Section A: Clarification of effectiveness data

Evidence

A1. In order to verify that the clinical data reported in your submission has been correctly presented, could you please provide copies of the Clinical Study Reports cited in your submission?

These are provided.

Literature searches

A2. Please could you confirm which clinical trials registries (e.g. controlled-trials.com, UKCRN clinicaltrials.gov) and conference abstracts were searched?

No clinical trial registries or conference abstracts were searched.

A3. Please could you provide clarification of the approach used, and the content of, the hand-searching?

Based on initial, general keyword searching through PubMed (Medline), two reviews were initially identified: Madaan et al (2008) (1) and Kumra et al (2008) (2). These review articles and their respective bibliographies were used to inform the design of the search strategies. Interrogation of the articles also served to identify poster and abstract articles for inclusion in the search results (3, 4).

A4. The ERG has identified an additional publication of an analysis from the Findling et al RCT (Robb, et al, 2010, Journal of Child and Adolescent Psychopharmacology; 20(1): 33-38). Could you please comment on the relevance of this study to your submission?

This study was a *post hoc* analysis of a specific subset of scores (Hostility) from the Positive and Negative Syndrome Scale PANSS. The PANSS is made up of five psychopathological symptom domains of schizophrenia (Positive, Negative, Depression/Anxiety, Cognitive, Hostility).

The study is not of major relevance to our submission because:

(a) it is *post hoc* analysis conducted outwith the primary outcome measure of the PANSS Total score, and so must be considered less robust than a protocolled analysis;

(b) while it is encouraging that the data suggest that (compared with placebo) individual PANSS Hostility, Uncooperativeness and Poor Impulse Control Items can be significantly improved with aripiprazole 30mg/day, aripiprazole's proven effects on the PANSS Total score are of more relevance to our submission.

Thus, while of interest, we feel the data from Robb et al (2010) do not add anything of additional significance to our submission.

Comparators

A5. Could you please provide details of the methodology adopted for assessing studies for inclusion in the indirect comparison and the non-RCT evidence base supporting your submission?

Indirect comparison

As outlined in Section 5.7.1, the search strategies detailed in Section 5.2 were designed to identify trials that could be used in the indirect comparison as well as providing data for the clinical sections of the submission (i.e. RCTs). Sections 5.2.1 and 5.2.2 have outlined the criteria used to identify studies in adolescent patients with schizophrenia.

In section 5.2.2 of the submission we have reported the following.

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 (5, 6) (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 (7-9) or they did not contain sufficient data for comparison (e.g. abstract by Haas (2007) (3)).

In addition, to ensure that the trials were appropriate to include in the indirect comparison we have outlined the details of patient characteristics in section 5.7.7. The treatment groups in the aripiprazole study (5, 10) and the olanzapine study (6) were generally well matched for demographic and baseline characteristics. The average age of patients in Findling et al (2008) (5) was 15.4 years in the placebo arm and 15.6 years in the aripiprazole 10 mg arm, compared with an average age of 16.3 years in the placebo arm and 16.1 years in the olanzapine arm in the Kryzhanovskaya et al (2009) study (6). Both studies recorded outcomes at 6 weeks and measured outcomes in a similar way. We have assumed that the similarity of the trials included in the indirect comparison avoids bias in the estimates of the indirect comparison (11).

Non-RCT evidence.

The aim of the search was to identify prospective, non-randomised evidence regarding the efficacy and safety of aripiprazole for the treatment of adolescents with schizophrenia. Of the 152 non-randomised records identified by the Master search, the flow chart below outlines the reasons for exclusion; no study captured by the searches were considered relevant to the decision problem.

After the first round of exclusions (E1), 63 records were interrogated for inclusion of aripiprazole as a study intervention (E2). Of these, 4 studies were identified (as described in section 5.8 of submission document). The first two rounds of exclusion were based on title and abstract; the final round of exclusion was done based on full text.

Flow chart

Number	Reason for exclusion
E1 (n=89)	
19	Non-prospective study (e.g. retrospective, observational)
10	Non-english record
1	Duplicate
24	Non-specified interventions
3	Not schizophrenia (other or mixed diagnosis excluded)
9	Not schizophrenia (other or mixed diagnosis excluded)
23	No relevant outcome data on efficacy or safety of interventions to treat schizophrenia
E2 (n=59)	
59	Studies did not include aripiprazole as an intervention
E3 (n=4)	
3	Included adult patients only
1	No relevant outcome data (phase II tolerability and pharmacokinetic study [see section 5.8 of submission document])

A6. Please provide details of the methodologies for the studies included in the indirect comparison.

Details of the pivotal clinical trial used to support this submission (study 31-03-239) were outlined in Section 5.3 (both the Findling publication (5) and the CSR 31-03-239 (10) were used to inform the summary of the clinical trial). Both the aripiprazole clinical trial and the olanzapine clinical trial were reviewed according to the quality criteria requested in the NICE STA template.

The methodology of the olanzapine clinical trial (6) is summarised in Table 1 below.

Table 1: Summary of methodology of the Kryzhanovskaya et al (2009) study (6)

Location	Multicentre, United States (20 sites) and Russia (5 sites)
Design	Randomised, double-blind, placebo-controlled study
Duration of study	Three periods; a 2- to 14-day screening and washout period; a 6-week double-blind, acute period with olanzapine or placebo; and an optional 26-week open-label period with olanzapine
Inclusion Criteria	• Adolescents aged 13 to 17 years with schizophrenia of the paranoid, disorganised, catatonic, undifferentiated, and residual types • Total score ≥ 35 on the anchored version of the Brief Psychiatric Rating Scale for Children (BPRS-C) with a score ≥ 3 on at least one of the following BPRS-C items at randomisation; hallucinations, delusions, or peculiar fantasies
Exclusion Criteria	• Previous participation in a clinical trial of oral olanzapine • Treatment within 30 days of the trial with a drug without regulatory approval for any indication • Documented olanzapine allergic reaction • Previous non-response to an adequate dose/duration of olanzapine treatment • Pregnancy, nursing or refusal to practice acceptable contraception • Acute/unstable medical conditions

	• Current/expected use of any concomitant psychotropic medications (except for certain benzodiazepines and anticholinergics) • Clinically significant laboratory abnormalities • DSM-IV-TR substance dependence within 30 days (except nicotine and caffeine) • Current DSM-IV-TR diagnosis of a comorbid psychiatric or developmental disorder
Intervention(s) (n) and comparator(s) (n)	Olanzapine 2.5 or 5.0 mg/day (which could be increased to a maximum of 20.0 mg/day or decreased by an increment of 2.5 or 5.0 mg/day at the investigator's discretion (n = 72) Placebo (n = 35)
Method of randomisation	Patients were randomly assigned in a 2:1 ratio to either olanzapine or placebo nightly. The method of randomisation was not reported
Method of blinding	The study included a 6-week double-blind period – the method of blinding was not reported
Primary outcomes	Mean change from baseline-to-endpoint change in the investigator-rated BPRS-C total score
Secondary outcomes	Baseline-to-endpoint changes on the CGI-S, PANSS, and the Overt Aggression Scale (OAS). Changes on the CGI-I were evaluated at endpoint. A secondary measure was patients' response rate, defined a priori as a 30% or greater reduction in the BPRS-C total score from baseline to endpoint and a CGI-S score of 3 or lower (mildly ill) at the last measurement
Statistical analyses	Data were analysed on an ITT basis, with a two-sided α level of 0.05. An analysis-of-covariance model with the terms country, therapy and baseline was used to evaluate continuous efficacy data. Categorical data were analysed using a Fisher exact test, and a mixed-model repeated-measures analysis of covariance was used to analyse the change in the BPRS-C total score from baseline to each post-baseline visit. Time-to-event analyses were performed using a log-rank test. The LOCF method was used to analyse mean changes from baseline to endpoint

A7. Please provide all of the results from the RCT (Study No. 31-03-239) that was included in the indirect comparison. It is noted that only a table on the quality assessment for this study has been provided in the submission.

Results from the two studies included in the indirect comparison are outlined in Section 5.7.4. All the data for aripiprazole were taken from the CSR but have also been reported in the publication (Findling et al (5)), therefore both the publication and the CSR have been referenced in the indirect comparison section. A quality assessment was carried out for both the included studies (Section 9.3 for the aripiprazole study, and Section 9.5 for the olanzapine study).

A8. The submission includes clozapine as a third line treatment in the economic model, despite not being listed as a comparator in the submission. Please could you clarify why a systematic search to identify studies which include data for this treatment was not undertaken and why the results, methodology and quality assessment of any identified studies were not presented in the submission.

Clozapine is not considered as a comparator in the submission because, according to clinicians, it would not be given first- or second-line, and is therefore not given in place of aripiprazole or olanzapine. Therefore, we did not carry out any clinical searches on clozapine in the first instance.

However, according to expert opinion, clozapine is commonly used as an end-of-line treatment (in treatment resistant patients), and was therefore considered in the economic model in order to include health states that accurately described what treatments patients may receive after two previous second generation antipsychotics have failed.

In terms of outcomes, only relapse rates and adverse events are considered in the model for clozapine. The relapse rates were taken from the same paper as relapse rates for other treatments in the model, Moeller et al, 2006 (12). We assumed that the adverse events for clozapine would be the same as those for aripiprazole (because adverse events while on clozapine are thought to be worse, according to expert opinion, compared with other second generation antipsychotics this was felt to be a conservative assumption). The effect of including additional disutility while on clozapine was tested in sensitivity analysis and found not to affect the results. The costs of clozapine were also considered.

A9. Section 2.6: Please provide further details and justification of whether the conference abstract identified for risperidone had sufficient data for the clinical review, and explain why the data was deemed insufficient for model parameters.

The conference abstract for risperidone only reported the change in PANSS scores as an outcome. The patients' baseline PANSS scores are not reported and no numbers or percentages of patients were reported for withdrawals or adverse events. For example, the abstract outlines which adverse events were most common but does not provide the numbers of patients experiencing the events. Therefore, we consider that the data provided to be insufficient for inclusion in the indirect comparison.

When the results of this trial are fully published in a peer reviewed journal, the results of risperidone can be evaluated and added to the clinical and cost-effectiveness evidence.

Population

A10. Section 3.1.1: Your submission states that 'other areas of mental health disorders such as learning disabilities are not appropriate for this review'. Please could you clarify what is meant by this, and provide your inclusion and exclusion criteria used to identify people with learning difficulties?

As described in the submission, the diagnosis of schizophrenia requires a definitive methodological approach using precise DSM-IV and K-SADS-PL criteria. Thus "inclusion and exclusion criteria used to identify people with learning difficulties" are not relevant – patients are diagnosed as either suffering or not suffering from schizophrenia, using these diagnostic tools.

In this phrase in our submission we attempted to clarify that while some individuals with learning difficulties may exhibit psychoses, unless they fulfil the DSM-IV/K-

SADA-PL criteria for schizophrenia they are (by definition) not schizophrenic, and so are not appropriate for inclusion in our submission on aripiprazole in adolescent schizophrenia.

Clinical evidence

A11. Please could you provide information as to why 'head to head studies with less than two arms including the intervention of interest were excluded' from the clinical evidence, and provide a list of these 78 excluded studies, Please also provide a list of all other excluded studies and the reasons for their exclusion from stages e2 and e3 of the screening process.

"Head to head studies with <2 arms including interventions of interest" were excluded from the review (see Section 5.2.1 of the main submission document). "Interventions of interest" included olanzapine, risperidone, quetiapine, placebo, haloperidol, amisulpride, aripiprazole (as per Section 5.2.1 of the main submission document).

Studies including intervention arms with at least two of the "interventions of interest" were included in the review, while studies with less than two arms of interest were excluded. For instance:

- Hertling et al. (Neuropsychobiology 2003;47(1): 37-46) was excluded as it compared risperidone with flupenthixol in a head-to-head fashion (i.e. <2 arms of interest).
- Whereas, Sikich et al. (American Journal of Psychiatry 2008;165(11): 1420-1431) was included as it compared molindone, olanzapine and risperidone (at least two arms of interest).

The rationale for this approach was to identify a relevant data set that would allow indirect comparison with the technology under assessment (i.e. aripiprazole). Without at least 2 arms of interest, an evidence network could not be created.

(See Appendix A for a list of the 78 excluded studies excluded for reasons of being a "head to head study with <2 arms including interventions of interest". See Appendix B for a list of all other excluded studies and the reasons for their exclusion from stages e2 and e3 of the screening process).

A12. Please provide justification for the LOCF approach to data analysis, and provide for each study arm, information on how many observations in each week were carried forward?

The core data set for all efficacy analyses was the intent-to-treat (ITT) dataset that contains data from all randomised subjects regardless of protocol violation. If a subject received a treatment other than the one to which he or she was randomised, this subject was included in the ITT data set on an "as-randomised" basis. In order to handle missing data and restrictions imposed by different types of analyses (e.g. change from baseline analysis), other data sets derived from the ITT data set were used for the efficacy analyses, such as the observed cases (OC) data set and the last observation carried forward (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, as is standard practice in schizophrenia clinical trials.

A13. There is inconsistency in the reporting of analyses from the included trial (Study No. 31-03-239), with some outcome data reported for baseline and endpoint only, whereas others are provided for 0,1,2,3,4,5 and 6 weeks. Please could you clarify the reason for this?

All efficacy outcomes are reported for all weeks 0-6, except for those relating to functioning and quality-of-life. The CGAS and PQLES-Q total and overall scores are only measured and reported at baseline and endpoint (i.e. Week 6). Although there was no rationale provided in the CSR, parameters relating to functioning and quality-of-life are unlikely to show changes on a weekly basis, and so measurements at these times would be meaningless. It is therefore more appropriate, and more clinically relevant, to measure the change after 6 weeks of treatment.

A14. Please provide clarification why P-QLES-Q was classed as an 'other' (not primary or secondary) outcome measure in your submission, the definition of 'other' in this context, and what the implications are for interpreting the P-QLES-Q data as presented.

The P-QLES-Q was classified as 'other' in the clinical trial because it cannot be classed as either an efficacy or safety measure. It is a quality-of-life scale (consisting of 14 items pertaining to daily activities and satisfaction, and an overall assessment item) and thus reliant upon subjective responses from the patient depending on "how they feel" at a particular point in time.

A15. For each of the PANSS, GCI, CGAS, and P-QLES-Q, please provide details of what would be a clinically meaningful change or difference in these measures, and whether the sample size used was considered adequate to provide reasonable power to detect this meaningful change or difference.

There are no agreed parameters by which clinically meaningful changes/differences in PANSS, GCI, CGAS and P-QLES-Q can be pre-defined, and how they link with each other. While a certain level of change in symptom score may, by clinical consensus, be considered clinically meaningful, such considerations are very reliant on the clinical judgement, experience and knowledge of the disease area of the assessing clinician, and their evaluation of the expected/likely clinical responses.

Because such a clinical judgement is *a priori* (not requiring a statistical estimation/interpretation of the data), sample size would not be a factor in considering whether the number of patients were adequate to show a clinically meaningful change or difference.

Section B: Clarification of health economic model

B1. Please could you provide more detail of the methods, quality and results of the study that was used to estimate the relative risk of relapse in the economic model. It is noted that the study from which the relative risk was sourced was not reviewed in your submission.

Summaries of the methodology and results of the study by Moeller et al, 2006 (12) are provided in Table 2 and Table 3. These are followed by a qualitative assessment of the study limitations.

Table 2: Methodology of Moeller et al, 2006 (12)

Location	USA
Design	Retrospective cohort study examining psychiatric relapse rates, defined as hospitalisation for a psychiatric event, for persons with schizophrenia who switched antipsychotic agents.
Duration of study	12 months
Inclusion Criteria	• Kansas Medicaid enrolees with a diagnosis code for schizophrenia • Aged ≥ 18 years • Continuously enrolled in Medicaid during the 12-month study period • Switched from any antipsychotic to either aripiprazole (cases) or 1 or the other atypical antipsychotics (comparisons)
Intervention(s) (n) and comparator(s) (n)	Patients were classifed as switchers if they had previously received an antipsychotic agent and had a prescription for a new atypical antipsychotic agent. Switchers were sorted into the following groups; Cases; those switching to aripiprazole Comparisons; those switching to another SGA (clozapine, olanzapine, quetiapine, risperidone, or ziprasidone)
Outcome variable	Hospitalisation for a psychiatric diagnosis within 6 months of the date of switch; occurrence of hospitalisation, time to admission, length of stay
Analyses	Cases and comparisons were compared with respect to basic demographics, concurrent conditions, and prior psychiatric-related health care use in bivariate analyses using descriptive statistics. Time to relapse was modelled using Cox proportional hazards

Table 3: Results of Moeller et al, 2006 (12)

Patient disposition and demographics	• 965 patients met eligibility criteria; 444 aripiprazole (cases) and 521 SGAs comparisons • Aripiprazole patients were younger than patients receiving SGAs (42.6 vs. 47.1 years, respectively; $p < 0.001$). Study populations were comparable with respect to gender and race • Neurotic, personality, and non-psychotic mental disorders; substance abuse; and depression were the most frequent comorbidities in both treatment groups • Patients on aripiprazole were less likely to suffer from depression than patients on SGAs (26.8% vs. 34.4%, respectively; RR = 1.43; 95% CI = 1.08 – 1.88) • The most commonly reported medical comorbidites were cardiovascular diseases, lipid disorders, diabetes and pulmonary diseases. Rates did not differ between groups • Prior to the switch aripiprazole patients were more likely than SGA patients to have tried more antipsychotic medications (2.83 vs. 2.60, respectively; $p < 0.001$). More patients in the aripiprazole group than the SGA group were switched from an atypical antipsychotic (82.8% vs. 73.5%, respectively; RR = 0.58; 95% CI 0.43 – 0.78). Use of other psychotropic medications was comparable • Previous psychiatric hospitalisations and outpatient visits

	were comparable
Relapse/Time to relapse	Based on psychiatric hospitalisations rates of relapse did not differ between groups: • Six months after being switched from their previous antipsychotic regimen 20% of aripiprazole and 19.4% of SGA patients were hospitalised (RR = 0.92; 95% CI = 0.67 - 1.26) Time to relapse was not statistically different between groups: • Mean times to psychiatric hospitalisation were 65.7 days for the aripiprazole group and 73.8 days for the SGA group
Predictors of relapse	Significant variables in the Cox proportional hazards model included other psychiatric diagnoses and past number of psychiatric-related hospitalisations: • Comorbid diagnoses of depression (adjusted hazard ratio [AHR] = 1.44; 95% CI = 1.05 – 1.98), substance abuse (AHR = 1.80; 95% CI = 1.32 -2.74), and neurotic, personality, and non-psychotic mental disorders (AHR = 2.27; 95% CI = 1.58 – 3.26) all increased the risk of psychiatric hospitalisations • Prior psychiatric hospitalisations also increased the risk of post-switch hospitalisation (AHR -= 1.38; 95% CI = 1.22 – 1.55) Use of apripiprazole versus other SGAs had no effect on the risk of hospitalisation (AHR = 1.16; 95% CI = 0.86 – 1.56)

Quality assessment of Moeller et al, 2006 (12)

A large patient population was included in the study. The selection/eligibility criteria were adequately described. There were, however, some differences between the study groups. Patients in aripiprazole group were on average younger than the SGA group (42.6 vs. 47.1 years, respectively) and received more community support visits, case management, and antipsychotic medications. This may suggest that aripiprazole patients had better access to services, or that they had a more severe form of schizophrenia, than those in the SGA group. Also, more patients in the SGA group suffered from comorbid depression than in the aripiprazole group (34.4% vs. 26.8%, respectively). A higher incidence of depression may be associated with a poorer outcomes and higher rates of relapse and rehospitalisation.

The patient population was recruited from a single US state's Medicaid plan and may not be able to be generalised/extrapolated to other populations. In addition, accurate coding of healthcare services and diagnoses had to be assumed.

The comparator group contained a mixture of SGAs, so individual SGAs could not be compared with aripiprazole. The newer agents are typically classified as a group; however their side effect profiles may differ. These effects could impact on relapse rates and efficacy. In addition, the study included patients who may have been receiving multiple antipsychotics after the switch - not monotherapy with either aripiprazole or SGAs. However, the study was designed to represent real-life prescribing practices.

Moellar et al (2006) examine relapse rates in an adult population which is a recognised limitation of the model. The model was based on the best available data in the absence of relapse rates for adolescents.

B2. Please provide more detail of the methods, quality and results of the study used to obtain HRQoL data for your submission.

The details of the study used to source utility values (13) have been described in section 6.4.6. This section outlines the methods and results of the study and comments have been made on the suitability of the study to inform the economic model included in this submission. The details of the study were provided in conjunction with the requirements outlined in the STA template.

It is difficult to review the overall quality of QoL studies and as far as we are aware there is no proforma to carry out such an evaluation. However, in terms of applicability, Briggs et al 2008 (13) carried out their study in a relevant population (patients with schizophrenia I the UK) and collected utilities for relevant health states such as stable schizophrenia and side effects of treatments.

This study is freely available therefore we have therefore attached a link here: http://www.hqlo.com/content/pdf/1477-7525-6-105.pdf

The health states were developed by the authors in such a way as to ensure that they were clinically relevant and meaningful. They did this by: carrying out a literature review to identify initial health states for discussion; carrying out cognitive interviews in patients with schizophrenia to ensure they were meaningful and clear to patients; and by carrying out a cognitive debrief with lay persons, again to ensure the states were clear and meaningful.

Of the 75 laypersons and 50 patients recruited, all but one participant (from the patient group) completed the study. The patient group completed an EQ-5D questionnaire to validate the baseline health state (stable schizophrenia). The mean utility measured by the EQ-5D was 0.86, which is lower than the utility elicited from the patients in the TTO questionnaire, but very similar to the utilities elicited from the lay population.

The utility values for health states used in the model (either in the base case analysis or in sensitivity analysis) were reported for patients and laypersons as shown in Table 4.

Table 4: Utility values as reported in Briggs et al 2008 (13)

Health State	**Mean utility (standard error**	
	Patient sample	**Lay sample**
Stable schizophrenia	0.919 (0.023)	0.865 (0.021)
Weight gain	0.825 (0.028)	0.779 (0.024)
Relapse	0.604 (0.042)	0.479 (0.033)
EPS	0.722 (0.037)	0.574 (0.032)

In order to be consistent in the model, the utility values elicited from patients were used. In Briggs et al (2008), there were differences in the utilities observed in the patient group and the layperson group although the direction of results was the same. We have provided results from the model using utilities from the layperson sample as a sensitivity analysis to show the effect of these differences.

Please note, for this sensitivity analysis we used the model with the revised cost according to clarification point B5. In this sensitivity analysis we have considered that the disutility for somnolence is zero (i.e. that the quality-of-life for somnolence is not considered) as this utility comes from a separate source. We have provided results

from deterministic analysis and PSA. In the PSA analysis the disutility for somnolence was varied from 0-100%.

The base case analysis is presented in Table 5 with the sensitivity analysis showing the results of using the alternative utilities in Table 6. The PSA analysis is presented in Table 7 and Figure 1. The PSA results are based on 10,000 simulations.

Table 5: Base case analysis (using revised model as discussed in clarification point B5)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Aripiprazole - olanzapine - clozapine	£22,981	2.597	-£72.63	0.004	Dominant
Olanzapine - aripiprazole - clozapine	£23,054	2.593	-	-	-
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

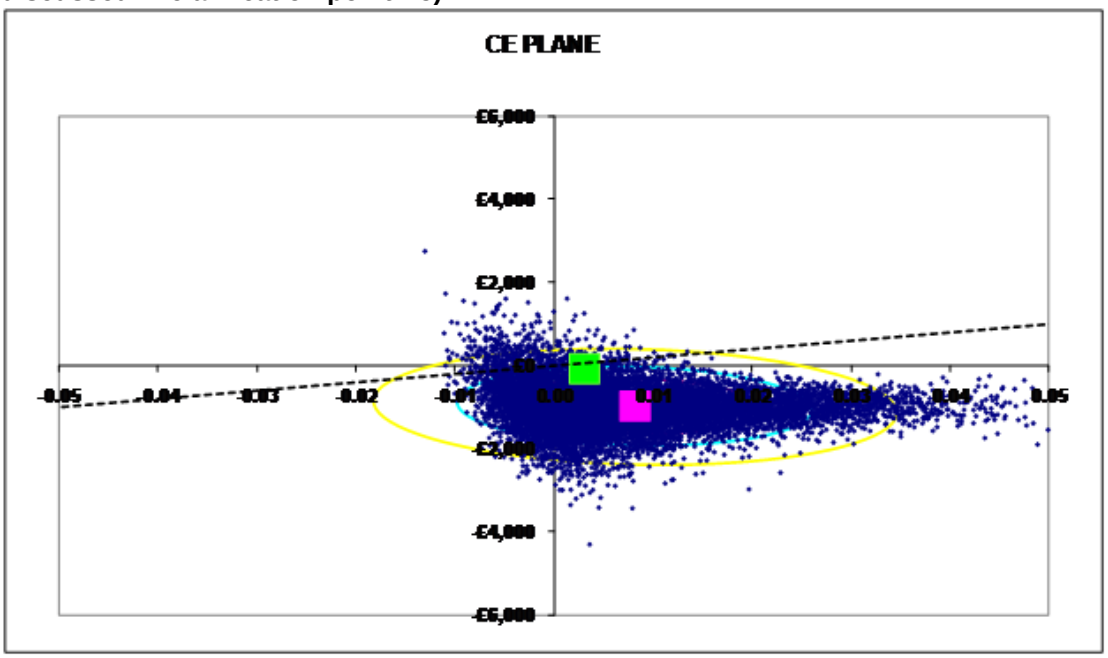
Table 6: Results of additional utility value sensitivity analysis (layperson utility values from Briggs et al 2008 (13)) (using revised model as discussed in clarification point B5)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Aripiprazole - olanzapine – clozapine	£22,981	2.439	-£72.63	0.003	Dominant
Olanzapine - aripiprazole – clozapine	£23,054	2.436	-	-	-
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Table 7: PSA results of additional utility analysis (using revised model as discussed in clarification point B5)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Aripiprazole - olanzapine - clozapine	£23,212	2.437	-£996	0.008	Dominant
Olanzapine - aripiprazole - clozapine	£24,208	2.428	-	-	-
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Figure 1: CE plane - PSA results of additional utility analysis (using revised model as discussed in clarification point B5)



Briggs et al (2008) examined utilities in an adult population which is a recognised limitation of the model. The model was based on the best available data in the absence of utility values for adolescents.

B3. Could you provide more detail on the methods of the prescription cost analysis study described in your submission?

We used the prescription cost analysis data provided at the NHS information centre (http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-2008).

We used the number of prescriptions from the PCA and calculated the proportion of each formulation prescribed. The most common formulation was then used as the cost for the treatment. These calculations were also included in the economic model (sheet: prescription cost analysis). The calculations we carried out are shown in column S of this sheet. The highest and lowest costs for the treatments included in the model were used in the PSA.

A recognised limitation of this approach is that the number of adolescent patients cannot be determined from this analysis, therefore the prescription numbers take into account are those for patients of all ages.

B4. It is noted that your submission refers to MIMS online 2010 (no access date given) as the source used for drug acquisition costs, while your electronic model lists the source for drug acquisition costs as BNF No 59, March 2010. Please state which source is correct and provide the date this information was accessed, if using electronic sources. Please not that the technology appraisal process prefers the use of the price quoted in the BNF, where available.

Prices for drugs were taken from MIMS online 2010 (accessed during April 2010). This is because the current version of the BNF does not yet reflect the changes in price according to the PPRS. The model reference is incorrect.

B5. The submission states that the acute hospital cost per day used in the model was based on the national average unit cost for HRG code PA52 (page 99 and 102). The 2008/09 NHS Reference Costs lists the national average unit cost for PA52C (Behavioural Disorders with length of stay 8 days or more) as £23,595. In table 42 you have listed this cost as £24,581 (which is the national average unit cost for PA53B (Eating Disorders with length of stay 8 days or more)). Please clarify which HRG code and cost is correct and the reference you have used.

The correct code is PA52C and the correct cost is £23,595 (taken from 2008/09 NHS Reference Costs). This would mean that the overall cost of relapse per patient is £17,016 rather than £17,700.

We have corrected this error in the model and have presented revised results in Table 9 for the base case scenario (Table 8 shows the original base case results for comparison).

Table 8: Original base case result

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					

Table 9: Revised base case result (with updated cost)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Aripiprazole - olanzapine - clozapine	£22,981	2.597	-£72.63	0.004	Dominant
Olanzapine - aripiprazole - clozapine	£23,054	2.593	-	-	-
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

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Appendix A

List of 78 records appended with code G exclusion at first round of exclusions.

- Code G: Head to head studies with <2 arms including interventions of interest

1. A double-blind comparison of raclopride and haloperidol in the acute phase of schizophrenia. The British Isles Raclopride Study Group. Acta Psychiatr Scand. [Clinical Trial Comparative Study Randomized Controlled Trial]. 1992 Nov;86(5):391-8.
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Appendix B

Exclusion criteria	Exclusion Code	e2 (n=114)		e3 (n=27)	
		No.	*Ref.*	*No.*	*Ref.*
(Non systematic) review, letter, commentary, case report/series	a	1	(1)	2	(2, 3)
No relevant outcome data on efficacy or safety of interventions to treat schizophrenia	b	1	(4)		
Adult (>17yrs) or child (<13yrs) population	c	103	(5-44)(45-89)(90-107)		
Not schizophrenia (other or mixed diagnosis excluded)	d	1	(108)	2	(109, 110)
Non-english	h	3	(111-113)		
No data on adolescent population (i.e. no subgroup analysis of adolescent pop)	j			17	(114-130)
Systematic review or meta analysis	k			5	(131-135)
Full text unavailable	l	1	(136)		
non-RCT (e.g. non randomised trial, observational, retrospective study)	x	4	(137-140)	1	(141)

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