Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

aripiprazole 5mg, 10mg, 15mg, 30mg tablets, 10mg, 15mg orodispersible tablets, 1mg/mL oral solution (Abilify®) SMC No. (891/13)

Otsuka Pharmaceutical (UK) Ltd

09 August 2013

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 (Abilify®) is accepted for restricted use within NHS Scotland.

Indication under review: treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

SMC restriction: restricted to initiation and management under the supervision of a child/adolescent psychiatrist.

Aripiprazole demonstrated superior efficacy to placebo in reducing manic symptoms at 4 weeks. Aripiprazole has not been directly compared to other atypical antipsychotics, none of which are licensed for this indication although they are used off-label in clinical practice.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

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Indication

Treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

Dosing Information

Aripiprazole 10mg once daily without regard to meals. Treatment should be initiated at 2mg (using 1mg/mL oral solution) for 2 days, titrated to 5mg for 2 additional days to reach the recommended daily dose of 10mg. The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks.

Enhanced efficacy at doses higher than a daily dose of 10mg has not been demonstrated, and a daily dose of 30mg is associated with a substantially higher incidence of significant undesirable effects including extrapyramidal syndrome (EPS) related events, somnolence, fatigue and weight gain. Doses higher than 10mg/day should therefore only be used in exceptional cases and with close clinical monitoring.

Product availability date

24 January 2013

Summary of evidence on comparative efficacy

Bipolar I disorder is an episodic, often chronic, illness characterised by manic or depressive episodes followed by symptom-free periods. In children and adolescents, it is characterised by elevated mood and other mood disturbances, including aggression, irritability and hyperactivity. In these patients, bipolar disorder is cyclical with high rates of rapid cycling and the clinical course can often be protracted, chronic and difficult to treat. Aripiprazole is an atypical antipsychotic that acts as a partial agonist at dopamine D2 and serotonin 5-HT1a receptors, and an antagonist at serotonin 5-HT2a receptors. It is licensed for moderate to severe manic episodes in bipolar I disorder and for the prevention of a new manic episode in adult patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment. However this use in adults was not recommended by SMC in June 2009. This submission relates to a licence extension to include the treatment of moderate to severe manic episodes in bipolar I disorder in adolescents ≥13 years.

The evidence to support the new licensed indication comes from the results of one pivotal, randomised, double-blind, phase III study. The study comprised two double-blind phases: a 4-week acute phase followed by a 26-week extension phase.[1,2] Eligible patients were aged 10 to 17 years, with a confirmed Diagnosis and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) diagnosis of bipolar I disorder and current manic or mixed episodes, with or without psychotic features. They had a Young Mania Rating Scale (YMRS) total score ≥20. This is an 11-item clinician-administered instrument (total score 0 to 60) with higher scores indicating greater symptom severity. Patients with co-morbid attention-deficit/hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder, or anxiety disorders (except post-traumatic stress disorder and obsessive-compulsive disorder) were also allowed to enrol. All eligible patients (n=296) completed a medication washout period before being randomised to receive aripiprazole 10mg once daily (n=98), aripiprazole 30mg once daily (n=99) or placebo (n=99). Aripiprazole was started at a dose of 2mg daily on days 1 and 2, 5mg daily on days 3 and 4 and 10mg daily on day 5. Patients in the 30mg group had their dose

increased by 5mg every two days to 30mg daily from day 13. Rescue medication and extrapyramidal symptom relief was allowed with benzodiazepines and anticholinergics but not within 4 or 12 hours of efficacy or safety assessments respectively. During the extension phase, stimulant medications were also permitted on the investigator's judgement.

The primary outcome was the change from baseline to week 4 in the YMRS total score and key results are presented in the table below. Data were also presented to the European Medicines Agency to 12 weeks and for lower and higher age groups (10 to 12 years and 13 to 17 years).[3]

Table: Results for change in YMRS total score

	Total study population[1,2]		
YMRS total score	Aripiprazole 10mg (n=96)	Aripiprazole 30mg (n=99)	Placebo (n=94)
At baseline	29.8	29.5	31.1
LS mean change at week 4	-14.2	-16.5	-8.2
Difference versus placebo at week 4 (95% CI)	-5.99 (-8.49 to -3.50) P<0.0001	-8.26 (-10.7 to -5.77) p<0.0001	
Difference versus placebo at week 30 (95% CI)	-5.89 (-8.70 to -3.08) P<0.0001	-6.73 (-9.53 to -3.94) p<0.0001	
	Subgroup of patients aged 13 to 17 years[3]		
	Aripiprazole 10mg (n=65)	Aripiprazole 30mg (n=59)	Placebo (n=58)
At baseline	29.0	30.3	31.9
LS mean change at week 4	-13.9 p<0.05	-16.8 p<0.001	-10.1
LS mean change at week 12 (p-value for difference versus placebo)	-15.6 p<0.05	-16.8 p<0.001	-9.7

LS = least square, CI = confidence interval. Analyses conducted using last observation carried forward.

The proportion of patients who were responders (defined as ≥50% reduction in YMRS total score from baseline) at week 4 was significantly higher in the aripiprazole 10mg and 30mg groups versus placebo: 45% and 64% versus 26% respectively in the total study population.[1] The proportions of patients who were responders at week 30 were 50%, 56% and 27% respectively.[2] Results were not reported for the 13 to 17 years subgroup.

Aripiprazole was associated with significant improvements over placebo at weeks 4 and 30 in Children's Global Assessment Scale (CGAS) score, Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity scores for mania and overall bipolar illness, General Behaviour Inventory Scale (GBI) total scores parent/guardian for mania and in Attention Deficit Hyperactivity Disorders Rating Scale (ADHD-RS-IV) total score. There were no significant differences between aripiprazole and placebo in terms of depressive symptoms as measured by CGI-BP severity scores for depression, GBI total scores for depression and Children's Depression Rating Scale-Revised (CDRS-R) score. There was no significant difference between aripiprazole and placebo in quality of life as measured by the Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-Q-LES-Q).[1,2,3]

Additional analyses of the subgroup aged 13 to 17 years also found that the treatment effect was smaller in patients without ADHD and did not reach statistical significance. However the numbers of patients were too small for robust statistical analysis.[3] The summary of product characteristics notes that in this post hoc analysis, the improvement over placebo was more pronounced in the patients with associated co-morbidity of ADHD compared to the group without ADHD, where there was no difference from placebo.

Summary of evidence on comparative safety

There are no direct comparative safety data versus other antipsychotic agents. During the pivotal study, there was an increased risk of experiencing adverse events (i.e. extrapyramidal syndrome related symptoms, somnolence and weight gain) in younger patients (10 to 12 years) and so aripiprazole was not recommended in patients under 13 years. In addition, a daily dose of 30mg was associated with a substantially higher incidence of significant undesirable effects including extrapyramidal syndrome related events and was not recommended.[3]

There was no increase in prolactin levels. At week 30, low serum prolactin levels (defined as <3nanograms/mL in females and <2nanograms/mL in males) were reported in 28% of female patients and 53% of males patients.

In the licensed subgroup (aged 13 to 17 years) and for the licensed maximum duration (12 weeks) weight increased by 1.6kg, 1.3kg and 0.5kg in the aripiprazole 10mg, 30mg and placebo groups respectively ($p<0.05$ for aripiprazole 10mg versus placebo).[3]

Other reported adverse events included: somnolence (29%, 27% and 5.2% respectively), headache (21%, 22% and 24% respectively), extrapyramidal disorder (9.1%, 29% and 1.7% respectively), akathisia (12%, 20% and 1.7% respectively), fatigue (18%, 14% and 3.4% respectively), nausea (12%, 14% and 8.6% respectively), vomiting (11%, 6.8% and 10% respectively) and blurred vision (11%, 6.6% and 0 respectively).[3]

Summary of clinical effectiveness issues

Aripiprazole is the first antipsychotic agent to be licensed for the treatment of manic episodes of bipolar I disorder in this age group. The only other medicine licensed for this use in adolescent patients is lithium carbonate (Liskonum®). However, SMC clinical experts indicate that atypical antipsychotics are currently used off-label in clinical practice. The key evidence to support the use of aripiprazole in adolescents with bipolar I disorder comes from post-hoc subgroup analyses of the pivotal study, in patients aged 13 to 17 years, which accounted for 63% of the total study population.[3] Results demonstrated superiority of aripiprazole compared to placebo in reducing the YMRS total score at week 4 and at week 12. The study included two aripiprazole doses (10mg and 30mg) but due to a less favourable benefit:risk balance, the 30mg dose was not recommended by the European Medicines Agency.[3]

During the pivotal study, the discontinuation rate was high with 80% (237/296) of patients completing 4 weeks and 32% (68/210) of patients completing 30 weeks.[1,2] At week 12, the maximum recommended duration for this indication, approximately 50% aripiprazole treated patients remained on treatment compared with approximately 25% of placebo treated patients.[3] The study duration was 30 weeks, including the extension phase, but there are no data on the prevention of recurrence of manic episodes of bipolar I disorder.

The pivotal study was conducted mainly in outpatients in the United States and approximately half of the study patients had a current or past history of ADHD. Although the patient numbers were small, a further subgroup analysis suggested that aripiprazole was not significantly better than placebo in reducing the YMRS total score at weeks 4 or 12 in the subgroup of patients without ADHD.[3] It is unclear if this would affect the generalisability of the study results to a population where the incidence of co-morbid ADHD was lower.

There are no studies directly comparing aripiprazole with other antipsychotics in the treatment of bipolar I disorder in the adolescent population. However no other antipsychotics are licensed for these patients. The submitting company presented a network meta-analysis, using Bayesian methods, to compare the efficacy and safety of aripiprazole with olanzapine, risperidone and quetiapine. The network meta-analysis included four studies: the pivotal aripiprazole study described above plus one placebo-controlled study each of olanzapine, risperidone and quetiapine. A number of efficacy and safety outcomes were analysed including YMRS responses at weeks 1, 2 and 3; discontinuation rate at week 3; incidence of extrapyramidal symptoms, clinically significant weight gain, clinically significant increase in prolactin and somnolence. The results found some numerical but no significant differences between aripiprazole and olanzapine, risperidone or quetiapine with the exception of significantly less clinically significant weight gain with aripiprazole versus olanzapine and quetiapine, and significantly less clinically significant increase in prolactin with aripiprazole versus olanzapine, risperidone and quetiapine. However, these significant differences were associated with very wide credible intervals indicating uncertainty. There were a number of limitations in the network meta-analysis including: uncertain transparency of the literature review and study selection process; not being specific to the licensed population for aripiprazole (≥13 years); inappropriate pooling of aripiprazole 10mg and 30mg doses and of risperidone doses; combination of different outcomes (differing definitions of clinically significant increases in prolactin, and adverse events measured at differing time-points); and a lack of heterogeneity assessment.

Aripiprazole offers a licensed antipsychotic treatment option for adolescent patients for acute treatment of manic episodes but there are no data on longer term management and prevention of recurrence. Aripiprazole may be expected to have similar efficacy to other antipsychotics but the relative tolerability may differ slightly. SMC clinical experts indicate that side effect profile is an important consideration.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of aripiprazole as either a first, second or third line treatment option against a usual care strategy in the treatment of adolescents aged 13 or over with moderate to severe manic episodes. Usual care was assumed to be risperidone first line, quetiapine second line and olanzapine third line. In each case, aripiprazole was assumed to displace olanzapine from the current care sequence. Lithium was used for patients who failed to respond to each line of therapy. A Markov model with a time horizon of 3 years was used and all patients were assumed to be treated as inpatients when treatment commences. Side-effects of weight gain, somnolence and EPS were included in the analysis.

Clinical data on relative efficacy and side effects were taken from the pooled results of the network meta-analysis (NMA). Patients who responded to treatment were assumed to be discharged from hospital after 5 weeks and patients who did not respond to treatment were assumed to move onto the next treatment in the sequence, with the same efficacy assumed for each treatment regardless of the order in therapy it was used.

Resource use was estimated largely by clinical expert assumption and included consultant psychiatrist, nurse and dietician visits for patients experiencing weight gain. Utility values were taken from published literature and included multipliers to adjust for side effects or being hospitalised.

The base case results are shown in the table below:

Base-case results – All Strategies vs. Usual Care	**Total costs (£)**	**Total quality adjusted life years (QALYs)**	**Incremental costs (£) vs. Usual Care**	**Incremental QALYs vs. Usual Care**	**ICER (£) (cost per QALY) vs. Usual Care**
Usual Care	£72,333	2.41079			
Aripiprazole First Line	£72,092	2.41903	-£240	0.00824	Dominant
Aripiprazole Second Line	£71,881	2.41994	-£451	0.00915	Dominant
Aripiprazole Third Line	£72,485	2.41832	£152	0.0075	£20,224

The results suggest that compared to a current care strategy (risperidone first line, quetiapine second line, olanzapine third line), aripiprazole would be considered a cost-effective treatment addition at all possible lines of therapy, being dominant in first line and second line use, and with a cost per QALY of £20k in third line use. The differences in costs and QALYs are small.

Extensive one-way and scenario-based sensitivity analysis was provided. This indicated that the most important determinant of cost-effectiveness was the relative efficacy assumed. As a first line option, aripiprazole became dominated (more expensive, less effective) when the aripiprazole response at week 3 was reduced by 30% or had an ICER of £806,985 when the efficacy of risperidone was increased by 30%. If the response rates for aripiprazole in weeks 1 and 2 were subject to more pessimistic assumptions, the ICERs went from dominant to £14k to £111k (patients would not be discharged from hospital so quickly in these scenarios). Aripiprazole was also dominated as a second and third line option when lower levels of response for aripiprazole at 3 weeks were assumed. The instability in the ICERs to these changes will reflect the very small QALY gains that were estimated.

Two notable pieces of scenario analysis were presented. The first showed the impact of using only the 10mg dose results from the NMA. This resulted in a cost per QALY of £177,549 when aripiprazole is used as a first line treatment, remaining dominant as a second line treatment (but with very small cost savings and QALY gains of £175 and 0.00377) or a cost per QALY of £32,122 as a third line treatment. A helpful scenario analysis was also provided to show the impact of assuming that not all patients would be treated as inpatients at the start of the model. Assuming outpatient treatment at the start of therapy of 3 outpatient visits and 8 CPN visits in the first 4 weeks of treatment, the cost-effectiveness at 1st line use changed from dominant to £5,122 (as a consequence of no earlier discharge leading to savings in inpatient days or the disutility associated with being in hospital). As a 2nd or 3rd line treatment, aripiprazole was dominant.

The sensitivity analysis above highlights that the small costs and QALY gains in the base case are associated with some uncertainty. In addition, the following issues are noted:

- As noted above, there are some issues in terms of the generalisability of the clinical study and some weaknesses of the network meta-analysis which was used to estimate relative efficacy.
- The pooled NMA showed non-significant differences in response rates but these differences were used in the base case analysis. Sensitivity analysis was provided to show the impact of removing these non-significant results. This increased the cost per QALY to £29k, £24k and £43k for first, second and third line use respectively. Small QALY gains remained due to differences in side effects between therapies. The results were sensitive to the use of only the NMA results for the (recommended) 10mg dose, as noted above.

- The results were sensitive to the assumption regarding all patients being inpatients at the start of treatment. SMC clinical experts were asked to comment on this assumption and the responses indicate a mixed pattern of care with treatment initiation in both outpatient and inpatient settings. The cost per QALY figures for the outpatient setting are less favourable.
- The base case results presented above do not include recent falls in the generic prices of quetiapine and olanzapine but the company has provided revised analysis to take these into account. In these new base case analyses, aripiprazole remained dominant as a first and second line treatment and had a cost per QALY of £26k in third line.
- The effect of combining some of these issues was explored. If the new generic prices were used and non-significant differences were removed from the analyses the cost per QALY figures became £55.6k, £51k and £57k in first, second and third line use respectively. If generic prices were applied to the outpatient scenario analysis, the cost per QALY figures became £18k, £1.5k and dominance for first, second and third line use respectively. If non-significant differences were removed, updated generic prices used and the outpatient scenario modelled, the ICERs were £95.7k, £68.9k and £66.2k respectively. These analyses show the potential upward uncertainty in the results when relevant variables are altered simultaneously.

As noted above, the cost-effectiveness results show small QALY gains for the treatment which led to large variations in the results when assumptions in the model were changed. While this means that the cost-effectiveness is associated with some uncertainty, the economic case was considered to be demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The British Association of Psychopharmacology published a revised second edition of its evidence-based consensus guidelines for treating bipolar disorder in 2009.[4] This recommends 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, aripiprazole, olanzapine, quetiapine and carbamazepine should be considered as alternative treatments if lithium is ineffective or poorly tolerated. Lamotrigine or quetiapine should be considered for patients at greater risk of depressive relapse. The guideline development was supported by several pharmaceutical companies.

NICE published a national clinical practice guideline in 2006: The management of bipolar disorder in adults, children and adolescents in primary and secondary care.[5] 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 following additional recommendations are made when prescribing medication for children or adolescents with an acute manic episode:

- drugs should be initiated at lower doses.
- height and weight should be checked at initial presentation and monitored regularly
- prolactin levels should be measured

- when considering an antipsychotic, the risk of increased prolactin levels with risperidone and weight gain with olanzapine should be considered
- where there is an inadequate response to an antipsychotic, adding lithium or valproate should be considered. Valproate should normally be avoided in girls and young women because of risks during pregnancy and risk of polycystic ovary syndrome.

The Scottish Intercollegiate Guidelines Network published Guideline 82: Bipolar Affective Disorder in May 2005 and updated in July 2005.[6] However, this guideline covers adults (aged 18 years or over) with bipolar affective disorders and is less relevant to this submission.

These guidelines predate the licensing of aripiprazole for the treatment of bipolar I disorder in children and adolescents.

Additional information: comparators

No other antipsychotic agents are licensed for the treatment of bipolar I disorder in patients aged <18 years. The BNF for children, whilst acknowledging the unlicensed status, includes dosage advice for children aged 12 to 18 years for olanzapine, quetiapine and risperidone. It also notes that if the response to antipsychotic agents is inadequate, lithium or valproate may be added.

Cost of relevant comparators

Drug	Dose Regimen	Cost for 12 weeks (£)
Aripiprazole	10mg once daily	288
Olanzapine*	5 to 20mg daily	5 to11
Quetiapine*	200 to 300mg twice daily	16 to 21
Risperidone*	2.5mg daily in one or two divided doses	7
Lithium carbonate (Liskonum®)**	225 to 675mg twice daily	4 to 12
Sodium valproate (Episenta®)*	1 to 2 grams daily	35 to 69
Valproic acid (Depakote®)*	1 to 2 grams daily	54 to 109

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMIMs May 2013. *olanzapine, quetiapine, risperidone and valproate are not licensed for the treatment of bipolar I disorder in patients aged <18 years. ** The lithium carbonate dose should be adjusted according to serum lithium levels. Doses for these agents are from the BNF for children. The doses listed in the table are for the usual maintenance dose but these drugs are initiated at lower doses and subsequently titrated.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 108 in year 1 and 110 in year 5, with an estimated uptake rate of 10% in year 1 and 22% in year 5. The company has also estimated that there will be a discontinuation rate of 17.60% in all 5 years.

The gross impact on the medicines budget was estimated to be £3.7k in year 1 and £8.4k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £3.6k in year 1 and £8.2k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Findling RL, Nyilas M, Forbes RA et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomised, double-blind, placebo-controlled study. J Clin Psychiatry 2009;70:1441-51.

2. Findling RL, Correll CU, Nyilas M et al. Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomised, placebo-controlled study. Bipolar Disorders 2013;15:138-149.

3. European Medicines Agency European Public Assessment Report (EPAR) for Abilify® EMEA/H/C/000471/II/0082 www.ema.europa.eu [accessed 7 May 2013]

4. Goodwin GM. Consensus group of the British Association for Psychopharmacology. Evidence-based guidelines for treating bipolar disorder: revised second edition – recommendations from the British Association for Psychopharmacology. J Psychopharmacology 2009;23:346-388.

5. National Institute for Health and Care Excellence (NICE). Clinical guideline 38. Bipolar disorder: the management of bipolar disorder in adults, children and adolescents in primary and secondary care, July 2006. www.nice.org

6. Scottish Intercollegiate Guidelines Network (SIGN). Guideline 82: Bipolar Affective Disorder, May 2005. www.sign.ac.uk

This assessment is based on data submitted by the applicant company up to and including 10 July 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.