Response to:

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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

Prepared by:

Bristol-Myers Squibb Pharmaceuticals Limited
and
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1st October 2010

CONFIDENTIAL VERSION

Response to the Appraisal Consultation Document:	
Confidential information is highlighted and underlined, e.g. [redacted]	
Approved Name of Medicinal Product:	Aripiprazole
Brand Name:	Abilify
Company:	Bristol-Myers Squibb Pharmaceuticals Ltd and Otsuka Pharmaceuticals (UK) Ltd
Submitted by:	[redacted]
Position:	[redacted] Research
Date:	1st October 2010

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.

Please find attached a detailed description of the additional analysis undertaken. Below is a summary of the key findings.

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 have 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 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.

To summarise our efficacy findings based on the available data from placebo-controlled, randomised clinical trials in adolescent schizophrenia:

- 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.

- There is a paucity of data available regarding the use of aripirazole in adolescents with schizophrenia, who also have learning difficulties.

Aripiprazole is the only licensed, commonly prescribed antipsychotic for adolescent schizophrenia.

No differences were identified in the clinical effectiveness between the 2nd generation antipsychotics.

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 second generation antipsychotics.

Aripiprazole is associated with a better safety and tolerability when compared with other 2nd generation antipsychotics

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. The sequence with the highest QALYs is Aripiprazole - Risperidone - Olanzapine – Clozapine. The lowest cost sequence is Risperidone - Olanzapine - Aripiprazole – Clozapine.

Table 1: Total costs and QALYs for each of the requested scenarios

	Sequence	Total costs	Total QALYs
A	1. Ari - 2. Ris - 3. Ola - 4. Clo	£23,530	2.2974
B	1. Ris - 2. Ari - 3. Ola - 4. Clo	£22,812	2.2918
C	1. Ris - 2. Ola - 3. Ari - 4. Clo	£22,714	2.2899
D	1. Ris - 2. Ola - 3. Que - 4. Clo	£23,428	2.2818

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.

Table 2: ICERs for each of the requested scenarios

		A	B	C	D
		1. Ari - 2. Ris - 3. Ola - 4. Clo	1. Ris - 2. Ari - 3. Ola - 4. Clo	1. Ris - 2. Ola - 3. Ari - 4. Clo	1. Ris - 2. Ola - 3. Que - 4. Clo
A	1. Ari - 2. Ris - 3. Ola - 4. Clo	-	£127,422	£107,422	£6,479
B	1. Ris - 2. Ari - 3. Ola - 4. Clo	-	-	£49,893	Dominant
C	1. Ris - 2. Ola - 3. Ari - 4. Clo	-	-	-	Dominant
D	1. Ris - 2. Ola - 3. Que - 4. Clo	-	-	-	-

These results show that including aripiprazole in a treatment sequence is cost-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 licensed and commonly used atypical anti-psychotic for adolescent schizophrenia.

Conclusions

BMS/OPUK do not agree with the minded negative recommendation.

Aripiprazole is the only licensed commonly prescribed atypical antipsychotic for adolescent schizophrenia.

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.

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

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.

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.