Resubmission

aripiprazole 5mg, 10mg, 15mg, 30mg tablets; 10mg, 15mg orodispersible tablets; 1mg/mL oral solution (Abilify®) No. (498/08)
Bristol-Myers Squibb Pharmaceuticals Ltd/Otsuka Pharmaceuticals (UK) Ltd

08 May 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

aripiprazole oral formulations (Abilify®) are not recommended within NHS Scotland for the treatment of moderate to severe manic episodes in bipolar I disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Aripiprazole demonstrated superior efficacy to placebo in reducing manic symptoms at week three and a treatment effect comparable to other agents used in the treatment of bipolar I disorder was maintained at week 12. Aripiprazole also demonstrated superior efficacy to placebo in prevention of relapse. Aripiprazole has not been directly compared to other atypical antipsychotics in this indication, although there is only one other atypical antipsychotic licensed for prevention of new manic episodes.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of moderate to severe manic episodes in bipolar I disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Dosing information

For treatment of manic episodes, the recommended starting dose is 15mg once daily, which can be increased to a maximum daily dose of 30mg.

For recurrence prevention of manic episodes in patients who have been receiving aripiprazole the same dose is continued, with adjustments of daily dosage as required.

Product availability date

Licence extension approved 31 March 2008

Summary of evidence on comparative efficacy

Bipolar I disorder is a lifelong episodic illness characterised by manic or depressive episodes followed by symptom-free periods. Aripiprazole is an atypical antipsychotic that acts as a partial agonist at dopamine D2 and 5-HT1A receptors and an antagonist at 5-HT2 receptors.

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-set of the licensed indication, specifically as a therapeutic second-line option (after olanzapine) for patients with bipolar I disorder, in both the acute and long-term relapse prevention settings.

Clinical efficacy for the licensed indication is based on six oral placebo-controlled trials that enrolled adults with bipolar I disorder, with manic or mixed episodes. All studies assessed efficacy using the Young Mania Rating Scale (YMRS), an 11-item clinician-administered instrument, (total score 0 to 60) with higher scores indicating greater symptom severity.

Acute response studies

Two randomised, double blind three-week studies investigated acute response in 262 and 272 patients with manic or mixed episodes requiring hospitalisation and a YMRS score ≥20. Patients were randomised equally to aripiprazole 30mg daily (reduced to 15mg daily if necessary for tolerability), or placebo. Aripiprazole produced significantly greater reductions than placebo for the primary endpoint of adjusted mean change from baseline in YMRS total score, resulting in treatment differences in the studies of -4.8 (95% Confidence Interval [CI]: -7.8 to -1.8) and -5.3 (95% CI: -7.9 to -2.8). The ratios of treatment differences in response rate (defined as a ≥50% decrease from baseline in YMRS total score) were 2.1 (95% CI: 1.4 to 3.2) and 1.7 (95% CI: 1.2 to 2.2), and completion rates for aripiprazole versus placebo were 42% versus 21% and 55% versus 52% for the two studies.

Maintenance of effect studies

Two randomised, double blind 12-week studies investigated acute response and maintenance of effect in 480 and 485 patients requiring hospitalisation with an YMRS score ≥20. Patients were randomised to aripiprazole 15mg daily (increased to 30mg daily if required), placebo, or active-control treatment in a 1:1:1 ratio, for three weeks.

One study used lithium 900mg daily (increased to 1,200mg daily on day four and 1,500mg daily on day seven if required) and the other used haloperidol 5mg daily (increased to 10mg or 15mg daily if required) as the active control. Placebo-treated patients then received blinded aripiprazole for another nine weeks, while all other patients remained on the same, blinded treatment. The primary endpoint in both studies was the mean change in YMRS total score at three weeks. Aripiprazole showed similar maintenance of treatment effect to haloperidol and lithium at 12 weeks. Results are displayed in the table below.

Table: Primary and key secondary endpoints for the maintenance of effect studies

	Study one				**Study two**			
Outcome	**Aripiprazole**		**Lithium**		**Aripiprazole**		**Haloperidol**	
	Week 3	**Week 12**	**Week 3**	**Week 12**	**Week 3**	**Week 12**	**Week 3**	**Week 12**
Mean change in YMRS total score from baseline	-12.6	-14.5	-12.0	-12.7	-12.0	-17.2	-12.8	-17.8
Response rate (≥50% decrease from baseline in YMRS score)	47%	56%	46%	49%	47%	72%	50%	74%
Remission rate (YMRS total score ≤12)	40%	49%	40%	39%	44%	70%	45%	71%

YMRS=Young Mania Rating Scale.

Combination therapy study

A randomised, double blind six-week study investigated the efficacy of adjunctive aripiprazole in 384 manic or mixed episode patients with partial non-response to lithium or valproate monotherapy (YMRS score ≥16 at the end of the screening and baseline phases and with a decrease of ≤25% between these two phases). Patients were randomly assigned in a 2:1 ratio to adjunctive aripiprazole 15mg or 30mg daily or placebo, both in combination with valproate or lithium. Mean improvement from baseline in YMRS total score at week six was significantly greater with aripiprazole (-13.3) than with placebo (-10.7).

Relapse prevention study

A double-blind, randomised 26-week study, followed by a 74-week double-blind extension phase, investigated recurrence prevention in 161 manic or mixed episode patients who achieved remission on aripiprazole during a pre-randomisation, open-label, stabilisation phase. The primary endpoint was time to relapse, which was defined as discontinuation due to lack of efficacy. Patients were randomised equally to aripiprazole 30mg daily (reduced to 15mg daily if necessary for tolerability), or placebo. Aripiprazole demonstrated superiority over placebo in the time to relapse for any mood episode at 26 weeks. The proportions of patients who experienced relapse in the aripiprazole and placebo groups were 25% and 43%, respectively; hazard ratio (HR) for time to relapse 0.52 (95% CI: 0.30 to 0.91). This treatment effect was maintained at 100 weeks when the relapse rates in the aripiprazole and placebo groups were 32% and 52%, respectively; HR for time to relapse 0.53 (95% CI: 0.32 to 0.87).

Summary of evidence on comparative safety

In the 12-week lithium-controlled study, the incidence of treatment-emergent adverse events (AEs) was 91% in the aripiprazole group compared to 82% in the lithium group, and AEs led to discontinuation in 20% and 18% of patients, respectively. Treatment-related AEs with an

incidence ≥10% in the aripiprazole group were headache (24%), nausea (23%) and akathiesia (15%) and in the lithium group were nausea (24%), headache (22%) and tremor (12%).

In the 12-week haloperidol-controlled study, treatment-emergent AEs were reported in 68% of patients in the aripiprazole group and 73% in the haloperidol group, with discontinuation due to AEs in 14% and 11% of patients, respectively. Treatment-related AEs with incidence ≥10% in the aripiprazole group were insomnia (14%), akathiesia (11%), and in the haloperidol group were akathiesia (25%) and extrapyramidal syndrome (EPS) disorder (15%).

Over the 26-week maintenance phase of the prevention of recurrence study, the incidence of AEs with aripiprazole were similar to placebo with the most common treatment-related AEs in the aripiprazole group being anxiety, insomnia, depression and nervousness. There was a significantly greater incidence of clinically relevant weight gain at 26 weeks in the aripiprazole group (13%) compared with the placebo group (0%).

Across the rest of the study programme there was no significant difference between aripiprazole and placebo or active comparator for weight gain or the proportion of patients with weight gain ≥7%. The incidence of EPS-related events, as well as those leading to discontinuation in active-comparator studies was lower with aripiprazole than with haloperidol but higher than with lithium.

Summary of clinical effectiveness issues

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-set of the licensed indication, namely as a therapeutic second-line option (after olanzapine) for patients with bipolar I disorder, in both the acute and long-term relapse prevention settings. However there is no clinical evidence to support the efficacy of aripiprazole monotherapy in patients with mania that has not responded to first-line treatment with another agent.

There are no studies directly comparing aripiprazole with atypical antipsychotics for the indication under review, although only one other atypical antipsychotic is licensed for prevention of new manic episodes. Reports in the literature indicate similar efficacy and differing adverse events profiles. The National Institute of Health and Clinical Excellence (NICE) is currently updating a guideline on the treatment and management of schizophrenia in adults. It includes a meta-analysis of weight gain and diabetes amongst agents used in the treatment of schizophrenia and reported that aripiprazole has the lowest probability of weight gain and diabetes in the first year of initiation of treatment compared to olanzapine and risperidone.

Discontinuation rates in the 3-week placebo-controlled studies were high (45% to 58%) with 9% to 13% due to lack of efficacy. In one of the studies the protocol allowed non-responders at week two to discontinue double-blind treatment and receive open label aripiprazole and this accounted for a further 13% of discontinuations.

A recent systematic review and meta-analysis of over 3,000 patients in 13 randomised, placebo-controlled trials in acute bipolar mania has been conducted. Two studies were identified for each of the following medications: carbamazepine, haloperidol, lithium, olanzapine, quetiapine, risperidone, valproate semisodium and aripiprazole. All drugs showed significant benefit compared to placebo for reduction in mania scores. Compared with placebo, for all antipsychotics pooled, response to treatment (≥50% reduction in YMRS

scores) was increased (relative risk [RR] 1.74, 95% CI: 1.54 to 1.96); for all mood stabilisers pooled, response to treatment was doubled (RR 2.01, 95% CI: 1.66 to 2.43). Overall withdrawals were 34% fewer than placebo (24 to 43%) with antipsychotics, and 26% fewer (10 to 39%) with mood stabilisers. However, whilst there were fewer withdrawals than placebo for carbamazepine, aripiprazole and lithium an increase in risk of withdrawal could not be excluded. Small but significant increases in extrapyramidal side effects occurred with risperidone and aripiprazole. The authors concluded that the small differences between pooled effect sizes for each drug or group of drugs might be due to differences in the characteristics of patients included in the studies, to dosing variation, or to chance.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis of treatment sequences with aripiprazole in first or second-line use for the treatment of an acute mania episode. The analysis consisted of a Markov model with 23 health states and weekly cycles covering an acute mania phase, a maintenance of effect phase where the patient has been discharged from hospital but is not yet stable, a long run euthymic (or stable) phase, and acute depression episodes. In the model, lithium is used instead of risperidone or quetiapine for the prevention of recurrence of acute manic events due to the two atypicals not being licensed for recurrence prevention. The manufacturer's proposed positioning for aripiprazole is second-line after olanzapine. Aripiprazole used first-line was estimated in the submission to result in higher costs and fewer QALYs (£946K and 19.8 less QALYs per 1,000 cohort over 5 years) than the usual care comparator. The usual care comparator consisted of the use of atypical antipsychotics used in the following sequence: olanzapine first-line, risperidone second-line, and quetiapine third-line. Hence, aripiprazole in second-line use would displace risperidone, and in an alternative scenario the outcomes associated with displacing quetiapine (with risperidone used third-line) were estimated. The model design and comparators were appropriate.

A 5-year time horizon was adopted. Due to a lack of direct comparative evidence, data on probability of response and drop-out rates for aripiprazole and usual care treatment sequences were derived via indirect comparisons (network meta-analyses) for the acute mania phase and for the likelihood of not experiencing a mania or depression effect or treatment failure (drop-out) in the post acute mania phases. Resource use and utility data were derived from published sources including a recent NICE clinical guideline on bipolar disorder. In addition, the benefits of reduced weight gain and diabetes complication risk estimated for aripiprazole, primarily over olanzapine, risperidone and quetiapine, were incorporated into the economic model. The probability of weight gain (BMI increase of ≥7%) and diabetes was based on data for some of the atypical antipsychotics from an ongoing NICE clinical guideline in schizophrenia. Estimates for the incremental cost per QALY gained versus usual care were £3,895 in the base case where aripiprazole displaces risperidone second-line and £3,187 in the scenario where quetiapine is displaced. However, this result was based on only small differences in net cost and QALY outcomes (incremental cost of £62,000 and 15.9 additional QALYs per 1000 cohort), which was also confirmed by the one way sensitivity analysis performed. The results were most sensitive to one way sensitivity analysis on the confidence intervals for the outcome of patients maintained on treatment in post acute mania phases (ranging from aripiprazole 'dominant' to an ICER of £42,709 when the lower 95% confidence interval for aripiprazole treatment effect was used).

Whilst the analysis was well performed the main limitation of the indirect comparisons was an uncertainty over whether aripiprazole has any greater effectiveness over other atypical antipsychotics in the acute mania phase or over lithium (or other mood stabilisers) in the likelihood of remaining in the maintenance of effect/euthymic phases. A further concern was

uncertainty associated with the exclusion of three lithium versus placebo studies from the post acute mania network meta-analysis. These studies had previously been included in a meta-analysis conducted for the NICE clinical guideline on bipolar disorder (with two of these studies found to have had a relatively favourable outcome for lithium in prevention of relapse). However, the manufacturer subsequently provided reasonable justification for the approach used. The benefits of reduced weight gain and diabetes risk estimated for aripiprazole over the other atypical antipsychotics was incorporated in the economic model, but did not have a large impact on the cost/QALY results.

Hence, the cost-effectiveness of second-line use of aripiprazole remains uncertain, and the manufacturer has not presented a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network Guideline 82: Bipolar Affective Disorder, published in May 2005, states that acute manic episodes should be treated with oral administration of an antipsychotic drug or semisodium valproate. Lithium can be used if immediate control of overactive or dangerous behaviour is not needed or otherwise should be used in combination with an antipsychotic. Lithium is the treatment of choice for relapse prevention in bipolar affective illness. Carbamazepine can be used as an alternative to lithium when lithium is ineffective or unacceptable. The need for an update to this guideline is currently being considered.

NICE published a national clinical practice guideline in 2006: The management of bipolar disorder in adults, children and adolescents in primary and secondary care. It recommends treatment with an antipsychotic; valproate or lithium if a patient develops acute mania when not taking antimanic medication. If a patient experiences a manic episode while already taking an antipsychotic, the dose should be optimised. If there are no signs of improvement, the addition of lithium or valproate should be considered. Lithium, olanzapine or valproate should be considered for long-term treatment of bipolar disorder.

The British Association of Psychopharmacology published evidence-based guidelines for treating bipolar disorder in 2003. They recommend initiating an oral antipsychotic or valproate for patients experiencing severe manic or mixed episodes who are not already on long-term treatment for bipolar disorder. For patients who suffer a manic or mixed episode while receiving long term treatment with lithium, carbamazepine or valproate, the guidelines recommend optimising current therapy and adding in an antipsychotic or valproate. Lithium should be considered for initial monotherapy for relapse prevention. Valproate, olanzapine and carbamazepine should be considered as alternative treatments if lithium is ineffective or poorly tolerated. Lamotrigine should be considered for patients at greater risk of depressive relapse.

The guidelines predate the licensing of aripiprazole for the treatment of bipolar I disorder.

Additional information: comparators

Drugs used to treat and / or prevent recurrence in bipolar 1 disorder include lithium, haloperidol, antipsychotics (typical and atypical), carbamazepine and valproate semisodium. Olanzapine, quetiapine and risperidone are atypical antipsychotic drugs licensed to treat manic episodes. Olanzapine is the only atypical antipsychotic (other than aripiprazole) indicated for preventing recurrent manic episodes, and therefore is the most relevant comparator to aripiprazole.

Cost of relevant comparators

Drug	Daily dose regimen	Treatment of acute mania; cost for three weeks (£)	Prevention of new manic episodes; cost per year (£)
Aripiprazole tablets / orodispersible tablets	**15 to 30mg**	**76 to 152**	**1,321 to 2,642**
Aripiprazole oral solution	**15 to 30mg**	**229 to 457**	**3,964 to 7,927**
Atypical antipsychotics			
Quetiapine	400 to 800mg	79 to 158	
Olanzapine	5 to 20mg	37 to 119	634 to 2,066
Risperidone	1 to 6mg	6.45 to 37	
Typical antipsychotics			
Haloperidol	5 to 15mg	1.61 to 4.75	28 to 82
Others			
Lithium	900 to 1,350mg	2.02 to 4.06	35 to 70
Carbamazepine	400 to 600mg		39 to 59
Valproate semisodium	1g to 2g	11 to 23	196 to 393

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 03 March 2009.

Additional information: budget impact

The manufacturer estimated that the gross budget impact of aripiprazole in second-line use would be £670k in 2009 rising to £3.7 million in 2013, based on 337 patients in 2009 (2% market share) rising to 1,879 (10% market share) in 2013. If risperidone was displaced the net budget impact was estimated at £427k in 2009 rising to £2.3 million in 2013. If quetiapine was displaced the net impact was estimated at £27k in 2009 and £151k in 2013. If 50% of both risperidone and quetiapine were displaced then the net budget impact would be £200k in 2009 and £1.1 million in 2013. If lithium was displaced by aripiprazole, the budget impact figures would be higher than those presented by the manufacturer.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 20 April 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

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