NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Aripiprazole for the treatment of schizophrenia in adolescents (aged 15-17 years)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
BMS & Otsuka Pharmaceuticals	Bristol-Myers Squibb (BMS) and Otsuka Pharmaceuticals (UK) Ltd (OPUK) welcome the opportunity to review and comment on the Appraisal Consultation Document (ACD) relating to the ongoing Single Technology Appraisal of aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years. As requested by the committee, BMS/OPUK have undertaken further analysis of the clinical and cost-effectiveness of aripiprazole for the treatment of schizophrenia in people aged 15-17 years (see below for key findings).	Comment noted.
BMS & Otsuka Pharmaceuticals	Effectiveness: Aripiprazole is the only licensed, and commonly prescribed, antipsychotic for adolescent schizophrenia. Amisulpride, although licensed for use in adolescents, is infrequently prescribed due to its adverse events profile. The clinical effectiveness of aripiprazole for the treatment of schizophrenia in people aged 15-17 years has been established in clinical trials as well as in clinical practice. The Committee requested further information on the effectiveness of each of the atypical anti-psychotics routinely used in UK clinical practice. The level of analysis requested, the lack of suitable data and the lack of time afforded in the timeline to respond have meant BMS/ OPUK needed to take a pragmatic approach. A complete indirect comparison of all the requested end points has not been conducted, but has been presented as a clinical summary. However, BMS/OPUK have updated the existing indirect comparison used for the economic model. BMS/OPUK feel this is a reasonable compromise given the time available, as the clinical endpoints can be referenced to a comprehensive, independent, published review covering the majority of data requested. In addition to our own clinical trial data, we present clinical trial evidence for risperidone, olanzapine and quetiapine. There are no placebo-controlled randomised clinical trial data for amisulpride, neither are there placebo-controlled	Comment noted. The Committee understood from the clinical specialists that no single atypical antipsychotic drug is considered to be more clinically effective than the others. Risperidone is the most widely used first-line atypical antipsychotic for adolescents with schizophrenia in UK clinical practice because clinicians have extensive experience of using it to treat schizophrenia, and often achieve control with low doses and without troublesome adverse events. An alternative atypical antipsychotic can be considered if the first antipsychotic proves unsatisfactory. Other atypical antipsychotics such as aripiprazole, olanzapine, quetiapine or amisulpride may be used if control of schizophrenia is not achieved with risperidone. The clinical specialists also explained that clozapine is sometimes prescribed; however, because it needs careful monitoring for particular side effects, it is prescribed as rescue therapy only if the schizophrenia is refractory to at least three other antipsychotic treatments.See FAD section 4.3. Comment noted.

Consultee	Comment	Response
	data for clozapine. Not all the placebo-controlled studies provide all the clinical endpoints requested, so data have been extracted and presented where available.	
	We also present data from a recent review of prospective head-to-head and placebo-controlled comparisons of the efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders.	Comment noted.
	To summarise our efficacy findings based on the available data from placebo-controlled, randomised clinical trials in adolescent schizophrenia,:	Comment noted.
	• There are no significant differences in short term efficacy between the second generation antipsychotics aripiprazole, risperidone, olanzapine, quetiapine, amisulpride and clozapine.	
	• A sub-analysis of aripiprazole trial data (that was submitted to the CHMP) showed that efficacy was observed over 26 weeks in an open label extension trial.	Comment noted. The Committee understood from the clinical specialists that no single atypical antipsychotic drug is considered to be more clinically effective than the others. See FAD section 4.3.
	• There is a paucity of data available regarding the use of aripirazole in adolescents with schizophrenia, who also have learning difficulties.	Comment noted. The Committee concluded that there was not sufficient data to provide evidence on how the clinical and cost effectiveness of aripiprazole may differ for people with schizophrenia who have learning difficulties. Please see FAD section 4.15.
	Aripiprazole is the only licensed, commonly prescribed antipsychotic for adolescent schizophrenia.	Comment noted. The Committee noted that some of the atypical antipsychotics described by the clinical specialists do not have a marketing authorisation for the treatment of schizophrenia in adolescents, but acknowledged that specific licensing in adolescents is not a prerequisite to prescribing licensed adult medicines, particularly if there is widespread experience of their use. Please see FAD section 4.3.

Consultee	Comment	Response
	No differences were identified in the clinical effectiveness between the 2nd generation antipsychotics.	Comment noted. Please see responses above.
BMS & Otsuka Pharmaceuticals	Safety/tolerability The Committee accepted that accounts of the use of aripiprazole suggest that it may be as safe and as well tolerated as the other second-generation antipsychotics. The ACD requested data on adverse treatment effects – for example weight gain. Weight gain and lipid/ glucose abnormalities during development are some of the risk factors that predict adult obesity and metabolic/cardiovascular morbidity. The safety tolerability data available demonstrate: • that aripiprazole was not associated with any significantly worsened metabolic indices. • no significant increase in lipids (total cholesterol, LDL-cholesterol and and triglycerides) or glucose have been reported. • data from clinical trials show that aripiprazole has the lowest effect on weight compared with other second generation antipsychotics commonly used in children and adolescent patients. Elevated serum prolactin levels have been shown to have effects on sexual function, menstrual function, as well as being associated with decreased bone mineral density in women. Whilst prolactin levels increased most in patients receiving risperidone or olanzapine, there is no evidence of hyperprolactinaemia with aripiprazole in adolescent patients. With respect to neuromotor symptoms (i.e. EPS, which includes akathisia) most studies found no significant differences between the second generation antipsychotics. Based on the available data from placebo-controlled, randomised clinical trials in adolescent schizophrenia, there are important differences in side effects between	The Committee heard from the clinical specialists and patient experts that there are a number of dose-related adverse events associated with atypical antipsychotic treatments, including weight gain, sexual dysfunction, hyperprolactinaemia, aggression and akathisia/extrapyramidal symptoms. The Committee accepted that accounts of the use of aripiprazole suggest that it may be as safe and well tolerated as the other treatments. Please see FAD section 4.4. The Committee heard from the clinical specialists that some treatments are more likely to be associated with particular adverse events: olanzapine is more likely associated with weight gain, risperidone and amisulpride are more likely associated with hyperprolactinaemia, and aripiprazole is more likely associated with akathisia and a subjective feeling of aggression (for which benzodiazepine co-treatment may be used). The Committee accepted that all atypical antipsychotics are associated with adverse events and that accounts of the use of aripiprazole suggest that it may be as safe and well tolerated as the other treatments. See FAD section 4.4. Comment noted. The Committee considered the

Consultee	Comment	Response
	the second generation antipsychotics. Aripiprazole is associated with a better safety and tolerability when compared with other 2nd generation antipsychotics	evidence on adverse events for aripiprazole and each of the comparators presented in the manufacturer's additional analyses. The Committee noted that there is substantial variation between the atypical antipsychotics in the adverse events associated with each treatment. See FAD section 4.8.
BMS & Otsuka Pharmaceuticals	Cost-effectiveness The Committee requested that BMS/OPUK provide further information on the cost-effectiveness of aripiprazole, including further comparators and treatment sequences. The following steps have been taken to address the requests made by NICE: • Identification of additional data requested • Data were extracted from the two additional studies identified and indirect comparisons on relevant outcomes were performed • The original economic model was adapted to include a fourth treatment line and additional adverse events. • Lay utility values from Briggs et al. were incorporated and a range of doses for each comparator, including low doses (which are commonly prescribed for adolescents) were explored. • Inaccuracies identified by the ERG in the original model were also corrected • Base case results and sensitivity analyses were re-run using the adapted model Total costs and QALYs for these four treatment sequences are outlined in Table 1(*please note that this table is not reproduced here*). The sequence with the highest QALYs is Aripiprazole - Risperidone - Olanzapine – Clozapine. The lowest cost sequence is Risperidone - Olanzapine - Aripiprazole – Clozapine. The ACD does not state which scenario should represent the base case, therefore all scenarios were compared with each other in the model and the cost per QALYs are provided in Table 2 (*please note that this table is not reproduced here*). These results show that including aripiprazole in a treatment sequence is cost-	Comment noted. The Committee noted that the manufacturer's updated base-case analysis shows that first-line aripiprazole sequences result in ICERs ranging from £52,750 per QALY gained to £108,800 per QALY gained when compared with the best-case risperidone sequence. It considered that, in view of the PANSS scores not being included in the model, these results were likely to be an underestimate. Furthermore, they are outside the range considered

Consultee	Comment	Response
	effective or dominant (i.e. being more effective and less costly). Deterministic and probabilistic sensitivity analyses (PSA) confirmed the robustness of these results. Including aripiprazole in a treatment sequence is cost-effective or dominant compared with treatment sequences that do not include aripiprazole in the treatment of adolescents with schizophrenia. In sensitivity analysis the overall direction of the results remains the same and in PSA, the cost-effectiveness acceptability curves show how similar the treatment sequences are when compared with each other. Therefore, BMS/OPUK asks the Committee to recommend aripiprazole for the treatment of schizophrenia in adolescents, and allow access to this agent, the only	to be a cost-effective use of NHS resources. In view of these results and the testimony from the clinical specialists on the use of risperidone, the Committee concluded that starting treatment with aripiprazole rather than risperidone would not be a cost-effective use of NHS resources with ICERs ranging from £52,750 per QALY gained to £108,800 per QALY gained when compared with the best-case risperidone sequence. However the Committee was mindful that in people aged 15 to 17 years with schizophrenia who are intolerant of or have a contraindication to risperidone, or whose schizophrenia has not been adequately controlled with risperidone, the case for aripiprazole is more plausible. It noted that the manufacturer's economic analyses suggest little difference between sequences in which aripiprazole precedes olanzapine and vice versa; and although sequences which contain aripiprazole are suggested to be more cost-effective than if quetiapine is included instead, the Committee was concerned that the cost of quetiapine was unfairly calculated in the manufacturer's economic model, as optimal packs and doses may not have been considered. The Committee agreed that the differences in side effects between atypical antipsychotics were a more important consideration than the (small) differences in their costs and primary outcomes. Therefore the Committee agreed that aripiprazole should be available on equal terms with other antipsychotic comparators (apart from risperidone), given its good side-effect profile and comparable price to olanzapine and quetiapine. See FAD sections 4.12, 4.13 and 4.14. Comment noted. Aripiprazole is recommended as an option for the treatment of schizophrenia in people aged 15 to 17 years who are intolerant of

Consultee	Comment	Response
	licensed and commonly used atypical anti-psychotic for adolescent schizophrenia.	risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone .See FAD section 1.1.
BMS & Otsuka Pharmaceuticals	Conclusions BMS/OPUK do not agree with the minded negative recommendation.	 Comment noted.
	Aripiprazole is the only licensed commonly prescribed atypical antipsychotic for adolescent schizophrenia.	Comment noted. The Committee noted that some of the atypical antipsychotics described by the clinical specialists do not have a marketing authorisation for the treatment of schizophrenia in adolescents, but acknowledged that specific licensing in adolescents is not a prerequisite to prescribing licensed adult medicines, particularly if there is widespread experience of their use. See FAD section 4.3.
	The current review of available data found no differences in the clinical effectiveness between the second generation atypical antipsychotics, whilst aripiprazole has demonstrated a better safety and tolerability profile.	Comment noted. The Committee understood from the clinical specialists that no single atypical antipsychotic drug is considered to be more clinically effective than the others. See FAD section 4.3.
	Our analysis concludes that aripiprazole is a cost-effective option for the treatment of schizophrenia in adolescents when compared with scenarios that do not include aripiprazole. There is general agreement amongst clinicians that it is important for adolescents to have access to a range of treatment options. BMS/OPUK believe that aripiprazole offers a well tolerated, as well as a clinically effective and cost-effective treatment option for people aged 15 to 17 years with schizophrenia	The Committee noted that the manufacturer's updated base-case analysis shows that first-line aripiprazole sequences result in ICERs ranging from £52,750 per QALY gained to £108,800 per QALY gained when compared with the best-case risperidone sequence. It considered that, in view of the PANSS scores not being included in the model, these results were likely to be an underestimate. Furthermore, they are outside the range considered to be a cost-effective use of NHS resources. In view of these results and the testimony from the clinical specialists on the use of risperidone, the Committee

Consultee	Comment	Response
		concluded that starting treatment with aripiprazole rather than risperidone would not be a cost-effective use of NHS resources with ICERs ranging from £52,750 per QALY gained to £108,800 per QALY gained when compared with the best-case risperidone sequence. However the Committee was mindful that in people aged 15 to 17 years with schizophrenia who are intolerant of or have a contraindication to risperidone, or whose schizophrenia has not been adequately controlled with risperidone, the case for aripiprazole is more plausible. It noted that the manufacturer's economic analyses suggest little difference between sequences in which aripiprazole precedes olanzapine and vice versa; and although sequences which contain aripiprazole are suggested to be more cost-effective than if quetiapine is included instead, the Committee was concerned that the cost of quetiapine was unfairly calculated in the manufacturer's economic model, as optimal packs and doses may not have been considered. The Committee agreed that the differences in side effects between atypical antipsychotics were a more important consideration than the (small) differences in their costs and primary outcomes. Therefore the Committee agreed that aripiprazole should be available on equal terms with other antipsychotic comparators (apart from risperidone), given its good side-effect profile and comparable price to olanzapine and quetiapine. See FAD sections 4.12, 4.13 and 4.14.
	Special consideration should be given to the fact that there is a lack of licensed medications available for the treatment of adolescents with schizophrenia, and therefore an increased need for positive reimbursement recommendations. Last, but not least, it is important to highlight that adults with schizophrenia have free access to aripiprazole.	Comment noted. The Committee noted that some of the atypical antipsychotics described by the clinical specialists do not have a marketing authorisation for the treatment of schizophrenia in adolescents, but acknowledged that specific licensing in adolescents is not a prerequisite to

Consultee	Comment	Response
		prescribing licensed adult medicines, particularly if there is widespread experience of their use. See FAD section 4.3.
	In conclusion, BMS/OPUK request that the Committee should reconsider its draft recommendation and positively recommend aripiprazole for the treatment of schizophrenia in adolescents aged 15-17 years.	Comment noted. See section 1.1 for recommendation.
Royal College of Paediatrics and Child Health	The conclusion seems justified by the evidence, or rather the lack of it.	Comment noted
Royal College of Paediatrics and Child Health	Our concern as clinicians is that the NICE recommendation will be taken to mean that aripiprazole should not be used at all in adolescent psychosis, whereas the body of the document seems to indicate that it could take its place as one of the three antipsychotics to be used before clozapine is considered: in other words, it could be considered as a suitable second or third choice, depending on the clinical circumstances. This view, which at present is hidden in the body of the report, should be included in the conclusion.	Comment noted. Aripiprazole is recommended as an option for the treatment of schizophrenia in people aged 15 to 17 years who are intolerant of risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone. See FAD section 1.1.
Royal College of Paediatrics and Child Health	We note there is effective use of this preparation down to the age of 13 and there is nothing to distinguish the use from 15-17 to that in adults.	Comment noted. All technologies are appraised within their licensed indications. The licensed indication for aripiprazole is for the treatment of schizophrenia in people aged 15 years and older. It was outside of the Committee's remit to make a recommendation on the use of aripiprazole in people younger than 15 years of age with schizophrenia. See FAD section 2.1.
Royal College of Paediatrics and Child Health	We note that the appraisal is rather conservative (e.g. section 1.3 requesting comparison with placebo).	Comment noted. A comparison of each agent with placebo was requested in order for the manufacturer to update their indirect comparison. This allows synthesis of data from trials in which the technologies of interest have not been compared in head-to-head trials, but have been compared indirectly using data from a network of trials that compare the technologies with other interventions.

Consultee	Comment	Response
Royal College of Paediatrics and Child Health	We note that there does not appear to be a great deal of psychiatric expertise on the Appraisal Committee.	Comment noted. There was representation on the Committee from Dr Kathryn Abel (Reader and Consultant Psychiatrist/Director of Centre for Women's Mental Health). The Committee also sought guidance from the clinical experts at the appraisal committee meeting. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer consultees and commentators. They gave their expert personal view on aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD: • Clare Lamb, Consultant Psychiatrist, nominated by Welsh Assembly Government – clinical specialist • Tim McDougall, Nurse Consultant, nominated by Royal College of Nursing – clinical specialist • Clive Travis – patient expert • Janey Antoniou (written statement only, unable to attend the meeting) – patient expert.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
None		

Comments received from commentators

Commentator	Comment	Response
None		

Comments received from members of the public

Role*	Section	Comment	Response
NHS professional 1	1	I am the Lead Consultant for Lancashire Care Early Intervention Service (14 -35 yrs), with 3 adult consultant psychiatrists and on CAMHS consultant psychiatrist. We also have separate inpatient units for 14-16 yrs old and 16-18 yrs old.	Comment noted.
		In my view clinical scales are useful to quantify outcomes but impact on quality of life and social functioning are more important.	Comment noted. The Committee accepted that the PANSS score is a valid tool for the measurement of positive, negative and general psychopathology symptoms and that evidence from the 31-03-239 study demonstrates a reduction in schizophrenic symptoms in the aripiprazole groups. In the absence of data specific to the population in the scope, data on relapse health state utility, disutility associated with treatment-related adverse events and resource use assumptions were all derived from studies of adult rather than adolescent populations. See FAD sections 4.6 and 4.10.
		Aripiprazole is one of the 4 most commonly prescribed antipsychotics to clients in our service.	Comment noted. The Committee agreed with the clinical specialists that it is important for adolescents with schizophrenia to have a range of treatment options before considering rescue therapy with clozapine, and therefore considered that aripiprazole may be a suitable treatment option for people aged 15 to 17 years with schizophrenia. See FAD section 4.3.
		Data on tolerability is extremely important and aripiprazole has the edge having lower propensity for weight gain and sexual dysfunction.	The Committee heard from the clinical specialists and patient experts that there are a number of dose-related adverse events associated with atypical antipsychotic treatments, including weight gain, sexual dysfunction, hyperprolactinaemia, aggression and akathisia/extrapyramidal

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
			symptoms. The Committee accepted that accounts of the use of aripiprazole suggest that it may be as safe and well tolerated as the other treatments. The Committee noted that there is substantial variation between the atypical antipsychotics in the adverse events associated with each treatment. The Committee noted that olanzapine is associated with substantial weight gain, as to a lesser extent are quetiapine and risperidone, but that only very small changes in weight gain are seen with aripiprazole. It considered that weight gain may be of considerable importance to adolescents and was concerned that weight gain associated with olanzapine may not be just a short-term problem, but could be a long-term health risk. In terms of changes in prolactin levels, the Committee heard from the clinical specialists that risperidone is associated with higher levels of prolactin, as to a lesser extent is olanzapine. Aripiprazole treatment prolactin levels are generally lower than seen with the other comparator treatments. See FAD sections 4.4 and 4.8.
NHS professional 1	2	I generally use smaller doses of aripiprazole, starting 5ms on alternate days (it has a long half life) for 1-2 weeks, then 5 mgs daily and then according to clinical response. The liquid form is an advantage for smaller doses.	Comment noted. The Committee heard from the clinical specialists that adolescents with schizophrenia are usually treated with atypical antipsychotics at a low dose and are closely monitored. See FAD section 4.2.
NHS professional 1	3	The data submitted by manufacturers of the drug is required but for me most important is my/our own experience. We find aripiprazole to be clinically as efficacious as any other antipsychotic with better tolerability profile.	Comment noted. The Committee understood from the clinical specialists that no single atypical antipsychotic drug is considered to be more clinically effective than the others. The Committee accepted that accounts of the use of aripiprazole suggest that it may be as safe and well tolerated as the other treatments. See FAD sections 4.3 and 4.4.
NHS professional 1	4	I disagree that risperidone is the most commonly prescribe antipsychotic.	Comment noted. The Committee understood from the clinical specialists that no single atypical

Role*	Section	Comment	Response
		We recently completed an audit on prescribing practice in our service, looking at about 200 records. Olanzapine was the most frequently prescribed antipsychotic followed by aripiprazole and qutiepine.	antipsychotic drug is considered to be more clinically effective than the others. Risperidone is the most widely used first-line atypical antipsychotic in UK clinical practice because clinicians have extensive experience of using it to treat schizophrenia, and often achieve control with low doses and without troublesome adverse events. Other atypical antipsychotics such as aripiprazole, olanzapine, quetiapine or amisulpride may be used if control of schizophrenia is not achieved with risperidone. The Committee agreed with the clinical specialists that it is important for adolescents with schizophrenia to have a range of treatment options before considering rescue therapy with clozapine. See FAD section 4.3.
NHS professional 1	5	In my opinion aripiprazole should be licensed for the younger age group.	Comment noted. The licensed indication for aripiprazole is for treatment of schizophrenia in people aged 15 years and older. Technologies are only appraised within their licensed indications, therefore it is outside of the Committee's remit to make a recommendation on the use of aripiprazole in people younger than 15 years of age with schizophrenia. See FAD section 2.1.
NHS professional 1	6	NICE should consider involving clinicians working in Early Intervention Services and using their experience in formulating decisions.	Comment noted.