Scottish Medicines Consortium

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

8 August 2008

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 full submission

aripiprazole oral formulations (Abilify®) are not recommended for use within NHS Scotland for the treatment of moderate to severe manic episodes in bipolar 1 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 3 and treatment effect comparable to lithium or haloperidol was maintained at week 12. Aripiprazole also demonstrated superior efficacy to placebo in prevention of relapse.

It has not been compared to other atypical antipsychotics in this indication.

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

The licence holder has advised their intention to resubmit.

Overleaf is the detailed advice on this product.

Vice Chairman
Scottish Medicines Consortium

Published 08 September 2008

Indication

Treatment of moderate to severe manic episodes in bipolar 1 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, continue therapy at the same dose with adjustments of daily dosage as required.

Product availability date

31st 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. The estimated lifetime prevalence is about 0.4 to 1.6%. Aripiprazole is an atypical antipsychotic that acts as a partial agonist at dopamine D_2 and 5-HT_{1A} receptors and an antagonist at 5-HT_2 receptors.

The evidence of clinical efficacy in the indication under consideration comes from six placebo-controlled trials that enrolled adults with bipolar 1 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 3-week studies investigated acute response in 262 (study 1) and 272 (study 2) patients with manic or mixed episodes requiring hospitalisation and YMRS ≥20. Patients were randomised equally to aripiprazole 30mg daily (reduced to 15mg daily if needed for tolerability), or placebo. Aripiprazole produced significantly greater reductions than placebo in the primary endpoint of adjusted mean change from baseline in YMRS total score, resulting in treatment differences of –4.8, 95% Confidence Interval (CI): –7.8 to –1.8 in study 1 and –5.3, 95% CI: –7.9 to –2.8 in study 2. Treatment differences in response rate, (≥50% decrease from baseline in YMRS total score), were 2.1, 95% CI: 1.4 to 3.2 in study 1 and 1.7, 95% CI: 1.2 to 2.2 in study 2. Completion rates for aripiprazole versus placebo were 42% versus 21% and 55% versus 52% in studies 1 and 2, respectively.

Maintenance of effect studies Two randomised, double-blind 12-week studies investigated acute response and maintenance of effect in 480 (study 3) and 485 (study 4) patients requiring hospitalisation with YMRS ≥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 3 weeks. Study 3 used lithium 900mg daily (increased to 1200mg daily on day 4 and 1500mg daily on day 7 if required) and study 4 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 9 weeks, while all other patients remained on the same

blinded treatment. The primary endpoint in both studies was mean change in YMRS total score at 3 weeks.

Aripiprazole showed similar maintenance of treatment effect to haloperidol and lithium at 12 weeks.

Table 1: Results of studies 3 and 4

Outcome	Study 3				Study 4			
	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 total score)	47%	56%	46%	49%	47%	72%	50%	74%
Remission rate (YMRS total score ≤ 12)	40%	49%	40%	39%	44%	70%	45%	71%

Combination therapy study A randomised, double-blind 6-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 ≥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 6 (primary endpoint) 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 needed 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 for time to relapse (HR) 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 study 3 (12-week lithium-controlled study), the incidence of treatment-emergent adverse events (AEs) was 91% in the aripiprazole group compared with 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 akathisia (15%), and in the lithium group these were: nausea (24%), headache (22%) and tremor (12%).

In study 4 (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%), akathisia (11%), and in the haloperidol group these were: akathisia (25%) and extrapyramidal syndrome (EPS) disorder (15%).

In the 6-week combination therapy study in which aripiprazole or placebo was co-administered with lithium or valproate, the overall incidence of treatment-emergent AEs was 62% for the aripiprazole group and 54% for the placebo group. Akathisia was the only AE reported for patients in the aripiprazole group at ≥ 10%.

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

There are no studies directly comparing aripiprazole with other atypical antipsychotics for the indication under review, although reports in the literature indicate similar efficacy.

There is no evidence to demonstrate efficacy of aripiprazole monotherapy in patients with resistant mania that has not responded to first line treatment with another drug.

Discontinuation rates in the 3-week placebo-controlled studies were high, with approximately half discontinuing due to lack of efficacy.

A recent systematic review and meta-analysis of 3,089 patients in 13 randomised, placebo-controlled trials in acute bipolar mania was conducted in England. 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 with 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 non-psychotics pooled, response to treatment was doubled (RR 2.01, 95% CI 1.66 to 2.43). The authors concluded that the small differences between pooled effect sizes for each drug or group of drugs may 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 covering an acute mania phase of 1 to 3 weeks (involving hospitalisation), a maintenance of effect phase where the patient has been discharged but is not yet stable (4 to 12 weeks), a euthymic (or stable) phase (12 to 52 weeks) and acute depression episodes. The comparator was defined as usual care consisting of the use of atypical antipsychotics used in the following sequence: olanzapine first line, risperidone second line, and quetiapine third line, but with lithium 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 model design and comparators were appropriate. Resource use and utility data were derived from published sources including a recent NICE clinical guideline on bipolar disorder. However, a limitation was that adverse event costs and disutilities were not evaluated.

The main clinical benefit estimated for aripiprazole was in terms of prevention of recurrence of manic episodes but not in terms of improved outcomes associated with the manic episodes. As there were no comparative studies for aripiprazole versus other atypical antipsychotics, indirect comparisons were required. A network meta-analysis comparing aripiprazole clinical trial data with trial data for the comparators in the acute mania phase demonstrated that aripiprazole had a lower response rate (defined as a >50% improvement in YMRS score) to treatment and a higher drop out rate compared to olanzapine and similar outcomes relative to the other two atypical antipsychotics. In the post acute mania phases the outcome was remaining successfully maintained, and based on a second indirect comparison, aripiprazole had similar outcomes to olanzapine but better outcomes than lithium. Aripiprazole may have some advantages compared to alternative atypical antipsychotics, such as lower weight gain, but this was not a factor in the analysis. The indirect comparison for the post acute mania phases was based on a very limited number of studies and the comparative results uncertain.

The main finding is that first line use of aripiprazole is unlikely to be cost-effective versus usual care, resulting in additional costs of £938,000, and 9 fewer QALYs per 1000 patient cohort. When used second line after olanzapine and before risperidone or quetiapine, aripiprazole was estimated to result in fewer costs and better QALY outcomes. However, the differences in costs and outcomes were very small and given uncertainties with the transparency of the indirect comparison there may not be any significant difference between the treatments. Sensitivity analysis performed by the manufacturer suggested second line aripiprazole could remain dominant in many circumstances where resource use/cost was varied, but there were also several scenarios where cost-effectiveness was not demonstrated when the relative probability of response or maintenance of effect was varied. 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 (SIGN) Guideline 82: Bipolar Affective Disorder, published in May 2005, states that acute manic episodes should be treated with oral administration of an anti-psychotic 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 National Institute of Health and Clinical Excellence (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 anti-psychotic, 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.

Additional information: previous SMC advice

Following a full submission, SMC published advice in June 2003: olanzapine (Zyprexa®) is recommended for restricted use within NHS Scotland for the treatment of moderate to severe manic episodes. Olanzapine is the first atypical antipsychotic to be licensed for the treatment of acute mania and is at least as effective as comparator treatments. It was associated with fewer extrapyramidal side effects than haloperidol and was similar to placebo in the rate of Parkinson-like effects. The management of mania is complex due to the variable presentation of the condition, the wide range of treatment options and a lack of clear guidance on their optimum use. The use of olanzapine in the treatment of acute mania should be restricted to patients under the overall supervision of clinicians experienced in managing this complex disorder.

Following a full submission, SMC published advice in May 2004: olanzapine (Zyprexa®) is accepted for use within NHS Scotland for the prevention of recurrence in patients with bipolar disorder whose manic episode has responded to olanzapine treatment. Olanzapine has been shown to be significantly superior to placebo in delaying symptomatic relapse of mania or depression and of mania alone. Apart from weight gain, somnolence and treatment-emergent depression, most significant differences between olanzapine and active competitors favoured olanzapine.

Following a full submission, SMC published advice in July 2004: olanzapine (Zyprexa®) for intramuscular use is accepted for use within NHS Scotland for the control of agitation and disturbed behaviours in patients with schizophrenia or manic episode, when oral therapy is not appropriate. Intramuscular olanzapine has been shown to be at least as clinically and cost-effective as haloperidol or lorazepam in treating agitation and other symptoms associated with acute schizophrenia and bipolar disorder. Both the clinical and the economic case are limited by the entry criteria for trials, which effectively restricted entry to moderately agitated patients and excluded those who were severely agitated. However, the difficulties in conducting research in this clinical situation are recognised.

Following a full submission, SMC published advice in July 2004: quetiapine (Seroquel®) is accepted for use within NHS Scotland for the treatment of manic episodes associated with bipolar disorder as monotherapy or as adjunct therapy to mood stabilisers. Active comparators were included in the monotherapy trials but the studies were not designed to show differences between active comparator and quetiapine. It has not been compared to other atypical antipsychotics in this indication. Economic data suggest that quetiapine (Seroquel) is at least cost neutral, compared to other licensed approaches using atypical antipsychotics in this indication, either as adjunctive therapy or monotherapy.

Following a full submission, SMC published advice in August 2004: risperidone (Risperdal®) is accepted for use within NHS Scotland for the treatment of episodes of mania in bipolar disorder. Risperidone has similar efficacy to haloperidol in improving symptom scores, with fewer extrapyramidal side effects. In an economic model based on indirect comparison, monotherapy with risperidone appears to be cost-effective. No evidence is submitted on its cost-effectiveness profile in co-therapy.

Following an abbreviated submission, SMC published advice in September 2007: risperidone 3mg, 4mg orodispersible tablets (Risperdal Quicklet®) are accepted for restricted use within NHS Scotland for treatment of acute and chronic schizophrenia and similar psychosis and treatment of mania in bipolar disorder. These new strengths of risperidone orodispersible tablets should be used in patients for whom risperidone is an appropriate choice of antipsychotic and an orodispersible tablet is an appropriate formulation.

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. As only olanzapine is also indicated for preventing recurrent manic episodes, it is the most relevant comparator to aripiprazole.

Cost of relevant comparators

Drug	Daily dose regimen	Treatment of acute mania Cost per 3 weeks (£)	Prevention of relapse Cost per year (£)
aripiprazole tablets and 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 7,928**
atypical antipsychotics			
quetiapine	400 to 800mg	79 to 158	
olanzapine	5 to 20mg	37 to 119	634 to 2,066
risperidone	1 to 6mg	12 to 71	
typical antipsychotics			
haloperidol	5 to 15mg	1.61 to 4.82	28 to 84
others			
lithium	900 to 1500mg	2.02 to 4.06	35 to 71
carbamazepine	400 to 600mg		38 to 58
valproate semisodium	1,000 to 2,000mg	11 to 23	197 to 394*

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 29th May 2008. *Unlicensed use.

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 £2.3million 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 18 July 2008.

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.

European Medicines Agency (EMEA). European public assessment report (EPAR) for aripiprazole. www.emea.eu.int

Keck PE, Jr., Marcus R, Tourkodimitris S, Ali M, Liebeskind A, Saha A, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry. 2003;160(9):1651-8.

Sachs G, Sanchez R, Marcus R, Stock E, McQuade R, Carson W, et al. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. J Psychopharmacol. 2006;20(4):536-46.

Keck PE, Jr., Calabrese JR, McQuade RD, Carson WH, Carlson BX, Rollin LM, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. J Clin Psychiatry. 2006;67(4):626-37.

Keck PE, Jr., Calabrese JR, McIntyre RS, McQuade RD, Carson WH, Eudicone JM, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry. 2007;68(10):1480-91.

Smith LA, Cornelius V, Warnock A, et al. Pharmacological interventions for acute bipolar mania: a systematic review of randomized placebo-controlled trials. Bipolar Disorders 2007: 9: 551–560