term data on the rate of relapse in this patient group, the relative risk (RR) of relapse between treatments in the model compared with aripiprazole was taken from a published study that examined relapse rates in adults

with schizophrenia receiving aripiprazole compared with other atypical antipsychotics (42). This paper reports a 6-month rate of relapse with aripiprazole of 20% and a 6-month rate of relapse for all other included second generation antipsychotics (namely, clozapine, olanzapine, risperidone and quetiapine) of 19.4%. Although the study reports the RR of relapse between aripiprazole and all other second generation antipsychotics to be 0.92 (95% CI: 0.67 to 1.26), this does not appear to be correct even when rounding is taken into consideration. According to the calculation for RR, the RR of relapse in this case should be [redacted] (assuming 89 of 444 patients relapsed in the aripiprazole group and 101 of 521 patients relapsed in the SGA group), therefore this value was used in the model, that is, the relapse rate of aripiprazole used was 20% with a RR of relapse for other second generation antipsychotics of 0.97 The rates of relapse for aripiprazole and olanzapine were then transformed into 6-weekly probabilities using the following formula:

Six-weekly probability of relapse = 1-EXP(-(-LN(1-six-monthlyprobability)/26*6))

This gives a probability of relapse per 6-week period in the model of 5.02% for aripiprazole and 4.86% for olanzapine.

### Clozapine

Once patients receive clozapine, they remain on this treatment for the remainder of the model. Clozapine is considered as a rescue treatment in the model according to the SPC (41). Therefore as clozapine was not considered an appropriate comparator, it was not included in the initial systematic literature review. Therefore adverse event rates and rates of relapse for clozapine were taken from alternative sources.

Adverse event rates whilst on clozapine were assumed to equal the rates of adverse events whilst on aripiprazole. This is considered to be a conservative assumption as there is likely to be additional disutility associated with clozapine treatment according to clinical experts.

The risk of relapse for clozapine was taken from the same published study as that for aripiprazole and olanzapine (42) and transformed into a transitional probability by the method outlined above.

**6.3.3** Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

There is no long-term data to inform an assumption of variation of transitional probabilities over time. It appears that other economic analyses have also made this assumption (6). The probability of weight gain is only assumed to be possible in the first 6-week period of commencing a new treatment in the model. This is because patients already having this adverse event are unlikely to have the same degree of adverse event in consequent cycles.

**6.3.4** Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

N/A.

**6.3.5** If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[2]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Two clinical experts practising in the field of child and adolescent mental health were approached to provide an overview of the clinical pathway and treatment options used in adolescents with schizophrenia. Communication with the clinical experts was primarily via telephone interviews and follow up via email. During the development of the economic model an additional expert with experience in mental health and economic modelling was approached to validate the model structure and concept via a face-to-face discussion. The experts approached validated the following assumptions in the model:

- If patients do not discontinue with treatment in the initial 6-week period they will remain on the treatment unless they relapse.
- The rate of relapse for adults could be assumed to be the same for children/adolescents in the absence of this data for children.
- Clozapine is not used as a preferred first-line treatment but rather as a rescue therapy.
- Adverse events as a result of treatments were discussed and were thought to have an effect on patient's quality of life and should be taken into account in the

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

model. Clozapine was considered to have a higher level of treatment related adverse effect on quality of life than other treatments for schizophrenia.

**Summary of selected values**

**6.3.6** Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

A full table of all the input parameters including cost and utility values is included in Appendix 9.14.

**Table 38: Table of values used in the model for discontinuation and adverse events**

| Variable | Value | CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Probability of discontinuation due to adverse events with aripiprazole | 7.00% | 4.9% to 9.1% (beta) | 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 | 11.00% | 7.7% to 14.3% (beta) | Indirect comparison section 5.7 |
| Probability of relapse with aripiprazole | 5.02% | 13.58% to 25.22% (beta) | Relapse rates section 0 |
| Odds ratio for discontinuation due to adverse events with olanzapine vs aripiprazole | 1.570 | 0.06 to 43.87 (log) | Final probability calculated as shown in section 0 using odds ratios from indirect comparison section 5.7 |
| Odds ratio for discontinuation due to LOE with olanzapine vs aripiprazole | 0.03 | 0.00 to 0.31 (log) | Indirect comparison section 5.7 |
| Odds ratio for discontinuation due to other reasons with olanzapine vs aripiprazole | 3.73 | 0.48 to 28.70 (log) | 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 | 0.51 | 0.02 to 11.50 (log) | Indirect comparison section 5.7 |
| Odds ratio for somnolence with olanzapine vs aripiprazole | 5.34 | 0.54 to 53.01 (log) | Indirect comparison section 5.7 |
| 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

**6.3.7** Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

The rates of relapse for treatments in the model are assumed to continue beyond the follow-up period of the trials. These rates have been assumed not to vary over time so as not to bias the model in favour or against the intervention treatment.

**6.3.8** Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

- Patients who do not discontinue or relapse are assumed to be in a stable schizophrenia state and receive the utility attached to this state unless they have an adverse event in which case a disutility is applied. This assumption was validated by clinical experts as described in Section 6.3.5.

- Patients who discontinue their second-line treatment will subsequently receive clozapine. This is understood to reflect the patient pathway outlined in Section 2.6 and is in line with the SPC for clozapine (41) and was confirmed by experts as outlined in section 6.3.5.

- When patients relapse they receive a reduced utility of being in the relapse state, cost of relapse and a cost of switching to the next therapy.

- Patients on clozapine who relapse will incur a reduced utility of being in relapse and the cost associated with relapse for 6-weeks. Thereafter patients will remain in the clozapine stable schizophrenia state for subsequent cycles and will experience the same risk of relapse as in previous cycles. The justification for this assumption is that clozapine is considered the last choice of antipsychotic therapy available for adolescent patients as advised by clinical experts.

- Where adverse event data are missing for clozapine, it is assumed that the probability of having an adverse event is equivalent to aripiprazole. This is thought to be a conservative assumption as clinicians confirm that the rate of adverse events is likely to be higher for clozapine. The risk of serious adverse events with clozapine has not been included.

- The RR of relapse is taken from a study of an adult population as no data was sourced for adolescents. The assumption was made that the RR of relapse for adolescents is not different from the adult population. This assumption was validated by clinical experts as described in Section 6.3.5.

- The probability of having weight gain was only considered in the first cycle (6-week period) of receiving treatment. This is because it is likely that patients will not have a constant probability of weight gain of $\geq$ 7% if they have already experienced this adverse event.

- The probability of having somnolence was applied constantly to patients on treatment throughout the model.

The following assumptions on utilities and costs are included in the model:

- Due to the lack of data on quality-of-life in adolescents with schizophrenia, utility scores measured in adults were used in the model. Experts felt that the utilities were likely to differ for adolescents when compared with adults. There was no agreement on the direction of this potential difference, therefore the adult utilities were applied and a sensitivity analysis undertaken to examine the effect of these inputs on the model results.

- Costs used in the model are assumed to be similar to costs incurred by adults with schizophrenia. Cost data in the model were taken from a previous economic evaluation and uplifted to current prices. Some of the costs were altered to reflect services used by adolescents compared with adults in the NHS on the advice of the clinical experts (see Section 6.5).

## *6.4 Measurement and valuation of health effects.*

### Patient experience

**6.4.1** Please outline the aspects of the condition that most affect patients' quality of life.

Schizophrenia is a severe and long-term mental illness imposing a large burden on the sufferer. It is associated with significant social, psychological and occupational dysfunction impacting on quality of life. The stigma which results from being labelled 'mentally ill', as well as behaviours related to psychotic symptoms, is likely to also significantly impact quality of life. Reintegration back into society is one of the most important aims for the schizophrenic patient and is dependent upon not only the improvement in their symptoms, but also their social functioning, their ability to continue their education and (ultimately) their employability.

Antipsychotics are effective in managing the positive symptoms of schizophrenia; however they may also be associated with adverse events that may have an impact on quality of life. Healthcare professionals should consider the impact on quality of life of these adverse events when deciding on the choice of antipsychotic treatment. Dissatisfaction resulting from adverse events due to treatment may increase the risk of non-compliance resulting in a higher risk of relapse, social dysfunction and hospitalisation, with increased costs to healthcare providers.

**6.4.2** Please describe how a patient's HRQL is likely to change over the course of the condition.

See section 2.

### 6.4.3 HRQL data derived from clinical trials

HRQL data was collected in the aripiprazole clinical trial; however, it does not meet the NICE reference case as the EQ-5D was not used. For this reason alternative utilities were sourced from the literature (43).

### 6.4.4 Mapping

Mapping was not used to transform any quality-of-life data from the clinical trials.

### HRQL studies

**6.4.5** Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

A systematic review of the published literature was carried out in order to identify appropriate utility data for the economic model. Standard quality-of-life search filters were applied to the disease area search terms detailed previously (Section 5.1). The inclusion and exclusion criteria were designed to identify all studies assessing a preference based measure of quality-of-life, either generic or valued in a separate study with appropriate methods (i.e. standard gamble or time trade off) or a non-preference quality-of-life measures (specifically, SF-12 or SF-36) in the adolescent or child population with schizophrenia.

Three papers of potential interest were identified in this search (44-46). Law et al (2005) (46) considered patients from Hong Kong aged between 14 and 18 years with first episode schizophrenia, where SF-36 scores were reported in patients with first episode psychosis. Kebede et al (2004) (44) collected SF-36 scores from people aged 15-49 taking part in the Butajira Rural Health Programme in Ethiopia which included subjects with schizophrenia. Kebede et al (2005) (45) collected further SF-36 data from the patients described above, over a longer period of time. Scores were collected for patients who had recent onset schizophrenia and for patients with 'long-standing' schizophrenia.

A review of the above studies showed that none reported SF-36 scores that were linked to specific health states associated with schizophrenia, and were therefore not useful for the economic evaluation.

Due to this paucity of available utility data for the patient population of interest, the studies that were included for full review in the QoL search (N=35) were reviewed again to identify any adult studies that specifically assessed utilities linked to health states related to schizophrenia in a UK population. In addition, the references of the economic evaluations identified in section 6.1 (N=4) were searched for utility values that may be relevant to the de novo economic evaluation.

During this additional review, one study (Briggs et al 2008 (43)) was identified that was particularly relevant to the decision problem. The population considered in this study was adults with schizophrenia. Although this does not directly address the problem of a lack of utility data in adolescents, this study considered the impact on health related quality-of-life of schizophrenia and impact of treatment-related adverse events in a UK setting. The time trade-off technique was used to elicit utility values related to specific health states described in the paper. This study meets all of the criteria of a good quality utility elicitation study that is appropriate for use in an economic evaluation for submission to NICE. Therefore this study was used to source the utility data for the economic model. This study concludes that age, gender and PANSS scores did not influence the results independently of health state, which informed the use of discontinuation and relapse in the model (as opposed to PANSS score related outcomes).

Briggs et al 2008 (43) do not examine the effect of somnolence on quality-of-life. As this is included in the model, the utility value for somnolence was sourced from a cost-effectiveness analysis described in section 6.1 (40). None of the other utility studies identified appeared to report the utility value associated with this adverse event.

**6.4.6** Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Due to lack of data in the appropriate patient population, an alternative source of utility vales was considered. Briggs et al (2008) (43) examined the impact of schizophrenia and treatment related adverse events on the quality-of-life from the perspective of patients and lay persons. Forty-nine patients with stable schizophrenia and 75 lay persons all completed the study. Lay persons were recruited by newspaper advertisements and schizophrenic patients were recruited via a community mental health centre. The most common treatments reported by patients in this study were olanzapine, quetiapine and clozapine.

Health states described were stable schizophrenia (no side-effects), weight gain (side-effect), diabetes (side effect), hyperprolactinaemia (side-effect male), hyperprolactinaemia (side-effect female), EPS (side-effect), relapse. These health states were described in detail and were appropriate to the condition and treatment pathway and were relevant to this submission.

The patient in the study completed the EQ-5D utility questionnaire. The scores from this questionnaire were then mapped to a utility score generated from a UK lay population. This provides an indication of the health related utility of patients in their current health state (stable schizophrenia). Following explanation of the health states, a rating scale was administered and participants were asked to rank the states along the visual analogue scale (where 0 related to the worst possible health state and 100 related to the best possible health state). The participants then completed a time trade off exercise for each health state. Utility values were presented for both lay and patient groups separately. Of particular interest for this submission are the values elicited by the patient group as per the preferred method outlined in the NICE methods guide. The results for patients are presented in Table 39.

**Table 39: Table of utility results from the patient population in Briggs et al (2008) (43)**

| Health state | Mean utility (standard error) |
|---|---|
| Stable schizophrenia | 0.919 (0.023) |
| Weight gain | 0.825 (0.028) |
| Diabetes | 0.769 (0.036) |
| Hyperprolactinaemia | 0.815 (0.030) |
| Relapse | 0.604 (0.042) |
| EPS | 0.722 (0.037) |

In addition to the above results, Briggs et al (2008) found that age, gender and PANSS scores did not influence the utility results independently of the health state.

**6.4.7** Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

N/A. Utility values were not derived from the clinical trials.

### Adverse events

**6.4.8** Please describe how adverse events have an impact on HRQL.

The most common treatment related side-effects of aripiprazole as reported in the clinical trial have been highlighted in Section 5.9. The presence of treatment related adverse events has a substantial impact on patients HRQL and can lead to treatment discontinuation. Therefore, any reported side-effects must be carefully monitored and managed. Two of the most common adverse events for which clinical data could

be identified for aripiprazole and olanzapine in the indirect comparison have been included in the model (weight gain and somnolence).

### Quality-of-life data used in cost-effectiveness analysis

**6.4.9** Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

The values in Table 40 were used to calculate utilities for patients in the economic model. Patients in the stable schizophrenia state received a utility value of 0.919. Patients experiencing an adverse event while in the stable schizophrenia state had a disutility applied according to the percentage decrease in utility according to the values outlined in Table 40. This is to avoid a scenario where a patient with an adverse event had a higher utility than that of stable schizophrenia in sensitivity analysis. The values were applied equally to all therapies in the model.

**Table 40: Summary of quality-of-life values for cost-effectiveness analysis**

| State | Utility value | CI (distribution) | Reference in submission | Justification |
|---|---|---|---|---|
| Stable schizophrenia | 0.919 | 0.87 to 0.96 (beta) | Identified study reporting utility values in schizophrenia section 6.4.6 | Most appropriate study identified in QoL searches |
| Relapse | 0.604 | 0.52 to 0.69 (beta) | Identified study reporting utility values in schizophrenia section 6.4.6 | Most appropriate study identified in QoL searches |
| Weight gain | 0.825 | 0.77 to 0.88 (beta) | Identified study reporting utility values in schizophrenia section 6.4.6 | Most appropriate study identified in QoL searches |
| Somnolence | 0.905 | 0.87 to 0.94 (beta) | Identified economic reporting utility value for somnolence, section 6.1 | Most appropriate study identified in QoL searches |

**6.4.10** If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts were consulted (as outlined in Section 6.3.5) to validate the use of utility data from adults in adolescents. Given the lack of data available, the clinical experts validated the use of utilities elicited from adults in the model. The clinical experts thought that the utilities used would be likely to vary in adolescents, but there was no agreement as to the direction of this variation. The experts suggested they would like to see the results of sensitivity analyses on these parameters to test the overall effect of a higher or lower impact of treatment related adverse effects. All assumptions with relation to utility were consistently used across all comparators within the model.

The clinical experts were keen to highlight the effect that treatments for schizophrenia have on patients' quality-of-life.

**6.4.11** Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Patients experience either the utility of being in a stable schizophrenia health state or the utility of being in the relapse health state. In addition, patients may experience treatment related adverse events. Therefore disutilities were applied to patients on treatment who had an adverse event. The application of disutility due to adverse events covers the potential variances in quality of life while on treatment.

**6.4.12** Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Treatment related side-effects are included where they are relevant and where there are comparative data. However, additional adverse effects of treatment are likely to influence the quality-of-life of patients receiving atypical antipsychotics. In particular, Briggs et al 2008 (43) highlight the importance of the risk of diabetes.

Although studies mainly concentrate on the adult population, it is likely that metabolic side-effects such as weight gain and glucose intolerance may lead to an increased incidence of diabetes in later life for adolescents receiving treatment. Diabetes is likely to have a substantial effect on the patient's quality-of-life, in particular with respect to the complications that derive from this condition. However, due to lack of long-term studies, there is a paucity of data available on the link between metabolic outcomes and the development of diabetes for individual treatments.

Because more data were available for the adult schizophrenic population, the NICE guideline model (6) reported a calculation of the probability of developing diabetes/glucose intolerance for various antipsychotic drugs, and concluded that their calculated probabilities were similar to published data. This suggests that olanzapine is strongly associated with diabetic events whereas aripiprazole, risperidone and haloperidol are poorly associated. Therefore, if these data were transferred to the adolescent population, exclusion of this link is likely to disadvantage aripiprazole and can be considered conservative.

**6.4.13** If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

N/A.

**6.4.14** Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Depending on whether patients experience side-effects or not, their HRQL will vary within each cycle of the model. The number of side-effects experienced also affects HRQL.

**6.4.15** Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

N/A.

## *6.5 Resource identification, measurement and valuation*

### NHS costs

**6.5.1** Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The clinical management of schizophrenia is usually handled in the primary care and community care setting. When patients relapse they may spend time in hospital, therefore the cost of this was taken from NHS reference costs (HRG code PA52 , Behavioural disorders) mapped from ICD10 code F200 and the specific code for children/adolescents used.

**6.5.2** Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

One reference cost for management of patients who have a relapse has been used in the model (as outlined in section 6.5.1) as this reflects the cost to the NHS of patients who have relapsed and require treatment in hospital. See section 6.5.1.

### Resource identification, measurement and valuation studies

**6.5.3** Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

The systematic searches conducted to identify adolescent specific studies in schizophrenia were found to provide limited data.

In the interests of pragmatism, additional systematic searches were not carried out to identify specific UK resource use data for adolescents in the UK, as it is likely that these data are unavailable. Therefore, the economic model produced in the NICE guideline for adults with schizophrenia (6), which was identified in the cost-effectiveness searches (see Section 6.1.2 for further details), was used to provide an estimate of the resource use for the model. The use of data from the NICE guideline model was validated by clinical experts, and amended (where appropriate) based on their recommendations, in order to reflect the use of child services, as opposed to

adult services. The data taken from this study has been outlined in Sections 6.5.6 to 6.5.8 below.

**6.5.4** If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts were consulted (as outlined in Section 6.3.5) to validate the use of resource use from adult studies in adolescents. Clinical opinion was that adult data could be used (with a small variation) for use of child and adolescent mental health services, rather than adult services.

**6.5.5 Intervention and comparators' costs**.

Several formulations of the treatments (aripiprazole, olanzapine and clozapine) included in the economic model are available. Therefore in the base case analysis, UK prescription cost analysis was used to provide the most prescribed formulation, which was then used to calculate the daily cost of the antipsychotics included in the analysis. The range of costs shown was taken from the lowest calculated costs per day and the highest calculated cost per day for use in sensitivity analysis.

The most commonly prescribed formulation of aripiprazole was the 28 tablet pack of 10 mg of Abilify priced at £95.74 (Section 1.10 and (47)). At 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 of Zyprexa priced at £79.45 (47, 48). At a dose of 12.5 mg per day (mean modal dose according to the clinical trial (12)), olanzapine was costed at £3.55 per day in the model.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The most commonly prescribed clozapine formulation was 100 mg tablets (47, 48). At a dose of 325 mg per day (based on a usual dose for patients under 18 of between 200 and 450 mg daily (41)), clozapine was costed at £2.86 per day in the model(47).

Only clozapine requires patient monitoring. When prescribing clozapine the prescribing physician must register themselves and a nominated pharmacist as well as the patient with a patient monitoring service – the Clozaril Patient Monitoring Service (CPMS) (41). Other formulations of clozapine including Denzapine and Zaponex are subject to the same regulations regarding monitoring.

Monitoring of white cell count with a differential count must be carried out according to the SPC as follows:

- At least weekly for the first 18 weeks of treatment
- At least at 2 week intervals between weeks 18 and 52
- After 1 year of treatment with stable neutrophil counts, patients may be monitored at least at 4 week intervals
- Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation

This equated to a monitoring cost associated with 2-3 blood tests per 6-week cycle in the model. As blood tests are relatively difficult to cost, the resource use and costs associated with this service was assumed to be the cost of one hour of a mental nurse (including qualifications) of £28 per hour (49).

**Table 41: Unit costs associated with the technology in the economic model**

| Items | Aripiprazole (10mgs) (range) | Ref. | Olanzapine (12,5mgs) (range) | Ref. | Clozapine (325mgs) (range) | Ref. |
|---|---|---|---|---|---|---|
| Technology cost per day | £3.42 (£2.28, £6.84) | Section 1.10 and (47) | £3.55 (£3.55, £4.29) | (47) | £2.86 (£1.28, £2.86) | (47) |
| Monitoring cost per six week cycle | £0 | Self administered | £0 | Self administered | £24.17 | SPC (41) and (49) |
| Total cost per six week cycle | £144 | | £149 | | £120+£24.17 | |

### 6.5.6 Health-state costs.

Costs of treatment and calculations for the 6-week time periods included in each of the health states are outlined in section 6.5.5. Additional costs in the health states in the model include adverse events (outlined in Section 6.5.7), and the resource use

and costs associated with relapse. The resource use and costs associated with relapse are included in this section.

**Table 42: List of health states and associated costs in the economic model**

| Health states | Items | Value | Duration | Total cost | % people treated | Reference in submission |
|---|---|---|---|---|---|---|
| Relapse | Acute hospital stay (HRG PA52) | £534.00/day* | 42 | £22,428 | 77.30% | NICE guideline model (6) and expert advice, Section 6.5.3 |
| | Child and adolescent mental health services | £19.34/day** | 42 | £812.28 | 22.70% | NICE guideline model (6) and expert advice, Section 6.5.3 |
| | Olanzapine 15mgs per day | £4.26 | 42 | £179 | 100% | 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).

### 6.5.7 Adverse-event costs

Two adverse events (weight gain and somnolence) were included in the base case analysis, as described in Section 6.3.1. Resource use for the treatment of these adverse events were taken from the NICE economic evaluation (6) (see Section 6.5.3 for further details) and validated for use in the current model by clinical experts (Sections 6.3.5 and 6.5.4). An outline of the resource use and costs associated with these adverse events are given in Table 43. Additional therapies are not required for the adverse events listed here (Section 2.7).

**Table 43: List of adverse events and summary of costs included in the economic model**

| Adverse events | Items | % of patients | Unit Cost | No. of Units | Cost per six-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 |

### 6.5.8 Miscellaneous costs

Additional costs are incurred in the model when patients switch between antipsychotic medications. Patients moving to the next line treatment (because of intolerable side effects or relapse) were assumed to incur additional costs, associated with 3 visits to a consultant psychiatrist lasting 20 minutes each at a total cost of £322 (6, 49).

## *6.6 Sensitivity analysis*

**6.6.1** Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The structure of the model was discussed a priori with an expert in health economics with a specific interest in mental health to ensure that the proposed structure closely matched clinical practice and was appropriate for use in economic modelling. Data sourced from the literature were used to predict longer term relapse rates in the model. As there is uncertainty about the most appropriate data to use for extrapolation of outcomes beyond trial follow-up, this parameter was tested in sensitivity analysis.

**6.6.2** Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Variables used in the economic model were subject to considerable uncertainty. The clinical data in the model was based on an indirect comparison of two clinical trials that showed no significant differences in 5 of 6 outcomes investigated. In addition, long term data were sourced from published estimates for adults as no data were available specific to the age group considered in the scope of this appraisal. Although expert opinion was used to validate assumptions on resource use associated with treating adverse events and relapse, these data were originally sourced from published data on adults and were therefore also tested in sensitivity analysis.

Due to the level of uncertainty around input values, the model tests each variable individually, in one-way deterministic sensitivity analysis. The upper and lower values used were error margins reported in the indirect comparison or literature, or are estimated in the model using an upper and lower limit of +- 30% of the input value. The results of this analysis are presented in Section 6.7.7 using a tornado diagram.

**6.6.3** Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was undertaken on all parameters in the model using distributions outlined in Table 59: Table of model input parameters and sources in Appendix 9.14.

## *6.7 Results*

### Clinical outcomes from the model

**6.7.1** For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Clinical data from two six-week trials were used to provide the main efficacy and adverse event data in the model using an indirect comparison. Therefore clinical outcomes at six weeks in the model are as presented in the indirect comparison (see Section 5.7) and the table of data inputs in Section 6.3.6.

No longer-term data on the above outcomes were available from clinical trials and cannot therefore be compared to outcomes from the model. For this reason the rate of relapse used to predict patient pathways within the model is tested in sensitivity analysis.

**6.7.2** Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The Markov traces for aripiprazole - olanzapine - clozapine and olanzapine - aripiprazole - clozapine are shown in

Figure 10 and Figure 11. These figures show the proportion of patients in each of the Markov states over the three year time horizon (each cycle is six weeks). These figures show where probabilities are applied from the indirect comparisons within the decision tree (the first two six-week cycles) and the movement of patients thereafter on application of risk of relapse depending on the therapy.

**Figure 10: Markov trace diagram, aripiprazole - olanzapine - clozapine**

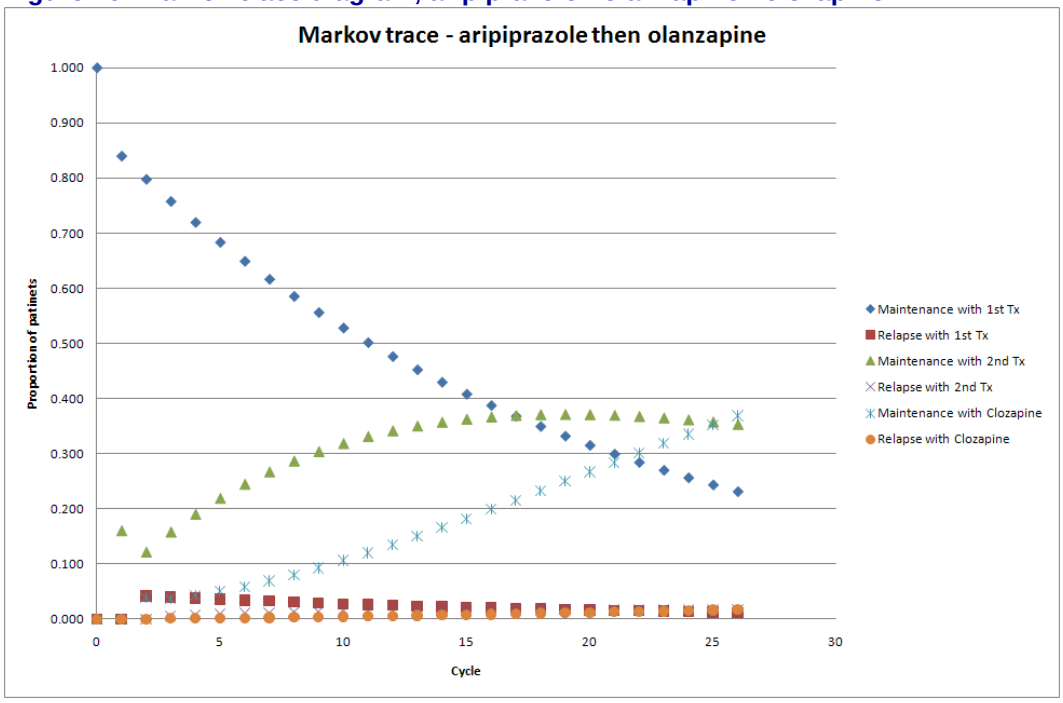
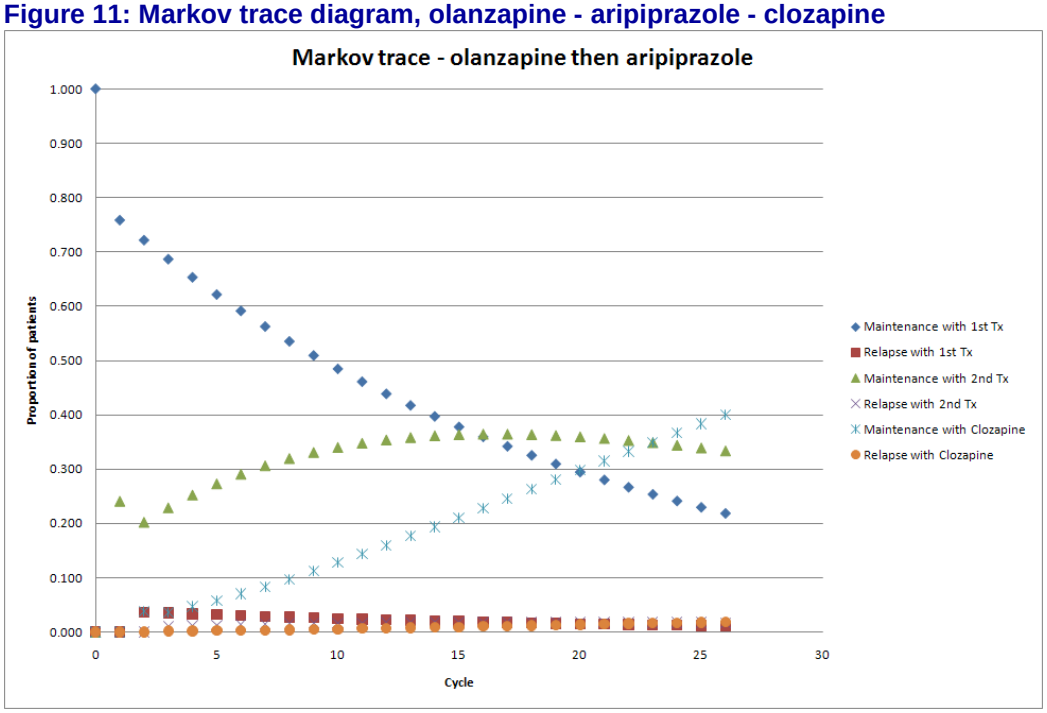



**Figure 11: Markov trace diagram, olanzapine - aripiprazole - clozapine**



**6.7.3** Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs are calculated using the utility values for each of the states in the model according to the number of people in each state and the length of time spent in the state. In each state, patients may also have an adverse event. When this occurs the appropriate utilities are deducted according to the number of people assumed to have the adverse events and the length of the cycle.

**6.7.4** Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

The model is not currently set up to report QALYs for individual outcomes therefore they are not presented here.

**6.7.5** Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

The model is not currently set up to report disaggregated incremental QALYs and costs by health state or resource use by category of cost therefore they are not presented here.

### Base-case analysis

**6.7.6** Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

**Table 44: Base case results**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Aripiprazole - olanzapine - clozapine | £23,723 | 2.597 | -£69.21 | 0.004 | Dominant |
| Olanzapine - aripiprazole - clozapine | £23,792 | 2.593 | - | - | - |
| ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years | | | | | |

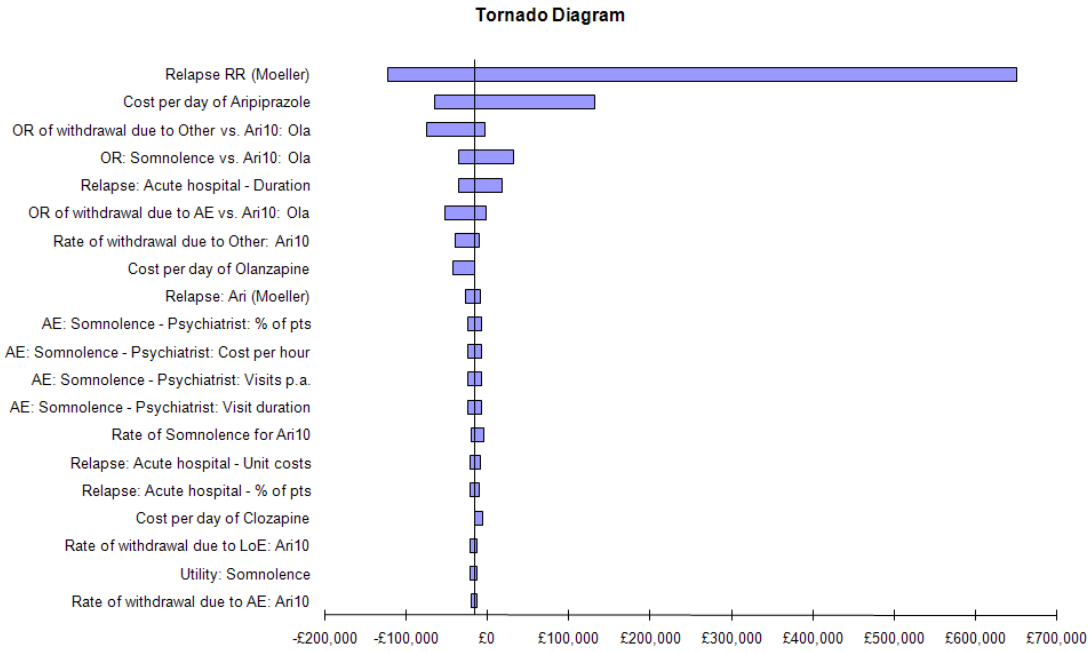
## Sensitivity analyses

**6.7.7** Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

A tornado diagram was generated to demonstrate the effect of varying individual parameters on the ICER. The top twenty parameters that influenced the ICER when varied in isolation are presented (see Figure 12). The model was most sensitive in changes to the RR of relapse and the cost per day of aripiprazole.

Only three parameters result in a cost per QALY for the aripiprazole - olanzapine - clozapine treatment arm of greater than the accepted cost per QALY threshold (£20,000) when compared with the olanzapine - aripiprazole - clozapine treatment arm when examined on an individual level. These are: RR of relapse, the cost per day of aripiprazole, and the odds ratio for somnolence. The rate of relapse is examined in further detail in Section 6.7.9. The results of the deterministic sensitivity analyses are discussed further in Section 6.7.10.

**Figure 12: Tornado diagram**




**6.7.8** Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

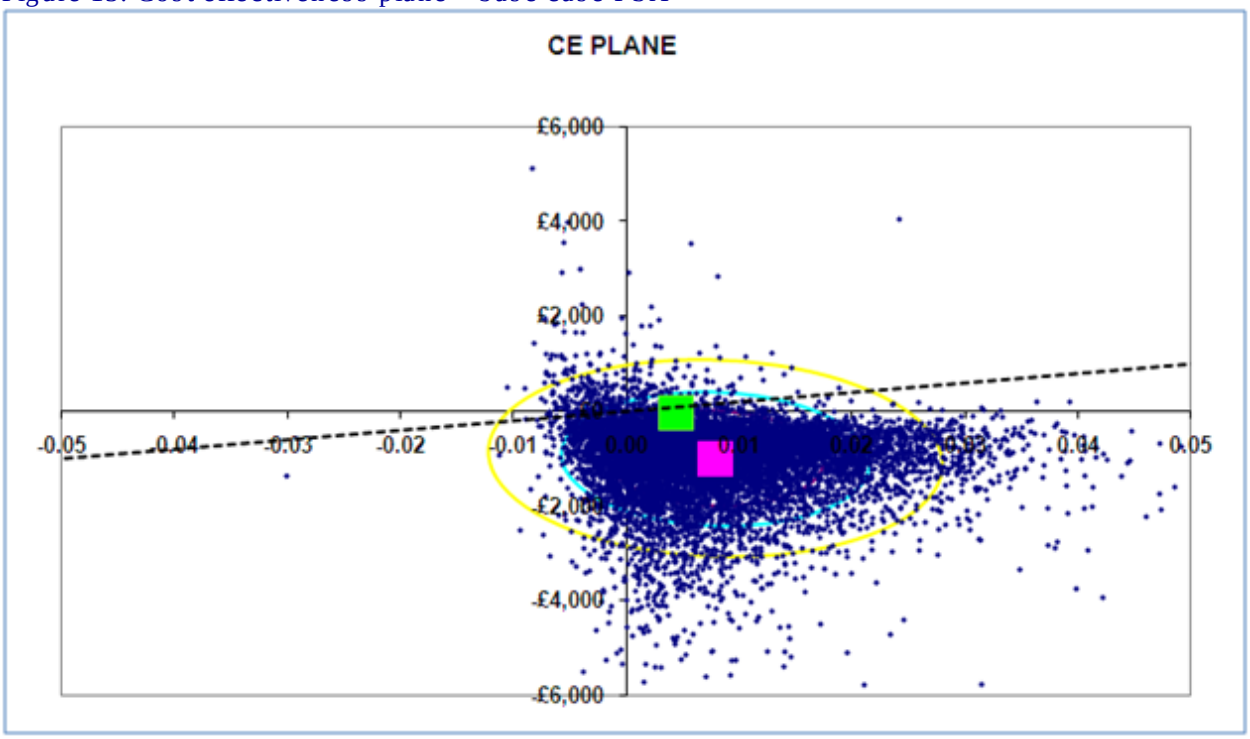
A PSA was undertaken to characterise the uncertainty associated with the mean parameter values in the model. Table 45 shows the mean total costs and QALYs, mean incremental costs and QALYs, and the ICER produced by running 10,000 simulations.

**Table 45: Results of the PSA analysis**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| 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 cost-effectiveness plane is shown in Figure 13. The green square highlights the base case ICER as presented in section 6.7.6 and the pink square shows the mean incremental cost per QALY from the PSA. Confidence ellipses have been added to the diagram showing where 50%, 75% and 95% of simulations lie on the plane. Approximately 80% of the simulations lie in the south east quadrant of the cost-effectiveness plane. This means that aripiprazole as a first line anti-psychotic (aripiprazole - olanzapine - clozapine) is dominant over olanzapine first line (olanzapine- aripiprazole - clozapine) in approximately 80% of simulations.

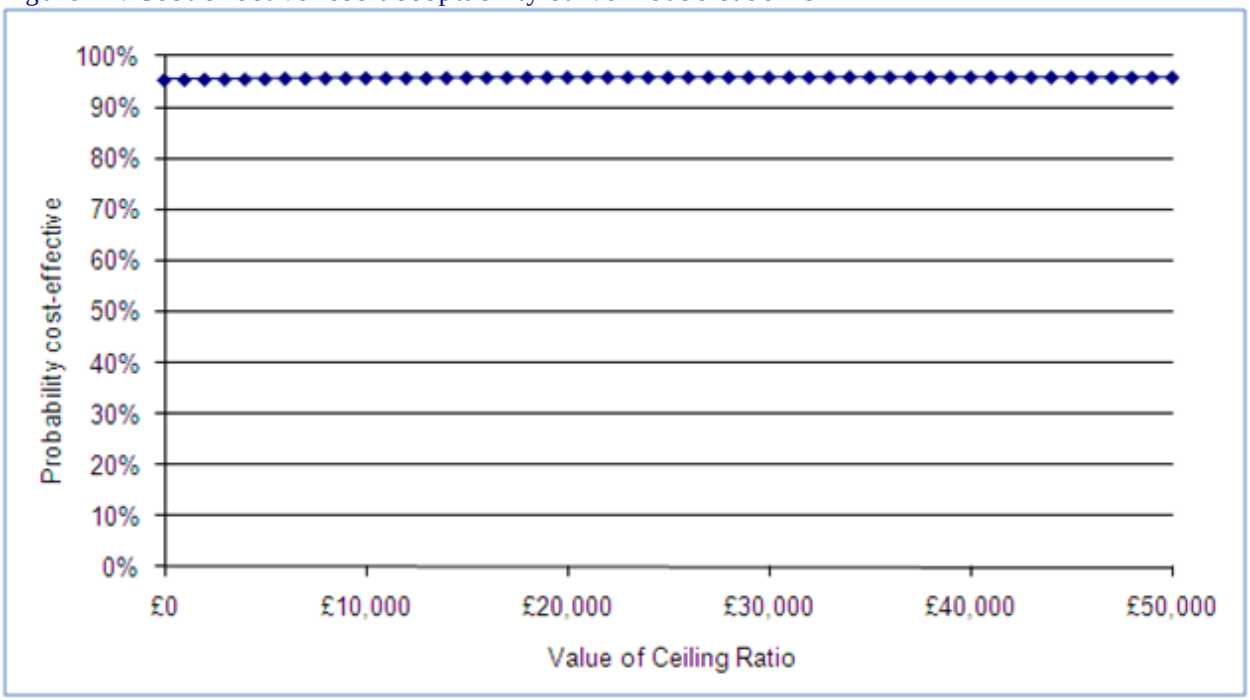
Figure 13: Cost effectiveness plane – base case PSA




The cost effectiveness acceptability curve is shown in

Figure 14. At a threshold value of £20,000 per QALY the probability of aripiprazole being cost effective is 95.99%.

Figure 14: Cost effectiveness acceptability curve – base case PSA




**6.7.9** Please present the results of scenario analysis. Include details of structural sensitivity analysis.

### Relative risk of relapse

The RR of relapse was tested in sensitivity analysis due to the lack of available data for adolescents on this parameter. Expert opinion assisted in validating the use of adult data in the model by indicating that relapse rates should not be affected by age. Generally, relapse appears to be reported as the number of hospitalisations required during the study period. However, hospitalisations in the clinical trials may not be related specifically to the treatment itself. As this outcome was not available for both aripiprazole and olanzapine in the adolescent studies, the data for relapse was sourced from an adult study. Sensitivity analysis on this parameter will test the structural assumption used to extrapolate outcomes beyond the trial follow-up.

The result of this sensitivity analysis is illustrated in the tornado diagram produced in section 6.7.7. If the highest RR of relapse is used in the model aripiprazole - olanzapine - clozapine is dominant over olanzapine - aripiprazole - clozapine. If the lowest RR of relapse is used in the model, the ICER appears very high at around £651,000 per QALY. Additional uncertainty in the model also affects the results as shown in the PSA where aripiprazole is dominant over olanzapine when uncertainty around all values in the model are taken into account (see Section 6.7.8 for further details).

The NICE guideline for adults with schizophrenia (6) conducted a mixed treatment comparison (MTC) in order to source annual probabilities of relapse. These probabilities were applied to the six-week cycles in the current model to examine the effect of using differential relapse rates for each of the treatments included. However, the NICE guideline MTC did not include clozapine therefore the RR of clozapine versus olanzapine was sourced from Davies et al 2008 (39) and applied in

the model for the purpose of this analysis. In addition, when analysing the MTC carried out within the NICE guideline, the definition of relapse differs between included studies. For example, the NICE clinical guideline states that Pigott et al 2003 reported the following definition of relapse: 'Impending decompensation based on 1 or more of the following: a CGI-I ≥5; a PANSS ≥5 on subscore items of hostility or uncooperativeness on 2 successive days; or a ≥20% increase in PANSS total score', whereas Beasley et al 2000 reported 'Hospitalisation for positive symptoms or ≥4 increase on BPRS positive score or increase of single BPRS item to 4 and increase from baseline ≥2' as their definition of relapse (6). Although this is highlighted as a limitation of the analysis, it is not clear if it was adjusted for in the MTC or what sort of bias this aspect may have introduced. In addition, the trials included in the MTC measured outcomes over different periods of time.

The six-week probability of relapse used in the model in the base case (from Moellar et al 2006 (42)) and scenario analysis (from the NICE MTC (6)) is shown in Table 46.

**Table 46: Six-week probability of relapse (base case and scenario analysis)**

| Probability of relapse (six-weeks) | Base case value (from Moellar et al 2006) | Scenario analysis value (from NICE guideline MTC) |
|---|---|---|
| Aripiprazole | 5.02% | 3.63% |
| Olanzapine | 4.86% | 2.54% |
| Clozapine | 4.86% | 2.79% |

In deterministic analysis the alternative data source for risk of relapse (from the NICE guideline MTC and Davies et al 2008) results in an ICER of £276,514 (results shown in Table 47). Although this analysis results in a substantially increased ICER compared with the base case, the NICE guidelines state that the MTC of efficacy data results were characterised by a high level of uncertainty which was reflected in their PSA. The MTC analysis contained only three aripiprazole studies, a smaller number of trials than that available for other treatment in the analysis. In addition, no value was available for clozapine from this analysis. The relapse rates used in the base case analysis were sourced from a single trial rather than relying on data combination techniques to estimate relapse rates from a wide variety of studies. This single study also provided the relapse rates for all treatments included in the model. PSA carried out on this scenario analysis (using 10,000 simulations) shows that aripiprazole - olanzapine - clozapine is dominant over olanzapine – aripiprazole - clozapine. The results of the PSA are shown in Table 48 and the cost-effectiveness plane is shown in Figure 15.

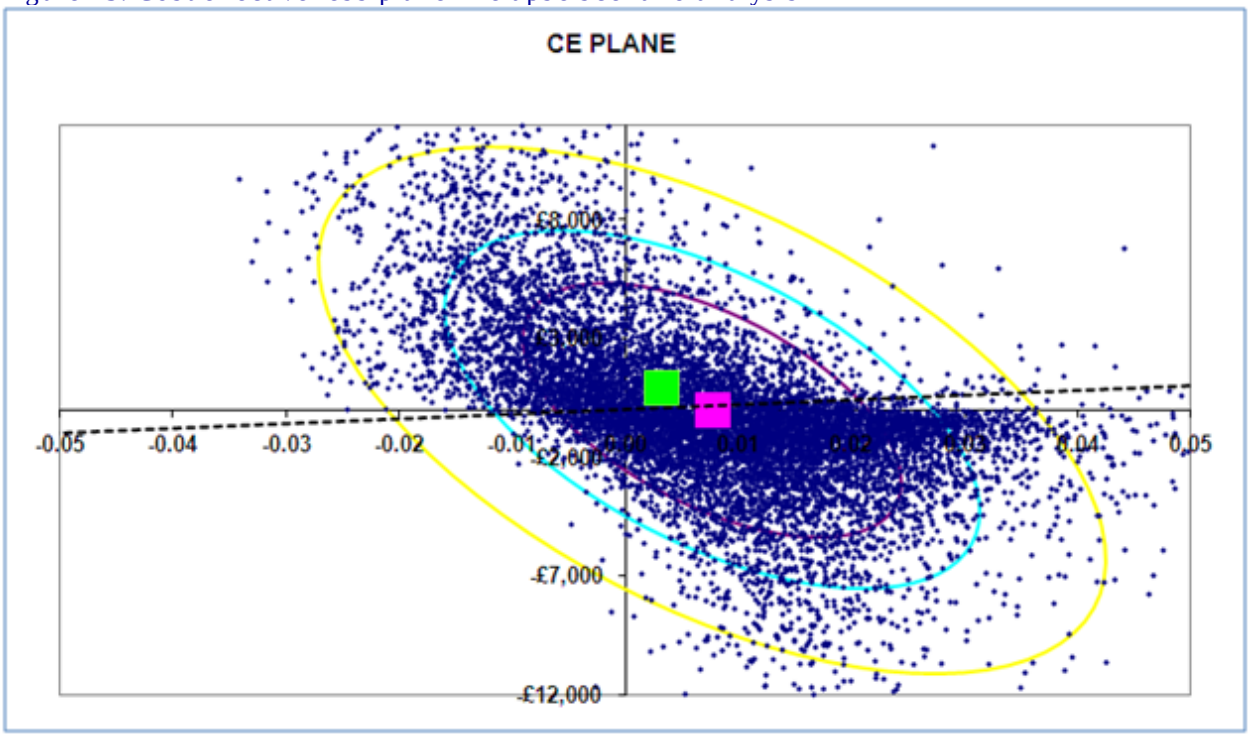
**Table 47: Deterministic model results of the relapse scenario analysis**

| Treatment | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Aripiprazole - olanzapine - clozapine | £17,040 | 2.611 | £904.22 | 0.003 | £276,514 |
| Olanzapine - aripiprazole - clozapine | £16,136 | 2.608 | - | - | - |
| ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years | | | | | |

**Table 48: PSA model results of the relapse scenario analysis**

| Treatment | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Aripiprazole - olanzapine - clozapine | £16,388 | 2.611 | -£16 | 0.008 | Dominant |
| Olanzapine - aripiprazole - clozapine | £16,404 | 2.603 | - | - | - |
| ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years | | | | | |

Figure 15: Cost effectiveness plane – relapse scenario analysis




## Benzodiazepines

The numbers of patients who received benzodiazepines in addition to their current treatment was available in the clinical trials for aripiprazole and olanzapine. Although this measure is considered a poor proxy for EPS in patients on treatment with antipsychotics, a scenario analysis was carried out to include the effect on costs and QALYs in the model if it were included. The number of patients who had benzodiazepines in the clinical trials was taken from the indirect comparison (see section 5.7). The cost of receiving benzodiazepines was considered to be a visit to the patient's psychiatrist and prescription of benzodiazepine (lorazepam). The disutility associated with EPS was taken from Briggs et al 2008 (43) and applied to

patients receiving benzodiazepines. Results of this scenario analysis using deterministic analysis are shown in Table 49.

**Table 49: Deterministic model results of the benzodiazepine scenario analysis**

| Treatment | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Aripiprazole - olanzapine - clozapine | £24,552 | 2.445 | £10.13 | -0.010 | Dominated |
| Olanzapine - aripiprazole - clozapine | £24,542 | 2.455 | - | - | - |
| ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years | | | | | |

Although the results in Table 49 show that inclusion of 'receiving benzodiazepines' in the model as a proxy for EPS makes aripiprazole - olanzapine - clozapine dominated by olanzapine - aripiprazole - clozapine, PSA (using 10,000 simulations) on this scenario analysis shows that the aripiprazole - olanzapine - clozapine dominates olanzapine - aripiprazole - clozapine on the basis of reduced costs and reduced QALYs (see Table 50). This is more clearly represented by the cost-effectiveness plane shown in

Figure 16.

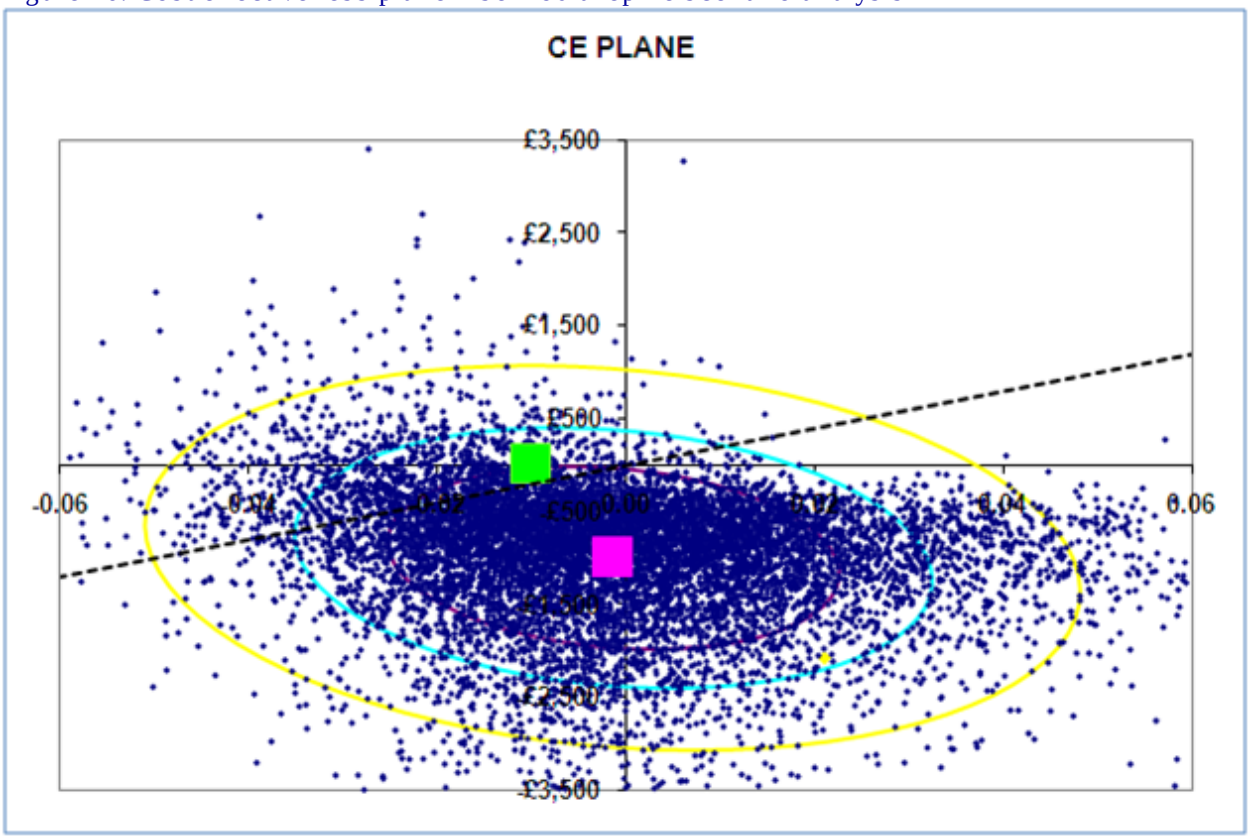
**Table 50: PSA model results of the benzodiazepine scenario analysis**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Aripiprazole - olanzapine - clozapine | £24,570 | 2.441 | -£1,006 | -0.001 | Dominant |
| Olanzapine - aripiprazole - clozapine | £25,576 | 2.442 | - | - | - |
| ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years | | | | | |

The cost effectiveness plane in

Figure 16 shows that aripiprazole - olanzapine - clozapine dominates (lies in the south east quadrant of the plane) in 42.9% of the simulations and lies in the south west quadrant of the cost-effectiveness plane in 54.1% of the simulations.

Figure 16: Cost effectiveness plane – benzodiazepine scenario analysis




## Treatment efficacy

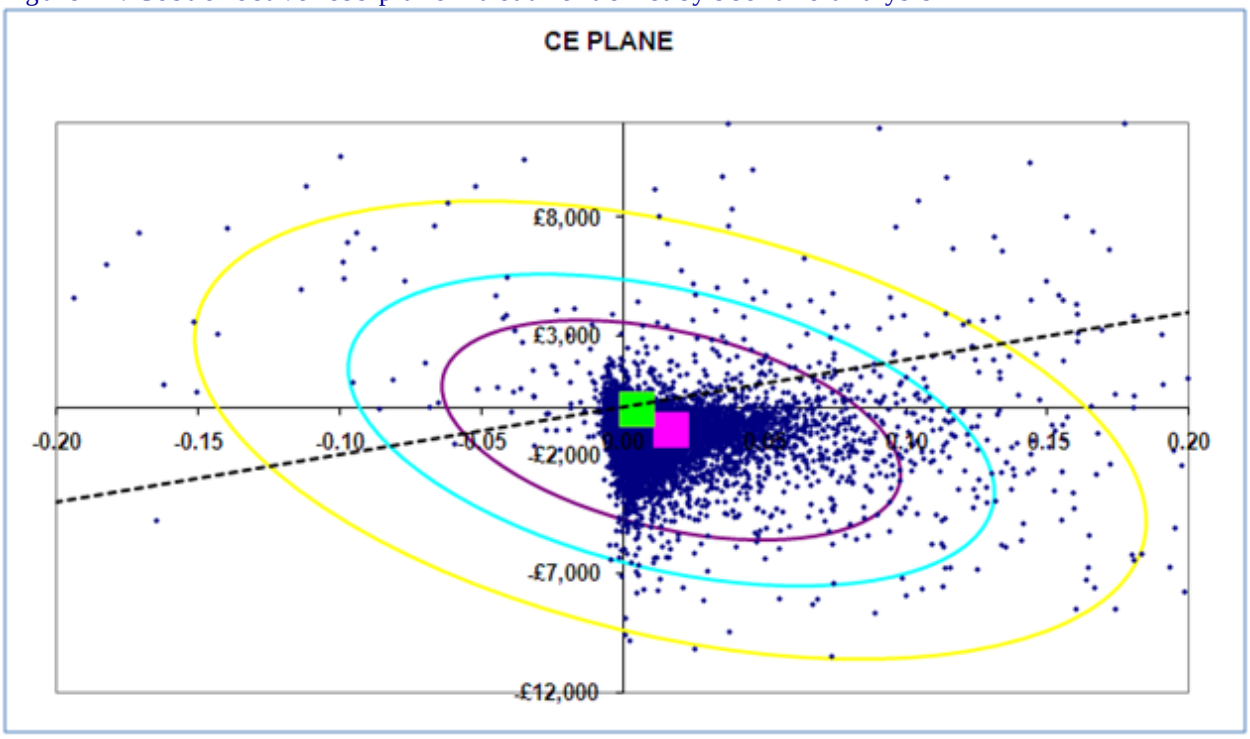
In the indirect comparison there are two ways of measuring the difference between treatment outcomes for aripiprazole and olanzapine. These are ORs and RRs. The base case analysis uses ORs. A scenario analysis was carried out using the RRs for withdrawals and adverse events in the model (Table 51).

**Table 51: Deterministic model results of the treatment efficacy scenario analysis (using RRs)**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|
| Aripiprazole - olanzapine – clozapine | £23,799 | 2.596 | -£106.24 | 0.005 | Dominant |
| Olanzapine - aripiprazole – clozapine | £23,905 | 2.591 | - | - | - |
| ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years | | | | | |

PSA (using 10,000 simulations) shows that the mean cost per QALY remains dominant when the RRs are used instead of ORs. The mean incremental cost saving was £978 and the mean incremental utilities were 0.017 (see Figure 17).

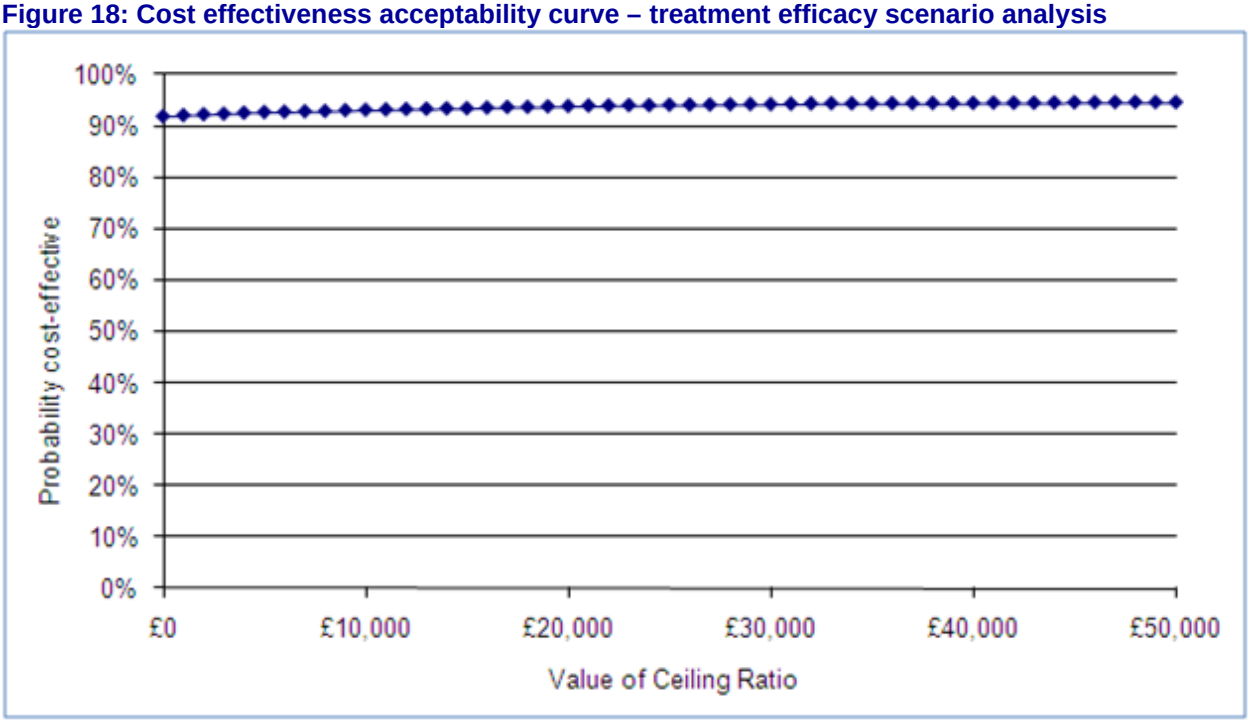
Figure 17: Cost effectiveness plane – treatment efficacy scenario analysis




The CEAC is shown in

Figure 18. At a threshold value of £20,000 the probability of aripiprazole being cost effective is 93.74%.

**Figure 18: Cost effectiveness acceptability curve – treatment efficacy scenario analysis**

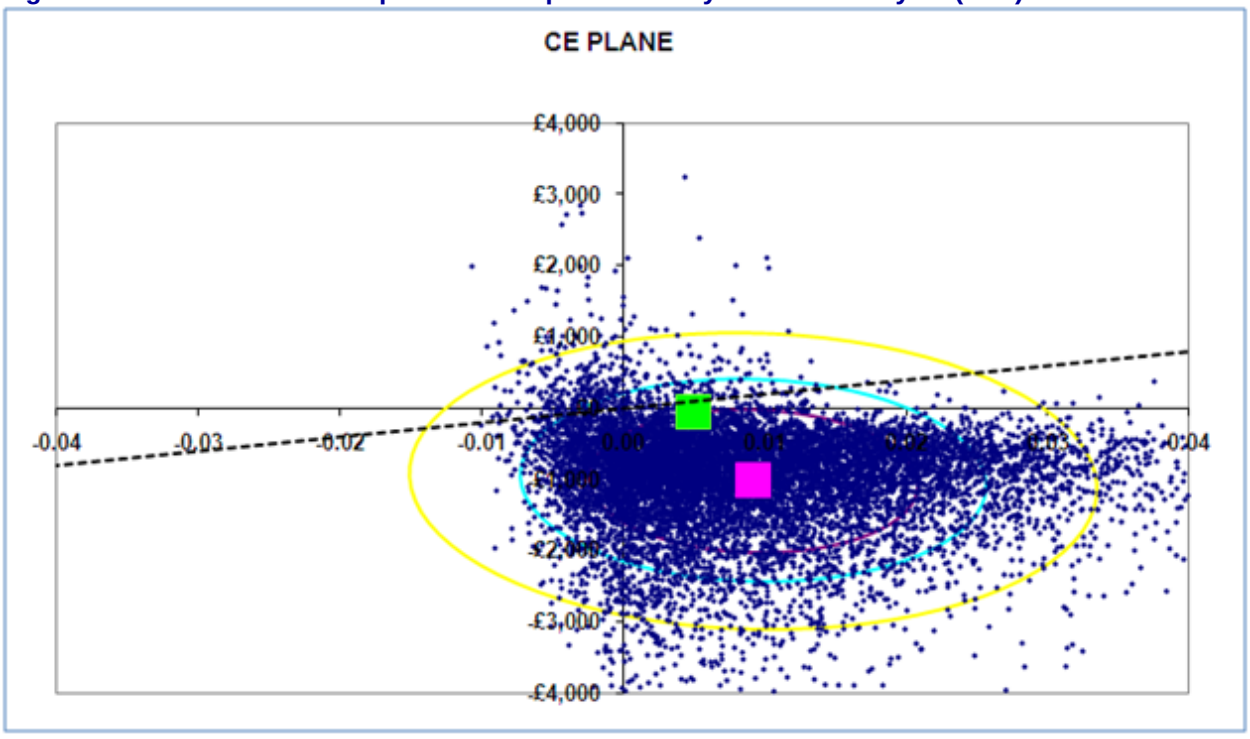


## Disutility with clozapine

The model does not account for serious adverse events that patients might experience whilst on clozapine, for example agranulocytosis. The mortality rate resulting from agranulocytosis while on the patient monitoring scheme is 0.01% (41). While the effects of this would be negligible in the current model, there may be a utility decrement associated with being on clozapine due to awareness of the potential for serious adverse events. Scenario analysis was used to show the impact of including an additional utility decrement that may be associated with clozapine. The highest and lowest utility decrements for other adverse events in the model (0.01 for somnolence and 0.2 for EPS (used in the benzodiazepine sensitivity analysis) respectively) were applied to patients on clozapine. The aripiprazole treatment arm remained more effective and less costly in each of these scenarios in deterministic analyses. When PSA was carried out on each of the above scenarios the direction of this result did not change.

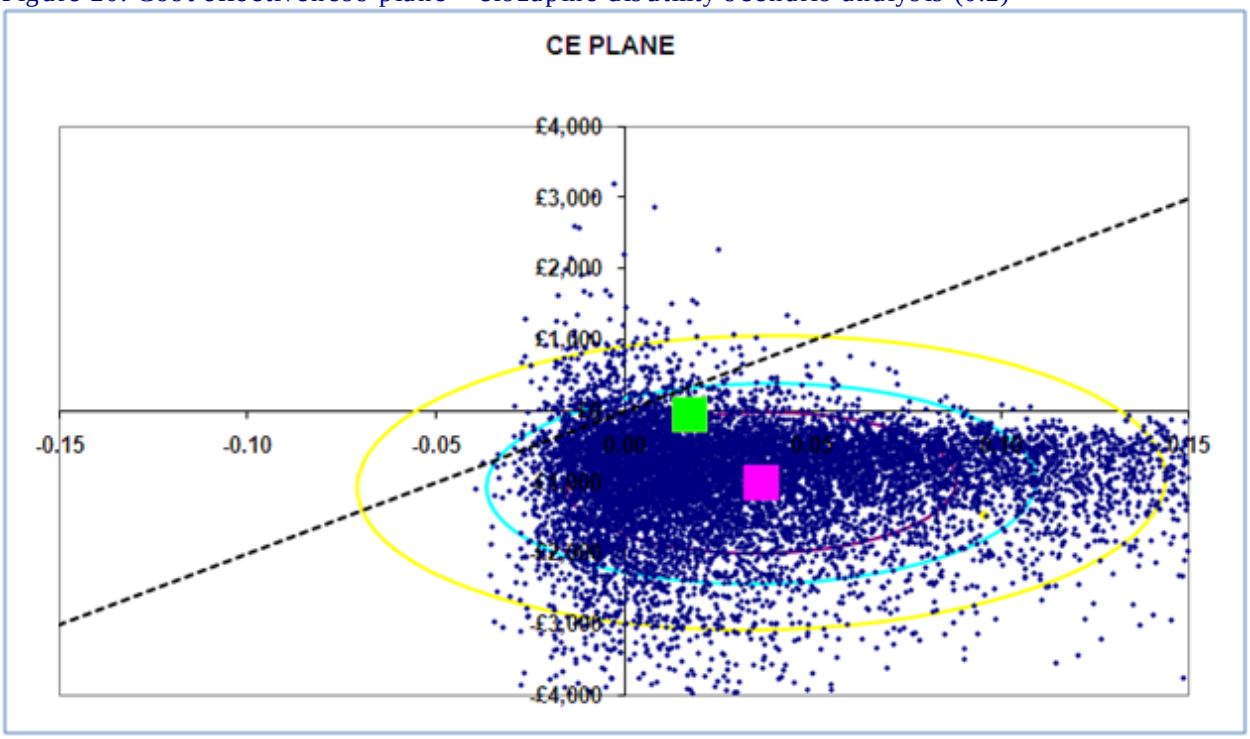
The cost-effectiveness plane in Figure 19 shows that the mean cost per QALY remains dominant when a disutility of 0.01 is applied to patients on clozapine. The CEAC showed that at a threshold value of £20,000 the probability of aripiprazole being cost effective is 95.76%.

**Figure 19: Cost effectiveness plane – clozapine disutility scenario analysis (0.01)**




The cost-effectiveness plane in Figure 20 shows that the mean cost per QALY remains dominant when a disutility of 0.2 is applied to patients on clozapine. The CEAC showed that at a threshold value of £20,000 the probability of aripiprazole being cost effective is 96.01%.

Figure 20: Cost effectiveness plane – clozapine disutility scenario analysis (0.2)




**6.7.10** What were the main findings of each of the sensitivity analyses?

**Deterministic sensitivity analysis**

When all parameters in the model were varied according to an applied distribution of uncertainty, three parameters influenced the ICER in such a way that aripiprazole was no longer cost effective at a £20,000 threshold value. These were; RR of relapse, OR of somnolence, cost per day of aripiprazole. The RR of relapse is discussed in the scenario analysis findings below.

The rate of somnolence with aripiprazole is lower than olanzapine in the base case. In the deterministic sensitivity analysis this value is varied according to the confidence intervals sourced from the indirect comparison (Section 5.7). The lowest value used in the deterministic sensitivity analysis for the OR of somnolence is 0.54. This results in olanzapine having a lower rate of somnolence than aripiprazole. When combined with the higher cost of aripiprazole, this increases the ICER to £31,500.

The cost per day of aripiprazole is based on the formulation with the highest market share. If the highest cost formulation of aripiprazole is used at a cost of £6.84 then it becomes more costly than olanzapine and the ICER rises to £131,000. However, this analysis does not take into account patient preference for this more expensive formulation (an oral solution) in place of tablets. In addition, it is unlikely that this formulation will be used in clinical practice as the majority of adolescents will take a once a day oral tablet. This is supported by the prescription analysis data (48) which shows the most prescribed formulation is the 10 mg tablets.

**Scenario analysis**

The model is sensitive to the RR of relapse. This is because this input parameter is responsible for the movement of patients in the Markov section of the model and is therefore the most influential variable. PSA shows that aripiprazole is dominant over olanzapine when uncertainty around all the values in the model is taken into account.

The inclusion of patients receiving benzodiazepines, as a proxy for EPS, also has a substantial effect on the model results. However, PSA shows that aripiprazole - olanzapine - clozapine dominates olanzapine - aripiprazole - clozapine on the basis of reduced costs and reduced QALYs, that is, the mean ICER lies in the south west quadrant of the cost effectiveness plane. This appears to be due to the high disutility associated with EPS in the model and the increased costs associated with treatment of this adverse event.

The use of RR or ORs from the indirect comparison for use in the model does not appear to greatly influence either the base case results in the deterministic analysis or the mean ICER reported in the PSA.

The inclusion of an additional disutility associated with clozapine did not change the base case result. Inclusion of this variable reduces the QALYs in each treatment arm as patients who relapse will incur additional disutility associated with receiving clozapine. However, this change is not enough to alter the direction of the results.

**6.7.11** What are the key drivers of the cost-effectiveness results?

The probability of relapse is the parameter that has the greatest effect on the ICER and is therefore a key model driver. This parameter defines how patients move through the model and has therefore been tested extensively in sensitivity analysis.

The uncertainty around input parameters is also a key driver of the results. Data on patients who discontinue and adverse events were taken from an indirect comparison of two placebo controlled studies and other published data. The results of the indirect comparison showed that only 1 of the 6 outcomes examined was statistically significant therefore the efficacy of the treatments considered is very similar. As the treatments have similar efficacy the QALYs between them are small and the model therefore becomes sensitive to even the smallest variations in input parameters.

## *6.8 Validation*

**6.8.1** Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model was validated using the following techniques:

- Clinical data, utilities and resource use data were double extracted and double checked by at least two modellers/health economists.

- Calculations in the model were checked by at least two modellers/health economists, e.g. the conversion of rates to probabilities in the model.

- The model concept and structural assumptions were validated prior to building the model with a health economic expert with an interest in the field of mental health.

- The model parameters were varied according to an model validation checklist which lists activities for the modeller to review expected versus actual results, for example, when setting all utility values to 1 the expected undiscounted QALYs should equal 3 (over the three year time horizon).

## *6.9 Subgroup analysis*

**6.9.1** Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

No subgroup analyses were undertaken.

## *6.10 Interpretation of economic evidence*

**6.10.1** Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The current analysis concludes that aripiprazole is a cost effectiveness treatment option for the treatment of schizophrenia in adolescents when compared with olanzapine. This is the first analysis which has specifically attempted to address the cost effectiveness of treatment in this population. Given the lack of data for the adolescent population, evaluation of adult analysis has shown similar trends.

Davies et al 2008 (39) concluded that the treatment sequence aripiprazole followed by risperidone was most cost-effective compared with a range of other treatment sequences. The current analysis also considers aripiprazole to be a cost effective treatment in comparison with olanzapine.

Barnett et al 2009 (38) concluded that aripiprazole treatment may result in fewer onsets of diabetes and fewer incidences of CHD compared with standard of care and as a result could be associated with long-term cost savings to the UK health care system. Although diabetes and CHD were not modelled in the current analysis, the conclusion made by Barnett et al 2009 (38) is supported by the NICE guideline model. The NICE guideline model reports a calculation of the probability of developing diabetes/glucose intolerance for various antipsychotic drugs and concluded that their calculated probabilities were similar to published data suggesting

that olanzapine was strongly associated with diabetic events whereas aripiprazole, risperidone and haloperidol were poorly associated.

The NICE guideline model (6) ranked treatments in order of their potential cost effectiveness but concluded that extensive sensitivity analysis showed that results were characterised by high uncertainty and probabilistic analysis showed that no antipsychotic medication could be considered clearly cost-effective compared to the other options included in the assessment. The current model is also characterised by high levels of uncertainty in terms of input data.

Heeg et al 2008 (40) reported that atypical treatment dominated the conventional group as it was cost saving and resulted in more QALYs. The results from the current analysis also conclude that atypical treatment is cost effective but only in comparison with other atypical treatment.

**6.10.2** Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

The evaluation covers the adolescent group of patients for which aripiprazole is licensed.

**6.10.3** What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

**Model strengths**

The economic evaluation follows the NICE reference case as closely as possible. In defining the decision problem, the scope was followed as closely as possible and where adjustments have been made these are justified in the context of available data. All comparators for which clinical trials for adolescent patients were available were included. Comparators listed in the scope were included in the systematic literature review. Olanzapine was included as the main comparator in the economic model as this was the only drug for which adolescent data could be sourced. The perspective on costs is that of the NHS and PSS and all available data were used to estimate the health effects on individuals. Outcomes were synthesised using data from a systematic review of the literature. QALYs were used to estimate health effects on individuals, HRQL was reported directly by patients and the source of preference data for valuation of changes in HRQL was a representative sample of the public. The discount rate applied was 3.5% for both costs and health effects.

The model follows the clinical pathway as accurately as possible and clinical expert input was used to validate the pathway. Expert opinion from both clinicians and an economist was used appropriately and in conjunction with the published literature in order to ensure that the model accurately reflects clinical practice.

The model contains clinical data for patients who discontinue and experience adverse events from trials of adolescents with schizophrenia. This is entirely appropriate for the patient population in this appraisal. The model does not rely solely on adult data but uses estimates from adult data where data for adolescents were not available. When adult data were used in the model, this was validated by clinicians and adjusted as necessary to reflect the differences in the adolescent

population. It was also used consistently and equally across all comparators in the model so as not to bias the results.

**Model weaknesses**

Many of the weaknesses in the model are due to lack of available data to inform model inputs. For example, the model considers only two treatments for schizophrenia in adolescents as only two trials were identified that were considered suitable for combination in an indirect comparison to provide comparator evidence for the model. The application of relapse rates was assumed constant over time due to lack of long-term data from which comparative data could be sourced. This lack of data contributes to the uncertainty in the model.

### 6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

No further analysis that has not already been justified has been omitted. Further clinical data are required to enhance the robustness of the model results.

# Section C – Implementation

## 7 Assessment of factors relevant to the NHS and other parties

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

As calculated using GPRD data in Section 2.2, the overall prevalence rate for males and females aged 15-17 years of age with schizophrenia is estimated at 16.68 (95% CI, 9.25-24.12) and 7.49 (95% CI, 2.73-12.26)/100,000 population respectively. When applied to the mid-2008 population estimates for people aged 15-17 years in England and Wales, this indicates a total of 256 (180 male patients and 76 female patients) in the adolescent age group.

The GPRD data also showed that a trend cannot be estimated in the prevalence of schizophrenia in this age group from one year to the next. Therefore, for the purpose of this analysis, it is assumed that all patients identified above may be considered for treatment with aripiprazole and that the same number of patients will be eligible for treatment over the next 5 years.

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

It is not possible to determine the current market share of atypicals in the adolescent group. Although prescribing data exists this relates to all prescribing and is not split by patient age. Therefore the budget impact of aripiprazole use over the next 5 years has been calculated based on the expected market share of aripiprazole and the cost of 10mg aripiprazole (£1,248 per patient per year).

7.3 What assumption(s) were made about market share (when relevant)?

Table 52 shows the assumptions made regarding market share using number of patients calculated in Section 7.1 for aripiprazole over the next 5 years assuming a positive recommendation for aripiprazole use first line.

**Table 52: Assumption on expected market share (and number of patients) for the next 5 years**

| | Year 1 (n) | Year 2 (n) | Year 3 (n) | Year 4 (n) | Year 5 (n) |
|---|---|---|---|---|---|
| Aripiprazole | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

As aripiprazole is currently being prescribed in the NHS alongside other antipsychotic treatments for adolescents, it is not thought that any additional costs associated with the implementation of guidance on aripiprazole will affect commissioners.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Cost of aripiprazole is detailed in Section 6.5.

7.6 Were there any estimates of resource savings? If so, what were they?

No, the budget impact presented here represents drug costs only.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The budget impact of aripiprazole use assuming the market share uptake outlined in Table 52 is shown in Table 53. The calculations are based on the annual drug cost of 10mgs of aripiprazole outlined in Section 7.2 and the expected patient population as outlined in Section 7.3, *[redacted]

**Table 53. Budget impact of aripiprazole - drug costs only**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Aripiprazole | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

As explained in Section 6.4.12, the model did not take into account the additional budget impact of diabetes or other metabolic conditions because of a lack of data in adolescents. Published data suggests that olanzapine is strongly related to diabetic events while aripiprazole, among other treatments, is poorly associated. If this aspect is included in the calculations, it may show that an increased uptake of aripiprazole is likely to generate further cost savings due to reduced diabetic events in adulthood.

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# 9 Appendices

## *9.1 Appendix 1*

**9.1.1** SPC/IFU, scientific discussion or drafts.

## *9.2 Appendix 2: Search strategy for Section 5.1 (Identification of studies)*

The following information should be provided.

**9.2.1** The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were searched through the OVID SP platform:

- Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations
- Ovid MEDLINE(R) 1950 to Present
- EMBASE 1980 to 2009 Week 49
- Cochrane library

**9.2.2** The date on which the search was conducted.

The searches were conducted on 11th of December 2009.

**9.2.3** The date span of the search.

No date restriction was applied to the searches (besides the inherent date capture of the specified databases, see above).

**9.2.4** The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

| **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present (11/12/09)** | |
|---|---|
| 1 | (Olanzapine or Zyprexa or Zyprexa or Zydis or Zalasta or Zolafren or Olzapin or Rexapin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] |
| 2 | (Risperidone or Risperdal or Ridal or Sizodon or Riscalin or Rispolept or Belivon or |

| | |
|---|---|
| | Rispen).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] |
| 3 | (Quetiapine or Seroquel or SeroquelXR or Ketipinor).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] |
| 4 | (Aripiprazole or Abilify).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] |
| 5 | (EOSS or (early onset and schizo*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] |
| 6 | (paranoid schizophrenia or paranoid psychosis).mp. |
| 7 | (schizo$ or hebephreni$).ti,ab. |
| 8 | exp Schizophrenia/ or exp Schizophrenia, Childhood/ |
| 9 | 5 or 6 or 7 or 8 |
| 10 | exp clinical trials/ or exp clinical trial/ or exp controlled clinical trials/ |
| 11 | exp crossover procedure/ or exp cross over studies/ or exp crossover design/ |
| 12 | exp double blind procedure/ or exp double blind method/ or exp double blind studies/ or exp single blind procedure/ or exp single blind method/ or exp single blind studies/ |
| 13 | exp random allocation/ or exp randomization/ or exp random assignment/ or exp random sample/ or exp random sampling/ |
| 14 | exp randomized controlled trials/ or exp randomized controlled trial/ or randomized controlled trials as topic/ |
| 15 | (clinical adj2 trial$).tw. |
| 16 | (crossover or cross over).tw. |
| 17 | (((single$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$)).tw. |
| 18 | (placebo$ or random$).mp. |
| 19 | (clinical trial$ or random$).pt. or treatment outcome$.mp. |
| 20 | 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 |
| 21 | (Haloperidol or Aloperidin or Bioperidolo or Brotopon or Dozic or Duraperidol or Einalon or Eukystol or Haldol or Halosten or Keselan or Linton or Peluces or Serenace or Serenase or Sigaperidol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] |
| 22 | (Amisulpride or Solian).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] |
| 23 | 1 or 2 or 3 or 4 or 21 or 22 |
| 24 | 9 and 20 and 23 |
| 25 | limit 24 to ("all child (0 to 18 years)" or "adolescent (13 to 18 years)") |

| **EMBASE 1980 to 2009 Week 49 (11/12/09)** | |
|---|---|
| 1 | (Olanzapine or Zyprexa or Zyprexa or Zydis or Zalasta or Zolafren or Olzapin or Rexapin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] |
| 2 | (Risperidone or Risperdal or Ridal or Sizodon or Riscalin or Rispolept or Belivon or Rispen).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] |
| 3 | (Quetiapine or Seroquel or SeroquelXR or Ketipinor).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] |
| 4 | (Aripiprazole or Abilify).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] |
| 5 | exp schizophrenia/ |
| 6 | (EOSS or (early onset and schizo*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] |
| 7 | (paranoid schizophrenia or paranoid psychosis).mp. |
| 8 | (schizo$ or hebephreni$).ti,ab. |
| 9 | 5 or 6 or 7 or 8 |

| | |
|---|---|
| 10 | exp clinical trials/ or exp clinical trial/ or exp controlled clinical trials/ |
| 11 | exp crossover procedure/ or exp cross over studies/ or exp crossover design/ |
| 12 | exp double blind procedure/ or exp double blind method/ or exp double blind studies/ or exp single blind procedure/ or exp single blind method/ or exp single blind studies/ |
| 13 | exp random allocation/ or exp randomization/ or exp random assignment/ or exp random sample/ or exp random sampling/ |
| 14 | exp randomized controlled trials/ or exp randomized controlled trial/ or randomized controlled trials as topic/ |
| 15 | (clinical adj2 trial$).tw. |
| 16 | (crossover or cross over).tw. |
| 17 | (((single$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$)).tw. |
| 18 | (placebo$ or random$).mp. |
| 19 | (clinical trial$ or random$).pt. or treatment outcome$.mp. |
| 20 | 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 |
| 21 | (Haloperidol or Aloperidin or Bioperidolo or Brotopon or Dozic or Duraperidol or Einalon or Eukystol or Haldol or Halosten or Keselan or Linton or Peluces or Serenace or Serenase or Sigaperidol).mp. |
| 22 | (Amisulpride or Solian).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] |
| 23 | 1 or 2 or 3 or 4 or 21 or 22 |
| 24 | 9 and 20 and 23 |
| 25 | limit 24 to (child or adolescent <13 to 17 years>) |

| **Cochrane library (Wiley) (11/12/09)** | |
|---|---|
| #1 | MeSH descriptor Schizophrenia explode all trees |
| #2 | (schizo* or hebephreni*):ti or (schizo* or hebephreni*):ab or (schizo* or hebephreni*):kw |
| #3 | (#1 OR #2) |
| #4 | (Olanzapine or Zyprexa or Zyprexa or Zydis or Zalasta or Zolafren or Olzapin or Rexapin) |
| #5 | (Risperidone or Risperdal or Ridal or Sizodon or Riscalin or Rispolept or Belivon or Rispen) |
| #6 | (Quetiapine or Seroquel or SeroquelXR or Ketipinor) |
| #7 | (Aripiprazole or Abilify) |
| #8 | (Haloperidol or Aloperidin or Bioperidolo or Brotopon or Dozic or Duraperidol or Einalon or Eukystol or Haldol or Halosten or Keselan or Linton or Peluces or Serenace or Serenase or Sigaperidol) |
| #9 | Amisulpride OR Solian |
| #10 | (#4 OR #5 OR #6 OR #7 OR #8 OR #9) |
| #11 | MeSH descriptor Adolescent explode all trees |
| #12 | MeSH descriptor Child explode all trees |
| #13 | (#11 OR #12) |
| #14 | (#3 AND #10 AND #13) |

**9.2.5** Details of any additional searches, such as searches of company databases (include a description of each database).

Additional hand-searching of review articles was conducted to identify additional sources of relevant data.

**9.2.6** The inclusion and exclusion criteria.

**Inclusion criteria**
The following studies were excluded from the review:

- Randomised controlled trials conducted in adolescents (13-17 years) with schizophrenia investigating the efficacy or safety of one or more of the following pharmacological interventions: olanzapine, risperidone, quetiapine, placebo, haloperidol, amisulpride, aripiprazole.
- Outcomes of interest included
    - PANSS
    - BPRS
    - Global state (CGI)
    - Discontinuations
    - Discontinuations due AE
    - Adverse events
    - Mortality (suicide)
    - Mental state (total symptoms, depression)
    - Social functioning
    - Recurrence
    - Health-related quality of life

**Exclusion criteria**
The following studies were excluded from the review:

- Non-systematic reviews, letters, commentaries, case report/series, surveys
- Studies that do not report relevant outcome data on efficacy or safety of stated interventions to treat schizophrenia
- Studies conducted in Adult (>17 years) or Child (<13 years) populations
- Studies including patients with other or mixed diagnoses, i.e. not schizophrenia or schizoform disorder alone.
- Studies examining an intervention outside of scope (as detailed in inclusion criteria)
- Head to head studies with <2 arms including interventions of interest (as detailed in inclusion criteria)
- Duplicate record

Non-randomised evidence (e.g. observational data, open label clinical trial) were excluded from the RCT search, but were labelled at exclusion phase for subsequent interrogation.

### 9.2.7 The data abstraction strategy

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Data were extracted from eligible publications into a pre-defined Microsoft Excel® spreadsheet by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

## *9.3 Appendix 3: Quality assessment of RCT(s) (Section 5.4).*

| **Study No. 31-03-239 (13, 18)** | | |
|---|---|---|
| **Study question** | **How is the question addressed in the study?** | **Grade (yes/no/not clear/N/A)** |
| Was randomisation carried out appropriately? | Subjects were randomised 1:1:1 via an interactive voice response system (IVRS) to receive aripiprazole 10 mg, aripiprazole 30 mg, or placebo following computer-generated randomisation codes prepared by the sponsor's Biostatistics Department. The randomisation was stratified by region (US, European region, and all other regions) | Yes |
| Was the concealment of treatment allocation adequate? | Blinding was maintained by the use of blister cards from which subjects took the same number of tablets per dose, regardless of treatment arm assignment. All tablets were identical in appearance. | Yes |
| Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease? | The three treatment arms were demographically similar and had similar baseline disease characteristics | Yes |
| Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)? | The study was double-blind and no un-blinding of treatment occurred in this study | Yes |
| Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? | Drop-outs were accounted for and were similar between groups | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | All outcomes appeared to be addressed in the clinical study report | No |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | All randomised patients were included in the efficacy analysis and the last observation carried forward dataset was used to account for missing data (missing data at a post-baseline visit was imputed with the value obtained at the nearest preceding visit) | Yes |
| Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

## *9.4 Appendix 4: Search strategy for Section 5.7 (Indirect and mixed treatment comparisons)*

Studies eligible for the indirect comparison were identified through the “master” clinical search described previously; see Section 5 and Appendix 2 (Section 9.2).

## 9.5 Appendix 5: Quality assessment of comparator RCT(s) in Section 5.7 (Indirect and mixed treatment comparisons)

| **Kryzhanovskaya et al, 2009 (12)** | | |
|---|---|---|
| **Study question** | **How is the question addressed in the study?** | **Grade (yes/no/not clear/N/A)** |
| Was randomisation carried out appropriately? | Method of randomisation was not reported | Not clear |
| Was the concealment of treatment allocation adequate? | Method of blinding was not reported | Not clear |
| Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease? | The two treatment groups did not significantly differ on any baseline characteristics | Yes |
| Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)? | The study was double-blind, but method of blinding was not reported | Not clear |
| Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? | Significantly fewer olanzapine-treated versus placebo-treated patients discontinued treatment because of lack of efficacy | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | All outcomes appeared to be addressed | No |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Data were appropriately analysed on an intention-to-treat basis. The last observation carried forward method was used to account for missing data | Yes |
| Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

## 9.6 Appendix 6: Search strategy for Section 5.8 (Non-RCT evidence)

Non-RCT evidence was identified through the "master" clinical search described previously, see Section 5.1 and Appendix 2 (Section 9.2).

## 9.7 Appendix 7: Quality assessment of non-RCT(s) in Section 5.8 (Non-RCT evidence)

It is difficult to assess the quality of single arm studies due to the lack of validated checklists, therefore we conducted qualitative appraisals for studies 31-03-241 and 31-05-243.

**Study 31-03-241**

**Summary**

Study 31-03-241 is a multinational, open-label, safety and tolerability study of flexible-dose aripiprazole (2 mg – 30 mg) in adolescent subjects with schizophrenia, and child and adolescent patients with bipolar I disorder, manic or mixed episode with or without psychotic features. The study enrolled subjects who had previously completed Study 31-03-239 (adolescents with schizophrenia) or had withdrawn from the double-blind extension phase of study 31-03-240 (children and adolescents with bipolar I disorder).

**Key features**

*Patient recruitment:* A total of 325 subjects were screened and all 325 were enrolled in the study; 239 adolescent subjects with schizophrenia and 86 child and adolescent subjects with bipolar I disorder. The selection/eligibility criteria were adequately described. All subjects were analysed for both efficacy and safety.

[redacted]

*Withdrawals and dropouts:* Withdrawals and dropouts were adequately reported. In the subpopulation of adolescent subjects with schizophrenia, a total of 58 (24.3%) subjects discontinued from the study; the rates of discontinuation due to adverse events (2.5%) and [redacted] were low. Subject withdrawal of consent (28/239 [11.7%]) and loss to follow-up (7/239 [2.5%]) were the most common reason for discontinuation.

*Analyses:* The frequency and severity of AEs, SAEs, and discontinuation from the study due to AEs were reported. Secondary outcomes included mean change from baseline on; the PANSS score, the CGAS, and the CGI score. Quality of life was assessed by the P-QLES-Q.

*Completeness of reporting:* Pre-specified outcomes were adequately reported. Patients were evaluated for tolerability and safety at weeks 1, 2, 3, 4, 8, 12, 18 and 26. In addition, a follow-up phone call was made at week 30 to assess adverse events.

**Study 31-05-243**

**Summary**

Study 31-05-243 is a multinational, open-label, ongoing study designed to provide continued treatment with aripiprazole, on a compassionate use basis, to those subjects who completed study 31-03-241, in countries where aripiprazole is not currently marketed to adolescent and young adult subjects with schizophrenia.

**Key features**

*Patient recruitment:* This study enrolled male and female adolescent (13-17 years) and adult (adolescents who reached 18 during participation in the double-blind or open-label parent studies) subjects with a DSM-IV diagnosis of schizophrenia who had completed study 31-03-241. The selection/eligibility criteria were adequately described. As of the clinical data cut-off date (21 June 2007), 85 subjects received aripiprazole. All subjects were analysed for both efficacy and safety.

[redacted]

*Withdrawals and dropouts:* Withdrawals and dropouts were adequately reported. Ten (11.8%) subjects discontinued the study prematurely, and the remaining 75 (88.2%) are ongoing. Among the discontinuations, 4 (4.7%) withdrew for adverse events, 3 (3.5%) met withdrawal criteria (aripiprazole became commercially available for 2 subjects and one had a positive drug screen for cocaine), 2 (2.4%) withdrew consent, and 1 (1.2%) withdrew due to lack of efficacy.

[redacted]

*Analyses:* The frequency and severity of AEs, SAEs, and discontinuation from the study due to AEs were reported. Secondary outcomes included; mean change from baseline in vital sign parameters, percentage of subjects showing weight gain or loss from baseline, mean change from baseline on the CGI-S scale and mean change from baseline on the P-QLES-Q total and overall score.

*Completeness of reporting:* Pre-specified outcomes were adequately reported. This study is ongoing.

## *9.8 Appendix 8: Search strategy for Section 5.9 (Adverse events)*

Adverse events relating to aripiprazole were taken from the phase III, randomised, controlled study comparing aripiprazole with placebo (study 31-03-239) in adolescents with schizophrenia, and the two open-label extension studies of aripiprazole in adolescents with schizophrenia (studies 31-03-241 and 31-05-243). These are the only clinical studies of aripiprazole in the adolescent schizophrenia population under consideration, consequently another review of the literature was deemed unnecessary.

## *9.9 Appendix 9: Quality assessment of adverse event data in Section 5.9 (Adverse events)*

Quality assessment of the studies from which adverse event data was taken has been reported in Appendix 3 and Appendix 7.

## *9.10 Appendix 10: Search strategy for cost-effectiveness studies (Section 6.1)*

The following information should be provided.

**9.10.1** The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The databases searched were

- Embase
- Medline
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

**9.10.2** The date on which the search was conducted.

The searches were carried out between the 8th December 2009 and the 8th January 2010.

**9.10.3** The date span of the search.

No date restrictions were imposed on the searches.

**9.10.4** The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

All the following searches were combined and inclusion/exclusion criteria applied.

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present**

**11/12/09**

| # | Searches | Results |
|---|---|---|
| 1 | quality-adjusted life years/ | 4287 |
| 2 | models, economic/ | 3851 |
| 3 | markov chains/ | 6258 |
| 4 | monte carlo method/ | 13478 |
| 5 | decision tree/ | 7246 |
| 6 | (pharmacoeconomic? or (pharmaco adj economic?)).tw. | 2515 |
| 7 | "quality adjusted life year?".tw. | 3533 |
| 8 | qaly?.tw. | 3004 |
| 9 | cba.tw. | 8127 |
| 10 | cea.tw. | 13978 |
| 11 | cua.tw. | 668 |
| 12 | markov$.tw. | 8960 |
| 13 | (monte adj carlo).tw. | 19533 |
| 14 | (decision adj2 (tree? or analys$)).tw. | 6033 |
| 15 | exp Cost-Benefit Analysis/ | 48473 |
| 16 | ((cost* and effectiv*) or (cost* and utilit*) or (cost* and benef*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 138516 |
| 17 | (cost adj2 qaly$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 699 |
| 18 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 | 203034 |
| 19 | (EOSS or (early onset and schizo*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 646 |
| 20 | (paranoid schizophrenia or paranoid psychosis).mp. | 1133 |
| 21 | (schizo$ or hebephreni$).ti,ab. | 85463 |

| | | |
|---|---|---|
| 22 | exp Schizophrenia/ or exp Schizophrenia, Childhood/ | 73826 |
| 23 | 19 or 20 or 21 or 22 | 104465 |
| 24 | exp models, economic/ | 7085 |
| 25 | 18 or 24 | 204856 |
| 26 | 23 and 25 | 1147 |
| 27 | limit 26 to ("all child (0 to 18 years)" or "adolescent (13 to 18 years)") | 146 |

**EMBASE 1980 to 2009 Week 49**

**11/12/09**

| # | Searches | Results |
|---|---|---|
| 1 | quality-adjusted life years/ | 4592 |
| 2 | exp "cost benefit analysis"/ or exp "cost effectiveness analysis"/ or exp "cost minimization analysis"/ | 89613 |
| 3 | markov chains/ | 27156 |
| 4 | exp Monte Carlo method/ | 8248 |
| 5 | exp "decision tree"/ | 346 |
| 6 | (pharmacoeconomic? or (pharmaco adj economic?)).tw. | 3200 |
| 7 | "quality adjusted life year?".tw. | 2923 |
| 8 | qaly?.tw. | 2485 |
| 9 | cba.tw. | 5694 |
| 10 | cea.tw. | 11171 |
| 11 | cua.tw. | 398 |
| 12 | markov$.tw. | 5615 |
| 13 | (monte adj carlo).tw. | 12663 |
| 14 | (decision adj2 (tree? or analys$)).tw. | 4809 |
| 15 | ((cost* and effectiv*) or (cost* and utilit*) or (cost* and benef*)).mp. | 144341 |
| 16 | (cost adj2 qaly$).mp. | 595 |
| 17 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 | 205704 |
| 18 | exp schizophrenia/ | 67323 |
| 19 | (EOSS or (early onset and schizo*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] | 619 |
| 20 | (paranoid schizophrenia or paranoid psychosis).mp. | 2322 |
| 21 | (schizo$ or hebephreni$).ti,ab. | 65080 |

| | | |
|---|---|---|
| 22 | 18 or 19 or 20 or 21 | 82053 |
| 23 | health economics/ or exp economic evaluation/ or exp pharmacoeconomics/ | 160612 |
| 24 | 17 or 23 | 264595 |
| 25 | 22 and 24 | 2341 |
| 26 | limit 25 to (child or adolescent <13 to 17 years>) | 84 |

### Econlit 1969 to November 2009

### 10/12/09

| # | Searches | Results |
|---|---|---|
| 1 | (EOSS or (early onset and schizo*)).mp. [mp=heading words, abstract, title, country as subject] | 1 |
| 2 | (paranoid schizophrenia or paranoid psychosis).mp. [mp=heading words, abstract, title, country as subject] | 0 |
| 3 | (schizo$ or hebephreni$).mp. [mp=heading words, abstract, title, country as subject] | 98 |
| 4 | schizophrenia.mp. [mp=heading words, abstract, title, country as subject] | 87 |
| 5 | 1 or 2 or 3 or 4 | 98 |

### Cochrane library / NHS EED

### 11/12/09

| ID | Search | Hits | Edit | Delete |
|---|---|---|---|---|
| #1 | MeSH descriptor **Schizophrenia** explode all trees | 4085 | edit | delete |
| #2 | (schizo* or hebephreni*):ti or (schizo* or hebephreni*):ab or (schizo* or hebephreni*):kw | 11121 | edit | delete |
| #3 | (#1 OR #2) | 11121 | edit | delete |
| #4 | MeSH descriptor **Adolescent** explode all trees | 63309 | edit | delete |
| #5 | MeSH descriptor **Child** explode all trees | 13 | edit | delete |
| #6 | (#4 OR #5) | 63318 | edit | delete |
| #7 | (#3 AND #6) [NHS EED] | 38 | edit | delete |

### Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present

### 08/01/10

| | | |
|---|---|---|
| 1 | quality-adjusted life years/ | 4093 |
| 2 | models, economic/ | 3740 |
| 3 | markov chains/ | 5922 |

| | | |
|---|---|---|
| 4 | monte carlo method/ | 13073 |
| 5 | decision tree/ | 6973 |
| 6 | (pharmacoeconomic? or (pharmaco adj economic?)).tw. | 2308 |
| 7 | "quality adjusted life year?".tw. | 3169 |
| 8 | qaly?.tw. | 2696 |
| 9 | cba.tw. | 7779 |
| 10 | cea.tw. | 13201 |
| 11 | cua.tw. | 643 |
| 12 | markov$.tw. | 8176 |
| 13 | (monte adj carlo).tw. | 18544 |
| 14 | (decision adj2 (tree? or analys$)).tw. | 5587 |
| 15 | exp Cost-Benefit Analysis/ | 46627 |
| 16 | ((cost* and effectiv*) or (cost* and utilit*) or (cost* and benef*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 130060 |
| 17 | (cost adj2 qaly$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 625 |
| 18 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 | 191266 |
| 19 | (EOSS or (early onset and schizo*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 590 |
| 20 | (paranoid schizophrenia or paranoid psychosis).mp. | 1084 |
| 21 | (schizo$ or hebephreni$).ti,ab. | 80477 |
| 22 | exp Schizophrenia/ or exp Schizophrenia, Childhood/ | 71267 |
| 23 | 19 or 20 or 21 or 22 | 98955 |
| 24 | exp models, economic/ | 6839 |
| 25 | 18 or 24 | 193031 |
| 26 | 23 and 25 | 1089 |
| 27 | (Aripiprazole or Abilify).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 1246 |
| 28 | 26 and 27 | 15 |
| 29 | from 28 keep 1-15 | 15 |

**EMBASE 1980 to 2009 Week 53**

**08/01/10**

| | | |
|---|---|---|
| 1 | quality-adjusted life years/ | 4628 |
| 2 | exp "cost benefit analysis"/ or exp "cost effectiveness analysis"/ or exp "cost minimization analysis"/ | 89984 |
| 3 | markov chains/ | 27316 |
| 4 | exp Monte Carlo method/ | 8368 |
| 5 | exp "decision tree"/ | 351 |
| 6 | (pharmacoeconomic? or (pharmaco adj economic?)).tw. | 3203 |
| 7 | "quality adjusted life year?".tw. | 2946 |

| | | |
|---|---|---|
| 8 | qaly?.tw. | 2508 |
| 9 | cba.tw. | 5707 |
| 10 | cea.tw. | 11207 |
| 11 | cua.tw. | 398 |
| 12 | markov$.tw. | 5653 |
| 13 | (monte adj carlo).tw. | 12781 |
| 14 | (decision adj2 (tree? or analys$)).tw. | 4828 |
| 15 | ((cost* and effectiv*) or (cost* and utilit*) or (cost* and benef*)).mp. | 144968 |
| 16 | (cost adj2 qaly$).mp. | 597 |
| 17 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 | 206681 |
| 18 | exp schizophrenia/ | 67618 |
| 19 | (EOSS or (early onset and schizo*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] | 625 |
| 20 | (paranoid schizophrenia or paranoid psychosis).mp. | 2335 |
| 21 | (schizo$ or hebephreni$).ti,ab. | 65316 |
| 22 | 18 or 19 or 20 or 21 | 82386 |
| 23 | health economics/ or exp economic evaluation/ or exp pharmacoeconomics/ | 161312 |
| 24 | 17 or 23 | 265850 |
| 25 | 22 and 24 | 2356 |
| 26 | (Aripiprazole or Abilify).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] | 3824 |
| 27 | 25 and 26 | 206 |

**Cochrane library/ NHS EED**

**08/01/10**

| ID | Search | Hits | Edit | Delete |
|---|---|---|---|---|
| #1 | MeSH descriptor **Schizophrenia** explode all trees | 4085 | edit | delete |
| #2 | (schizo* or hebephreni*):ti or (schizo* or hebephreni*):ab or (schizo* or hebephreni*):kw | 11121 | edit | delete |
| #3 | (#1 OR #2) | 11121 | edit | delete |
| #4 | (Aripiprazole or Abilify) | 504 | edit | delete |
| #5 | (#3 AND #4) Economic evaluations | 5 | edit | delete |

### 9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

We searched the NICE website for guidance relating to schizophrenia. Assessment group reports and manufacturer submissions are made available on the website and therefore any relevant guidance may contain evidence to inform the review of the literature and/or the *de novo* modelling approach if required.

Aside from the current appraisal, five additional hits were identified. The results of the search and a description are presented in Table 54. TA59 and CG45 were

excluded as they did not address the treatments or patient population outlined in the decision problem. The Schizophrenia guideline, CG82, encompassed updates to an earlier clinical guideline and technology appraisal and was therefore considered for review.

The full guideline prepared by the National Collaborating Centre for Mental Health contained an economic evaluation on the cost-effectiveness of pharmacological interventions for people with schizophrenia. This analysis was included for review according to the inclusion/exclusion criteria outlined in Section 9.12.6.

**Table 54: Results of the NICE website search (excluding current appraisal)**

| Result | Description |
|---|---|
| Schizophrenia (update) (CG82) | Clinical guideline on Schizophrenia (update). |
| Schizophrenia (replaced by CG82) (CG1) | Clinical guideline on Schizophrenia (replaced by CG82). |
| Schizophrenia - atypical antipsychotics (replaced by CG82) (TA43) | Technology appraisal on Schizophrenia - atypical antipsychotics (replaced by CG82). |
| Electroconvulsive therapy (ECT) (TA59) | Technology appraisal on Electroconvulsive therapy (ECT) |
| Antenatal and postnatal mental health (CG45) | Clinical guideline on Antenatal and postnatal mental health. |

### 9.10.6 The inclusion and exclusion criteria

Exclusion

- Not schizophrenia
- Not aripiprazole (unless population is adolescent/child population)
- Not a cost-effectiveness, cost-benefit, cost-minimisation, cost-consequence or cost-utility study
- Studies not relevant to the UK

Inclusion

- Adolescent/child population with schizophrenia and
- Either a cost-effectiveness, cost-benefit, cost-minimisation, cost-consequence or cost-utility study
- Any cost-effectiveness, cost-benefit, cost-minimisation, cost-consequence or cost-utility study involving aripiprazole (including adult population)

### 9.10.7 The data abstraction strategy

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Data were extracted from eligible publications into a pre-defined Microsoft Excel® spreadsheet by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

## 9.11 Appendix 11: Quality assessment of cost-effectiveness studies (Section 6.1)

**Table 55: Quality assessment of Barnett et al (2009)**

| | **Study name** Barnett et al (2009) UK cost-consequence analysis of aripiprazole in schizophrenia: diabetes and coronary heart disease risk projections (STAR study) (38). | |
|---|---|---|
| **Study question** | **Grade** | **Comments** |
| Study design | | |
| 1. Was the research question stated? | Yes | The objective of the study was to predict the long-term risks of diabetes and CHD for patients with schizophrenia receiving aripiprazole or SOC. Projected risk data were also used to estimate the associated costs of diabetes and CHD in the UK. |
| 2. Was the economic importance of the research question stated? | Yes | The burden of schizophrenia on health care budgets and other considerations were discussed in the introductory section. |
| 3. Was/were the viewpoint(s) of the analysis clearly stated and justified? | Yes | The model perspective was that of the UK NHS. |
| 4. Was a rationale reported for the choice of the alternative programmes or interventions compared? | Yes | The alternative interventions included were those reported in a clinical trial and were aripiprazole and standard of care. Standard of care was described as physician's choice of olanzapine, risperidone and quetiapine. |
| 5. Were the alternatives being compared clearly described? | Yes | |
| 6. Was the form of economic evaluation stated? | Yes | This was a cost-consequence study |
| 7. Was the choice of form of economic evaluation justified in relation to the questions addressed? | No | No explanation for use of a cost-consequence rather than a cost-effectiveness or cost-utility analysis was provided. |
| Data collection | | |
| 8. Was/were the source(s) of effectiveness estimates used stated? | Yes | Effectiveness data for aripiprazole and SOC was obtained from the STAR study. |
| 9. Were details of the design and results of the effectiveness study given (if based on a single study)? | Yes | The STAR study was a 26 week prospective, multi-label, randomised, open-label trial and was adequately described and a reference provided. |
| 10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)? | NA | |
| 11. Were the primary outcome measure(s) for the economic evaluation clearly stated? | Yes | The model was used to estimate the risks of diabetes, and CHD. The cost impact of both these outcomes was also reported. |
| 12. Were the methods used to value health states and other benefits stated? | NA | This cost-consequence analysis only included clinical outcomes (diabetes and CHD risk). |

| | | |
|---|---|---|
| 13. Were the details of the subjects from whom valuations were obtained given? | NA | As above. |
| 14. Were productivity changes (if included) reported separately? | Not clear | Indirect costs were included but these were taken from published sources and the details of these studies were not reported. |
| 15. Was the relevance of productivity changes to the study question discussed? | No | |
| 16. Were quantities of resources reported separately from their unit cost? | No | |
| 17. Were the methods for the estimation of quantities and unit costs described? | Not clear | Direct costs were included from published sources and were not described in detail. |
| 18. Were currency and price data recorded? | Yes | |
| 19. Were details of price adjustments for inflation or currency conversion given? | Yes | Costs were adjusted to 2007 prices using the NHS Pay and prices index. No price conversion was required. |
| 20. Were details of any model used given? | NA | Details of the statistical analysis used in estimating risks for diabetes and CHD were included. As this is a cost-consequence analysis, no model was reported. |
| 21. Was there a justification for the choice of model used and the key parameters on which it was based? | NA | As this is a cost-consequence analysis, no model was reported. |
| Analysis and interpretation of results | | |
| 22. Was the time horizon of cost and benefits stated? | NA | The year of the clinical study and the year of the cost data were reported. As this is a cost-consequence analysis, clinical outcomes and costs were not combined over a specific time period, therefore this was not reported. |
| 23. Was the discount rate stated? | Yes | Costs were discounted at 3.5% |
| 24. Was the choice of rate justified? | Yes | Reference was given to the NICE guidelines |
| 25. Was an explanation given if cost or benefits were not discounted? | No | Only costs were discounted |
| 26. Were the details of statistical test(s) and confidence intervals given for stochastic data? | Yes | |
| 27. Was the approach to sensitivity analysis described? | Not clear | One-way sensitivity analysis was carried out on cost data with variations in prevalence, yearly costs per event and discount rate but no further details of additional sensitivity analysis were provided. |
| 28. Was the choice of variables for sensitivity analysis justified? | Yes | Authors state that they wanted to test the sensitivity of their findings to the input assumptions used in the cost calculations. However, no further explanation was given. |
| 29. Were the ranges over which the parameters were varied stated? | Yes | The ranges around the three parameters varied in sensitivity analysis were provided. |

| | | |
|---|---|---|
| 30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?) | Yes | Yes, aripiprazole was compared with SOC. |
| 31. Was an incremental analysis reported? | Yes | |
| 32. Were major outcomes presented in a disaggregated as well as aggregated form? | No | As this was a cost-consequence analysis, outcomes were only presented in a disaggregated form. |
| 33. Was the answer to the study question given? | Yes | |
| 34. Did conclusions follow from the data reported? | Yes | |
| 35. Were conclusions accompanied by the appropriate caveats? | Yes | Limitations of the analysis were outlined in detail in the discussion section. |
| 36. Were generalisability issues addressed? | Yes | Generalisability was addressed in the discussion. |
| Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

**Table 56: Quality assessment of Davies et al 2008**

| | **Study name** Davies et al (2008) Cost-effectiveness of atypical antipsychotics for the management of schizophrenia in the UK (39) | |
|---|---|---|
| **Study question** | **Grade** | **Comments** |
| Study design | | |
| 1. Was the research question stated? | Yes | The objective of the analysis was to evaluate the cost-effectiveness of atypical anti-psychotic treatment sequences for the management of stable schizophrenia in the UK |
| 2. Was the economic importance of the research question stated? | Yes | The burden of schizophrenia to patients, families and carers, and the burden of schizophrenia and associated co-morbidities were discussed in the introductory section. |
| 3. Was/were the viewpoint(s) of the analysis clearly stated and justified? | Yes | The model perspective was that of the UK NHS. |
| 4. Was a rationale reported for the choice of the alternative programmes or interventions compared? | Yes | The alternative interventions included were a sequence of two atypical antipsychotics: aripiprazole, olanzapine, risperidone and quetiapine followed by clozapine. These were selected because olanzapine, risperidone and quetiapine are recommended treatment options in NICE guidelines and constitute the largest market share. Aripiprazole was included as a newly available treatment option licensed for used in the UK. |
| 5. Were the alternatives being compared clearly described? | Not clear | Olanzapine, risperidone and quetiapine were described as atypical antipsychotics. No further description was given. |

| | | |
|---|---|---|
| 6. Was the form of economic evaluation stated? | Yes | A Markov cost-utility economic evaluation was used |
| 7. Was the choice of form of economic evaluation justified in relation to the questions addressed? | No | |
| Data collection | | |
| 8. Was/were the source(s) of effectiveness estimates used stated? | Yes | Effectiveness data for aripiprazole was obtained from a randomised trial comparing aripiprazole with olanzapine. Data for other interventions were taken from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. |
| 9. Were details of the design and results of the effectiveness study given (if based on a single study)? | Yes | |
| 10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)? | NA | |
| 11. Were the primary outcome measure(s) for the economic evaluation clearly stated? | Yes | The model was used to estimate the incremental cost per quality-adjusted life year (QALY) |
| 12. Were the methods used to value health states and other benefits stated? | Not clear | Health-state utility values were taken from a direct UK utility elicitation study. The method of elicitation was not clear although a reference was given. |
| 13. Were the details of the subjects from whom valuations were obtained given? | No | Details of the subjects from whom valuations were obtained were not stated, although a reference was given. |
| 14. Were productivity changes (if included) reported separately? | NA | |
| 15. Was the relevance of productivity changes to the study question discussed? | No | |
| 16. Were quantities of resources reported separately from their unit cost? | Yes | |
| 17. Were the methods for the estimation of quantities and unit costs described? | Yes | Assumptions around clinician contact and medication use were described. |
| 18. Were currency and price data recorded? | Yes | |
| 19. Were details of price adjustments for inflation or currency conversion given? | Yes | Costs were adjusted to 2006 prices. No price conversion was required. |
| 20. Were details of any model used given? | Yes | A description and diagram of the model were included |
| 21. Was there a justification for the choice of model used and the key parameters on which it was based? | Not clear | The Markov model form was not explicitly justified; however the health states it was based upon were discussed. |
| Analysis and interpretation of results | | |
| 22. Was the time horizon of cost and benefits stated? | Yes | The time horizon of the model was 10 years |

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|---|---|---|
| 23. Was the discount rate stated? | Yes | A discount rate of 3.5% was applied to both costs and benefits |
| 24. Was the choice of rate justified? | No | |
| 25. Was an explanation given if cost or benefits were not discounted? | N/A | |
| 26. Were the details of statistical test(s) and confidence intervals given for stochastic data? | Yes | |
| 27. Was the approach to sensitivity analysis described? | Yes | In additional to probabilistic analyses, a range of sensitivity analyses were conducted on key parameters. |
| 28. Was the choice of variables for sensitivity analysis justified? | No | |
| 29. Were the ranges over which the parameters were varied stated? | Yes | For probabilistic sensitivity analysis 95% confidence interval ranges were used that had been stated in the paper. For other sensitivity analyses ranges were stated in the text. |
| 30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?) | Yes | All incremental cost per QALYs for different treatment sequences were compared with the treatment sequence risperidone / olanzapine. |
| 31. Was an incremental analysis reported? | Yes | |
| 32. Were major outcomes presented in a disaggregated as well as aggregated form? | Yes | Both costs and QALYs were presented separately |
| 33. Was the answer to the study question given? | Yes | |
| 34. Did conclusions follow from the data reported? | Yes | |
| 35. Were conclusions accompanied by the appropriate caveats? | Not clear | Some caveats were raised in the discussion section |
| 36. Were generalisability issues addressed? | No | |
| Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

**Table 57: Quality assessment of Heeg et al 2008**

| | **Study name** Heeg et al (2008) The cost-effectiveness of atypicals in the UK (40) | |
|---|---|---|
| **Study question** | **Grade** | **Comments** |
| Study design | | |
| 1. Was the research question stated? | Yes | The objective of the analysis was to evaluate the cost-effectiveness of atypical anti-psychotic treatment relative to conventional antipsychotics for the treatment of schizophrenia in the UK |

| | | |
|---|---|---|
| 2. Was the economic importance of the research question stated? | Yes | The lack of reliable economic and clinical data on the long-term impact of schizophrenia and treatment was discussed in the introductory section. |
| 3. Was/were the viewpoint(s) of the analysis clearly stated and justified? | Yes | The model perspective was that of the UK NHS and social care trusts. |
| 4. Was a rationale reported for the choice of the alternative programmes or interventions compared? | Yes | The alternative interventions included were atypical antipsychotics versus conventional antipsychotics. The analysis was carried out to examine the cost-effectiveness argument for NICE guidelines that suggested atypical antipsychotics should be considered as first line treatment of schizophrenia. |
| 5. Were the alternatives being compared clearly described? | Yes | A list of all the conventional and atypical treatments included in the analysis was provided. Doses and annual costs of the treatments were provided. |
| 6. Was the form of economic evaluation stated? | Yes | It was a cost-utility model |
| 7. Was the choice of form of economic evaluation justified in relation to the questions addressed? | Not clear | The authors stated that the non-product specific DES model represented the use of treatment and reflected clinical practice in the UK. |
| Data collection | | |
| 8. Was/were the source(s) of effectiveness estimates used stated? | Not clear | The authors stated that where possible, parameter estimates were updated based on published literature or with information from a secondary data base analysis. Only references were provided on sources of the effectiveness data for the treatments included. |
| 9. Were details of the design and results of the effectiveness study given (if based on a single study)? | NA | |
| 10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)? | Not clear | Not clear if any data synthesis was carried out. |
| 11. Were the primary outcome measure(s) for the economic evaluation clearly stated? | Yes | A list of model outcomes was provided, including symptoms (using PANSS), side effects and QALYs |
| 12. Were the methods used to value health states and other benefits stated? | Not clear | Published values were used but the methods of elicitation were not discussed in any detail. The application of the utilities in the model was discussed. |
| 13. Were the details of the subjects from whom valuations were obtained given? | No | Details of the subjects from whom valuations were obtained were not stated, although a reference was given. |
| 14. Were productivity changes (if included) reported separately? | NA | |
| 15. Was the relevance of productivity changes to the study question discussed? | No | |
| 16. Were quantities of resources reported separately from their unit cost? | Not clear | It is not clear if all unit costs have been provided. The treatment costs and doses were reported as are the setting and associated costs. However, it is not clear what other costs have been included if any. |

| | | |
|---|---|---|
| 17. Were the methods for the estimation of quantities and unit costs described? | Not clear | Drugs costs were adequately reported but additional methods of resource use estimation are unclear. |
| 18. Were currency and price data recorded? | Yes | Currency and price year could be stated more explicitly but were nonetheless included in the study. |
| 19. Were details of price adjustments for inflation or currency conversion given? | No | No details of adjustments for inflation or currency conversion were reported. It does not appear that these were required. |
| 20. Were details of any model used given? | Not clear | A short description of the model was provided but has been reported elsewhere so was not fully detailed in the methods. |
| 21. Was there a justification for the choice of model used and the key parameters on which it was based? | Not clear | The authors stated that the non-product specific DES model represented the use of treatment and reflected clinical practice in the UK. |
| Analysis and interpretation of results | | |
| 22. Was the time horizon of cost and benefits stated? | Yes | The time horizon of the model was 5 years |
| 23. Was the discount rate stated? | Yes | A discount rate of 3.5% was applied to both costs and benefits |
| 24. Was the choice of rate justified? | Yes | Justified in accordance with NICE guidelines |
| 25. Was an explanation given if cost or benefits were not discounted? | N/A | |
| 26. Were the details of statistical test(s) and confidence intervals given for stochastic data? | Yes | |
| 27. Was the approach to sensitivity analysis described? | Yes | Probabilistic analyses and scenario analysis were conducted. An ordinary least squares regression was also performed to examine the effect of individual parameters on the outcomes generated in the probabilistic analysis. |
| 28. Was the choice of variables for sensitivity analysis justified? | Yes | |
| 29. Were the ranges over which the parameters were varied stated? | Yes | For probabilistic sensitivity analysis standard errors and distribution types were reported. In scenario analysis ranges were not used but this was clearly stated. |
| 30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?) | Yes | The conventional treatment group was compared with the atypical antipsychotic treatment group.. |
| 31. Was an incremental analysis reported? | Yes | |
| 32. Were major outcomes presented in a disaggregated as well as aggregated form? | Yes | Both costs and QALYs were presented separately |
| 33. Was the answer to the study question given? | Yes | |
| 34. Did conclusions follow from the data reported? | Yes | |
| 35. Were conclusions accompanied by the appropriate caveats? | Yes | The discussion section attempted to justify and validate limitations in model input sources. |

| | | |
|---|---|---|
| 36. Were generalisability issues addressed? | No | |
| Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

**Table 58: Quality assessment of the economic study in NICE Clinical guideline CG82**

| | **Study name** NICE guidelines. Chapter 7: Economic model – cost effectiveness of pharmacological interventions for people with schizophrenia (6) | |
|---|---|---|
| **Study question** | **Grade** | **Comments** |
| Study design | | |
| 1. Was the research question stated? | Yes | The objective of the analysis was to evaluate the cost-effectiveness of antipsychotic treatment for people with schizophrenia in the UK clinical setting. Specifically, an economic assessment of antipsychotic medications aimed at promoting recovery (preventing relapse in people with schizophrenia in remission) was selected as the highest priority question. |
| 2. Was the economic importance of the research question stated? | Yes | The questions were chosen following examination of criteria including availability of existing economic evidence, resource implications and availability of clinical evidence, to produce meaningful and robust conclusions to inform the recommendations of the guideline. |
| 3. Was/were the viewpoint(s) of the analysis clearly stated and justified? | Yes | The model perspective was that of the UK NHS and personal social care services. |
| 4. Was a rationale reported for the choice of the alternative programmes or interventions compared? | Yes | The alternative interventions included were antipsychotic medications including, olanzapine, amisulpride, zotepine, aripiprazole, paliperidone, risperidone and haloperidol. The choice of comparators was based on available clinical data. |
| 5. Were the alternatives being compared clearly described? | Yes | Full details of the antipsychotic treatments were provided. |
| 6. Was the form of economic evaluation stated? | Yes | It was a cost-utility model |
| 7. Was the choice of form of economic evaluation justified in relation to the questions addressed? | No | |
| Data collection | | |
| 8. Was/were the source(s) of effectiveness estimates used stated? | Yes | Data from the clinical trials identified as part of the systematic review were provided and informed the effectiveness data in the model. Additional effectiveness estimates came from published studies. |
| 9. Were details of the design and results of the effectiveness study given (if based on a single study)? | NA | |

| | | |
|---|---|---|
| 10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)? | Yes – partially | Details of the methods of the mixed treatment comparisons carried out for the clinical data were provided. However, some of this could have been clearer. For example, the effect of including multiple definitions of relapse was not justified or explored in sufficient detail. |
| 11. Were the primary outcome measure(s) for the economic evaluation clearly stated? | Yes | The measure of outcome was the QALYs |
| 12. Were the methods used to value health states and other benefits stated? | Yes | Published values are used and methods of elicitation described in sufficient detail. |
| 13. Were the details of the subjects from whom valuations were obtained given? | Yes | People with schizophrenia taking part in clinical trials in the US. Health states were then valued by a sample of the US general public using the standard gamble technique. |
| 14. Were productivity changes (if included) reported separately? | NA | |
| 15. Was the relevance of productivity changes to the study question discussed? | No | |
| 16. Were quantities of resources reported separately from their unit cost? | Yes | |
| 17. Were the methods for the estimation of quantities and unit costs described? | Yes | Methods were described adequately and sources were appropriate. |
| 18. Were currency and price data recorded? | Yes | Currency and price year could be stated more explicitly but were nonetheless included in the study. |
| 19. Were details of price adjustments for inflation or currency conversion given? | Yes | All costs were uplifted to 2007 prices using the Hospital and Community Health Services Pay and Prices Index. No currency conversion was required. |
| 20. Were details of any model used given? | Yes | A description of the model along with a schematic was provided. A Markov model was used. |
| 21. Was there a justification for the choice of model used and the key parameters on which it was based? | Not clear | The authors outlined the model structure in detail but did not appear to justify the structure. |
| Analysis and interpretation of results | | |
| 22. Was the time horizon of cost and benefits stated? | Yes | Two time horizons were assessed: 10 years and lifetime. |
| 23. Was the discount rate stated? | Yes | A discount rate of 3.5% was applied to both costs and benefits. |
| 24. Was the choice of rate justified? | Yes | Justified in accordance with NICE guidelines. |
| 25. Was an explanation given if cost or benefits were not discounted? | N/A | |
| 26. Were the details of statistical test(s) and confidence intervals given for stochastic data? | Yes | |
| 27. Was the approach to sensitivity analysis described? | Yes | Deterministic and probabilistic analyses were conducted. Additional one-way scenario analyses were also presented. |

| | | |
|---|---|---|
| 28. Was the choice of variables for sensitivity analysis justified? | No | |
| 29. Were the ranges over which the parameters were varied stated? | Yes | A table was provided with deterministic values and probabilistic distributions for all input parameters in the model. |
| 30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?) | Yes | The antipsychotic treatments were compared against one another.. |
| 31. Was an incremental analysis reported? | Yes | It appears that a comparative analysis was undertaken in the base case deterministic analysis. Ranking of treatments in terms of utility values was also provided. This could have been reported in greater detail. |
| 32. Were major outcomes presented in a disaggregated as well as aggregated form? | Yes | Both mean costs and QALYs were presented separately |
| 33. Was the answer to the study question given? | Yes | |
| 34. Did conclusions follow from the data reported? | Yes | |
| 35. Were conclusions accompanied by the appropriate caveats? | Yes | The discussion section attempts to justify and validate limitations in model input sources. More detail could have been provided on the likely impact of these limitations. |
| 36. Were generalisability issues addressed? | No | |
| Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination | | |

## *9.12 Appendix 12: Search strategy for Section 6.4 (Measurement and valuation of health effects)*

The following information should be provided.

**9.12.1** The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

The databases searched were:

- Embase
- Medline
- Medline (R) In-Process

- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

**9.12.2** The date on which the search was conducted.

The searches were carried between the 8th and 10th of December 2009.

**9.12.3** The date span of the search.

No date restrictions were imposed on the searches.

**9.12.4** The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

All the following searches were combined and inclusion/exclusion criteria applied.

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present**

**9/12/09**

| # | Searches | Results |
|---|---|---|
| 1 | (euroqol or eq5d or eq 5d or eqvas or eq vas).mp. | 2004 |
| 2 | (sf36 or sf 36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36 or shortform36).mp. | 10885 |
| 3 | (sf6D or sf 6D or sf sixD or sf six D or short form 6D or short form six D or shortform 6D or shortform6D).mp. | 204 |
| 4 | (sf12 or sf 12 or sf twelve or short form 12 or short form twelve).mp. | 1542 |
| 5 | (hql or hrqol or qol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 15582 |
| 6 | (quality of life or life quality or quality of wellbeing or quality of well being or quality adjusted life or qaly).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 133435 |
| 7 | ((health* and year* and equivalent*) or hye).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 3799 |
| 8 | (health utilit* or hui or health preference*).mp. | 1095 |
| 9 | health utility index.mp. | 70 |
| 10 | (visual analog* scale or VAS).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 30636 |
| 11 | ((persontradeoff or person tradeoff or person trade off or person trade* or health) adj2 | 77394 |

| | | |
|---|---|---|
| | (status or standard gamble* or timetradeoff or time tradeoff or time trade off or time trade*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | |
| 12 | (TTO or time trade off or standard gamble or SG).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 5099 |
| 13 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 | 234462 |
| 14 | (EOSS or (early onset and schizo*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] | 646 |
| 15 | (paranoid schizophrenia or paranoid psychosis).mp. | 1133 |
| 16 | (schizo$ or hebephreni$).ti,ab. | 85455 |
| 17 | exp Schizophrenia/ or exp Schizophrenia, Childhood/ | 73826 |
| 18 | 14 or 15 or 16 or 17 | 104457 |
| 19 | 13 and 18 | 2380 |
| 20 | limit 19 to "all child (0 to 18 years)" | 431 |

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| # | Searches | Results |
|---|---|---|
| 1 | (euroqol or eq5d or eq 5d or eqvas or eq vas).mp. | 1652 |
| 2 | (sf36 or sf 36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36 or shortform36).mp. | 10123 |
| 3 | (sf6D or sf 6D or sf sixD or sf six D or short form 6D or short form six D or shortform 6D or shortform6D).mp. | 155 |
| 4 | (sf12 or sf 12 or sf twelve or short form 12 or short form twelve).mp. | 1215 |
| 5 | (hql or hrqol or qol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] | 12716 |
| 6 | (quality of life or life quality or quality of wellbeing or quality of well being or quality adjusted life or qaly).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] | 123560 |
| 7 | ((health* and year* and equivalent*) or hye).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] | 3105 |
| 8 | (health utilit* or hui or health preference*).mp. | 1165 |
| 9 | health utility index.mp. | 59 |

| | | |
|---|---|---|
| 10 | (visual analog* scale or VAS).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] | 29749 |
| 11 | ((persontradeoff or person tradeoff or person trade off or person trade* or health) adj2 (status or standard gamble* or timetradeoff or time tradeoff or time trade off or time trade*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] | 46607 |
| 12 | (TTO or time trade off or standard gamble or SG).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] | 4248 |
| 13 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 | 197774 |
| 14 | exp schizophrenia/ | 67323 |
| 15 | (EOSS or (early onset and schizo*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] | 619 |
| 16 | (paranoid schizophrenia or paranoid psychosis).mp. | 2322 |
| 17 | (schizo$ or hebephreni$).ti,ab. | 65080 |
| 18 | 14 or 15 or 16 or 17 | 82053 |
| 19 | 13 and 18 | 2676 |
| 20 | limit 19 to (child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) | 118 |

Cochrane library/NHS EED
8/12/09

| ID | Search | Hits | Edit | Delete |
|---|---|---|---|---|
| #1 | (euroqol OR eq5d OR eq 5d OR eqvas OR eq vas) | 963 | edit | delete |
| #2 | (sf36 OR sf 36 OR sf thirtysix OR sf thirty six OR short form 36 OR short form thirty six OR short form thirtysix OR shortform 36 OR shortform36) | 5025 | edit | delete |
| #3 | (sf6D OR sf 6D OR sf sixD OR sf six D OR short form 6D OR short form six D OR shortform 6D OR shortform6D) | 1672 | edit | delete |
| #4 | (sf12.p. OR sf 12 OR sf twelve OR short form 12 OR short form twelve) | 9929 | edit | delete |
| #5 | (hql OR hrqol OR qol) | 3081 | edit | delete |
| #6 | (quality of life OR life quality OR quality of wellbeing OR quality of well being) OR (quality adjusted life OR qaly) OR (health* AND year* AND equivalent* OR hye) OR (health utilit* OR hui OR health preference*) | 37991 | edit | delete |
| #7 | (#1 OR #2 OR #3 OR #4 OR #5 OR #6) | 42534 | edit | delete |
| #8 | MeSH descriptor **Schizophrenia** explode all trees | 4085 | edit | delete |
| #9 | (schizo* or hebephreni*):ti or (schizo* or hebephreni*):ab or (schizo* or hebephreni*):kw | 11121 | edit | delete |
| #10 | (#8 OR #9) | 11121 | edit | delete |
| #11 | (#7 AND #10) | 792 | edit | delete |
| #12 | MeSH descriptor **Child** explode all trees | 13 | edit | delete |

| | | | | |
|---|---|---|---|---|
| #13 | MeSH descriptor **Adolescent** explode all trees | 63309 | edit | delete |
| #14 | (#12 OR #13) | 63318 | edit | delete |
| #15 | (#14 AND #11) | 80 | edit | delete |

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10/12/09

| # | Searches | Results |
|---|---|---|
| 1 | (EOSS or (early onset and schizo*)).mp. [mp=heading words, abstract, title, country as subject] | 1 |
| 2 | (paranoid schizophrenia or paranoid psychosis).mp. [mp=heading words, abstract, title, country as subject] | 0 |
| 3 | (schizo$ or hebephreni$).mp. [mp=heading words, abstract, title, country as subject] | 98 |
| 4 | schizophrenia.mp. [mp=heading words, abstract, title, country as subject] | 87 |
| 5 | 1 or 2 or 3 or 4 | 98 |

### 9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The references of the economic evaluation identified in Section 6.1 were searched for utility studies that may be relevant to the de novo economic evaluation.

### 9.12.6 The inclusion and exclusion criteria.

Inclusion and exclusion criteria were applied as follows keeping in mind the NICE methods guide for utility data:

Exclusion

- Not adolescent or child population
- Not schizophrenia
- No quality of life data
- Condition specific non-preference based quality of life data
- Other non-preference based quality of life data with the exception of SF-36 and SF-12

Inclusion

- Adolescent or child population with schizophrenia and either
    - A preference based measure of quality of life, either generic or valued in a separate study with appropriate methods (i.e. standard gamble or time trade off) or
    - One of the following non-preference quality of life measures: SF-12 or SF-36

**9.12.7** The data abstraction strategy.

Identified studies were independently assessed by two reviewers in order to ascertain they met the pre-defined inclusion/exclusion criteria and any discrepancies were resolved by a third party. Data were extracted from eligible publications into a pre-defined Microsoft Excel® spreadsheet by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

## *9.13 Appendix 13: Resource identification, measurement and valuation (Section 6.5)*

A specific search was not carried out.

## 9.14 Appendix 14: full table of all model parameters sources and distributions

Table 59: Table of model input parameters and sources

| | Value | Reference | Lower value | Upper value | Distribution |
|---|---|---|---|---|---|
| RR of withdrawal due to AE vs. Ari10: Ola | 1.550 | Indirect comparison | [redacted] | [redacted] | Log |
| OR of withdrawal due to AE vs. Ari10: Ola | 1.570 | Indirect comparison | [redacted] | [redacted] | Log |
| Rate of withdrawal due to AE: Ari10 | 7.00% | Indirect comparison | [redacted] | [redacted] | Beta |
| RR of withdrawal due to LoE vs. Ari10: Ola | 0.050 | Indirect comparison | [redacted] | [redacted] | Log |
| OR of withdrawal due to LoE vs. Ari10: Ola | 0.030 | Indirect comparison | [redacted] | [redacted] | Log |
| Rate of withdrawal due to LoE: Ari10 | 5.00% | Indirect comparison | [redacted] | [redacted] | Beta |
| RR of withdrawal due to Other vs. Ari10: Ola | 3.400 | Indirect comparison | [redacted] | [redacted] | Log |
| OR of withdrawal due to Other vs. Ari10: Ola | 3.730 | Indirect comparison | [redacted] | [redacted] | Log |
| Rate of withdrawal due to Other: Ari10 | 4.00% | Indirect comparison | [redacted] | [redacted] | Beta |
| RR: Weight gain vs. Ari10: Ola | 0.340 | Indirect comparison | [redacted] | [redacted] | Log |
| OR: Weight gain vs. Ari10: Ola | 0.510 | Indirect comparison | [redacted] | [redacted] | Log |
| Rate of Weight gain for Ari10 | 4.76% | Indirect comparison | [redacted] | [redacted] | Beta |
| RR: Somnolence vs. Ari10: Ola | 4.440 | Indirect comparison | [redacted] | [redacted] | Log |
| OR: Somnolence vs. | 5.340 | Indirect comparison | [redacted] | [redacted] | Log |

| | Value | Reference | Lower value | Upper value | Distribution |
|---|---|---|---|---|---|
| Ari10: Ola | | | | | |
| Rate of Somnolence for Ari10 | 11.00% | Indirect comparison | [redacted] | [redacted] | Beta |
| RR: benzodiazepines vs. Ari10: Ola | 0.570 | Indirect comparison | [redacted] | [redacted] | Log |
| OR: benzodiazepines vs. Ari10: Ola | 0.390 | Indirect comparison | [redacted] | [redacted] | Log |
| Pts receiving benzodiazepines for Ari10 | 32.00% | Indirect comparison | [redacted] | [redacted] | Beta |
| Annual rate of relapse: Ari | 27.42% | NICE guidelines - CG82 Schizophrenia. Table 46, pg 219 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 1.30% | 85.31% | Beta |
| Annual rate of relapse: Ola | 19.96% | NICE guidelines - CG82 Schizophrenia. Table 46, pg 219 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 1.46% | 72.22% | Beta |
| RR of relapse: Cloz vs. Ola | 1.091 | Davies et al. (2008) (Secondary reference: Haro et al. 2006) | 0.78 | 1.53 | Log |
| RR of relapse: Cloz vs. Ari | 1.000 | Assumption | [redacted] | [redacted] | Log |
| Utility: Stable schizophrenia | 0.919 | Briggs et al. (2008) | 0.87 | 0.96 | Beta |
| Utility: Relapse | 34.28% | Briggs et al. (2008) | 28.81% | 40.31% | Beta |
| Utility: Weight gain | 10.23% | Briggs et al. (2008) | 8.73% | 11.88% | Beta |
| Utility: Somnolence | 1.52% | Heeg et al. 2008 (Secondary reference: Siddique et al, 2004.) | 0.57% | 2.39% | Beta |
| Utility: EPS | 21.44% | Briggs et al. (2008) | 17.59% | 25.68% | Beta |
| AE: Weight gain - GP: % of pts | 100% | NICE guidelines - CG82 Schizophrenia. Table 45, pg 218 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 70% | 130% | Gamma |
| AE: Weight gain - GP: Cost per hour | £35.00 | Curtis (2009) | £24.50 | £45.50 | Gamma |

| | Value | Reference | Lower value | Upper value | Distribution |
|---|---|---|---|---|---|
| AE: Weight gain - GP: Visits p.a. | 2 | NICE guidelines - CG82 Schizophrenia. Table 45, pg 218 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 1.4 | 2.6 | Gamma |
| AE: Weight gain - GP: Visit duration | 1 | NICE guidelines - CG82 Schizophrenia. Table 45, pg 218 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 0.7 | 1.3 | Gamma |
| AE: Weight gain - Dietician: % of pts | 20% | NICE guidelines - CG82 Schizophrenia. Table 45, pg 218 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 14% | 26% | Beta |
| AE: Weight gain - Dietician: Cost per hour | £34.00 | Curtis (2009) | £23.80 | £44.20 | Gamma |
| AE: Weight gain - Dietician: Visits p.a. | 2 | NICE guidelines - CG82 Schizophrenia. Table 45, pg 218 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 1.4 | 2.6 | Gamma |
| AE: Weight gain - Dietician: Visit duration | 1 | NICE guidelines - CG82 Schizophrenia. Table 45, pg 218 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 0.7 | 1.3 | Gamma |
| AE: Somnolence - Psychiatrist: % of pts | 100% | Assumption | [redacted] | [redacted] | Gamma |
| AE: Somnolence - Psychiatrist: Cost per hour | £322.00 | Curtis (2009) | £225.40 | £418.60 | Gamma |
| AE: Somnolence - Psychiatrist: Visits p.a. | 1 | Assumption | [redacted] | [redacted] | Gamma |
| AE: Somnolence - Psychiatrist: Visit duration | 0.33 | Assumption | [redacted] | [redacted] | Gamma |
| AE: EPS - Psychiatrist: % of pts | 100% | NICE guidelines - CG82 Schizophrenia. Table 45, pg 218 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 70% | 130% | Gamma |
| AE: EPS - Psychiatrist: Cost per hour | £322.00 | Curtis (2009) | £225.40 | £418.60 | Gamma |

| | Value | Reference | Lower value | Upper value | Distribution |
|---|---|---|---|---|---|
| AE: EPS - Psychiatrist: Visits p.a. | 1 | NICE guidelines - CG82 Schizophrenia. Table 45, pg 218 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 0.7 | 1.3 | Gamma |
| AE: EPS - Psychiatrist: Visit duration | 0.33 | NICE guidelines - CG82 Schizophrenia. Table 45, pg 218 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 0.23 | 0.43 | Gamma |
| AE: EPS - Benzo. (Lorazapam): % of pts | 100% | Assumption | [redacted] | [redacted] | Gamma |
| AE: EPS - Benzo. (Lorazapam) mg per day | 2 | British Medical Association. British National Formulary (BNF), No. 59. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; March 2010. | 1.40 | 2.60 | Gamma |
| AE: EPS - Benzo. (Lorazapam) Cost per day | £0.39 | British Medical Association. British National Formulary (BNF), No. 59. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; March 2010. | £0.29 | £0.49 | Gamma |
| Cost per day of Aripiprazole (10mgs) | £3.42 | British Medical Association. British National Formulary (BNF), No. 59. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; March 2010. | £2.28 | £6.84 | Gamma |
| Cost per day of Olanzapine (12.5mgs) | £3.55 | British Medical Association. British National Formulary (BNF), No. 59. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; March 2010. | £3.55 | £4.29 | Gamma |
| Cost per day of Clozapine (325mgs) | £2.86 | British Medical Association. British National Formulary (BNF), No. 59. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; March 2010. | £1.28 | £2.86 | Gamma |
| Relapse: Acute hospital - % of pts | 77.30% | Glover et al., 2006. Refer to NICE guidelines - CG82 Schizophrenia. Table 43, pg 216 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 54.11% | 100.49% | Gamma |
| Relapse: Acute hospital - Duration | 42 | Assumption - Duration of relapse is equivalent to cycle length (6 weeks) | [redacted] | [redacted] | Gamma |
| Relapse: Acute hospital - Unit costs | £534.00 | Reference costs | £373.80 | £694.20 | Gamma |
| Relapse: CAMHS - Duration | 42 | Assumption - Duration of relapse is equivalent to cycle length (6 weeks) | 0 | 56 | Gamma |

| | Value | Reference | Lower value | Upper value | Distribution |
|---|---|---|---|---|---|
| Relapse: CAMHS - Unit costs | £19.34 | Curtis (2009) | £13.54 | £25.14 | Gamma |
| Relapse: Olanzapine - % of pts | 100.00% | Assumption. Refer to NICE guidelines - CG82 Schizophrenia. Table 43, pg 216 (http://www.nice.org.uk/guidance/index.jsp?action=download&o=43607) | 70.00% | 130.00% | Gamma |
| Relapse: Olanzapine - Duration | 42 | Assumption - Duration of relapse is equivalent to cycle length (6 weeks) | [redacted] | [redacted] | Gamma |
| Switching | £322 | Curtis (2009) | £225 | £419 | Gamma |
| Relapse: Ari (Moeller) | 20.00% | Moeller et al. (2006) | 14.00% | 26.00% | Beta |
| Relapse RR (Moeller) | 0.97 | Moeller et al. (2006) (adjusted) | 0.679 | 1.261 | Log |

# 10 Related procedures for evidence submission

## *10.1 Cost-effectiveness models*

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

## *10.2 Disclosure of information*

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they

will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

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

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for

the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

### *10.3 Equity and equality*

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).