

**aripiprazole 400mg powder and solvent for prolonged release suspension for injection (Abilify Maintena<sup>®</sup>)** SMC No. (962/14)

## **Otsuka Pharmaceuticals and Lundbeck Ltd**

04 April 2014

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 prolonged release suspension for injection (Abilify Maintena<sup>®</sup>)** is accepted for use within NHS Scotland.

**Indication under review:** maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

In a comparative study, aripiprazole prolonged release suspension for injection was as effective as oral aripiprazole in reducing the risk of impending relapse over 26 weeks in stabilised schizophrenic patients. Weaknesses in the indirect comparison limit the reliability of relative efficacy and safety with prolonged release injection forms of other atypical antipsychotics.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

## Indication

Maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

## Dosing Information

For patients who have never taken aripiprazole, tolerability with oral aripiprazole must occur prior to initiating treatment with aripiprazole prolonged release injection. The recommended starting and maintenance dose is 400mg once monthly as a single intramuscular injection. After the first injection, treatment with oral aripiprazole 10mg to 20mg should be continued for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy.

## Product availability date

January 2014

## Summary of evidence on comparative efficacy

Schizophrenia is a chronic, disabling and progressive psychiatric disorder characterised by episodes of psychotic behaviour relapse between periods of relative symptomatic stability. The aim of treatment is the prevention of future relapses. 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.<sup>1</sup> It is licensed in oral formulations for the treatment of schizophrenia (for adults and adolescents  $\geq 15$  years), 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. A short-acting intramuscular injection is also licensed for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate. This submission relates to a new formulation of aripiprazole: a prolonged release (PR) injection for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

The key evidence to support the use of this new formulation comes from two clinical studies: one comparing with oral aripiprazole and the other with placebo only.<sup>1,2</sup> In both studies, eligible patients were aged 18 to 60 years, with a current diagnosis of schizophrenia (according to Diagnostic and Statistical Manual of Mental Health Disorders, Fourth Edition, Text Revision [DSM-IV-TR] criteria). They had at least a 3-year disease history, symptoms of exacerbation on interruption or stopping antipsychotic treatment, were currently treated with at least one antipsychotic and were considered by the investigator to require chronic antipsychotic treatment and would benefit from treatment with aripiprazole PR injection.

The active comparator study was a non-inferiority study comprising three phases: a conversion phase during which patients not already receiving aripiprazole had their antipsychotic therapy changed to aripiprazole oral (10 to 15mg/day over 4 to 6 weeks); a stabilisation phase during which patients were stabilised on open-label oral aripiprazole (10 to 30mg/day over 8 to 28 weeks) and a double-blind maintenance phase during which patients meeting all of the pre-specified disease stability criteria for 8 consecutive weeks were randomised to receive double-blind aripiprazole 400mg PR injection every 4 weeks (n=265), oral aripiprazole (10 to 30mg daily, n=266) or aripiprazole 50mg PR injection every 4 weeks (n=131) for 38 weeks.<sup>1</sup> The aripiprazole PR injection doses could be reduced to 300mg and

25mg, respectively, if required for tolerability. The aripiprazole 50mg/25mg group was included as a sub-therapeutic dose to test assay sensitivity.<sup>1</sup>

The stability criteria were: outpatient status; Positive and Negative Syndrome Scale (PANSS) total score  $\leq 80$ ; lack of specific psychotic symptoms on the PANSS (score of  $\leq 4$  on each of: conceptual disorganisation, suspiciousness, hallucinatory behaviour, unusual thought content); Clinical Global Impression-Severity of Illness (CGI-S)  $\leq 4$  (moderately ill) and Clinical Global Impression-Severity of Suicidality (CGI-SS)  $\leq 2$  (mildly suicidal) on part 1 and  $\leq 5$  (minimally worsened) on part 2.

The primary outcome was the estimated proportion of patients experiencing impending relapse from randomisation to the end of week 26 of the double-blind phase. Impending relapse was defined as meeting  $\geq 1$  of the following criteria:

- Clinical Global Impression-Improvement (CGI-I) of  $\geq 5$  (minimally worse) and either (a) an increase in any of the following individual PANSS items (conceptual disorganisation, hallucinatory behaviour, suspiciousness, unusual thought content) to a score of  $>4$  with an absolute increase of  $\geq 2$  on that specific item since randomisation, or (b) an increase in any of the following individual PANSS items (conceptual disorganisation, hallucinatory behaviour, suspiciousness, unusual thought content) to a score of  $>4$  and an absolute increase of  $\geq 4$  on the combined four of these PANSS items since randomisation.
- hospitalisation due to worsening of psychotic symptoms but excluding hospitalisation for psychosocial reasons.
- CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on part 1 and/or 6 (much worse) or 7 (very much worse) on part 2.
- violent behaviour resulting in clinically relevant self-injury, injury to another or property damage.

Kaplan-Meier curves of time to impending relapse at week 26 estimated the primary outcome occurred in 7.12% of the aripiprazole 400mg/300mg PR injection group, 7.76% of the oral aripiprazole 10 to 30mg group and 21.80% of the aripiprazole 50mg/25mg PR injection group. There was no significant difference between aripiprazole 400mg/300mg PR injection and oral aripiprazole: -0.64% (95% confidence interval [CI]: -5.26 to 3.99),  $p=0.787$ , and thus non-inferiority was demonstrated. Superiority of aripiprazole 400mg/300mg over aripiprazole 50mg/25mg PR injection (difference of -14.68% [95% CI: -23.09 to -6.27],  $p=0.0006$ ) confirmed the validity of the study design.<sup>1</sup>

There were no significant differences between aripiprazole 400mg/300mg PR injection and oral aripiprazole in the secondary outcomes of time to impending relapse, percentage of responders (stabilised at week 38) and percentage of patients achieving remission. There were statistically significant differences favouring aripiprazole 400mg/300mg PR injection in mean change in PANSS total scores, CGI-S scores and CGI-I scores and in time to discontinuation.<sup>1</sup>

The placebo-controlled study had a similar design to above but included an additional stabilisation phase, during which all patients stabilised on oral aripiprazole were switched to intramuscular aripiprazole 400mg/300mg PR over a 12 to 36 weeks period.<sup>2</sup> Eligible patients (those meeting all of the stability criteria above for 4 consecutive weeks during the oral stabilisation phase and for 12 consecutive weeks during the intramuscular stabilisation phase) were then randomised to receive double-blind aripiprazole 400mg/300mg PR injection every 4 weeks ( $n=269$ ) or placebo injection every 4 weeks ( $n=134$ ) for 52 weeks. The primary outcome was the time to exacerbation of psychotic symptoms/impending relapse as defined above. After a pre-planned interim analysis, after 64 impending relapse events, the primary outcome had been achieved and the study was stopped early. At the final analysis (after 80 impending relapse events), the time to impending relapse was significantly shorter in the aripiprazole than placebo group and the relapse rate was statistically significantly lower; 10% (27/269) and 40% (53/134) respectively; hazard ratio 5.03 (95% CI: 3.15 to 8.02).

No quality of life data were collected during the studies.

## Summary of evidence on comparative safety

A pooled analysis of safety data from these two key studies included 534 aripiprazole 400mg/300mg patients, 266 oral aripiprazole patients, 131 aripiprazole 50mg/25mg patients and 134 placebo patients.<sup>1</sup> During the double-blind phase of the studies, adverse events were reported in 73% (389/534), 80% (213/266), 81% (106/131) and 62% (83/134) of patients respectively. Serious adverse events were reported in 4.9% (26/534), 5.6% (15/266), 8.4% (11/131) and 6.7% (9/134) patients respectively.<sup>1</sup>

The most frequently reported adverse events were insomnia (11%, 14%, 14% and 9.0%, respectively), akathisia (8.1%, 6.8%, 8.4% and 6.0%), headache (7.9%, 11%, 5.3% and 5.2%), weight increase (9.4%, 13%, 5.3% and 9.7%), weight decrease (6.6%, 6.0%, 9.2% and 3.0%), nasopharyngitis (5.8%, 9.4%, 6.9% and 5.2%), injection site pain (5.2%, 2.3%, 0.8% and 3.7%) and anxiety (6.6%, 4.9%, 7.6% and 7.5%).<sup>1</sup> Extrapyramidal symptoms and extrapyramidal-related adverse events were reported in 18% (98/534) aripiprazole 400mg/300mg patients, 12% (31/266) oral aripiprazole patients, 12% (16/131) aripiprazole 50mg/25mg patients and 9.7% (13/134) placebo patients. The most frequently reported extrapyramidal adverse events and extrapyramidal-related adverse events in the aripiprazole 400mg/300mg group were akathisia (8.2% [44/534]) and parkinsonism (6.9% [37/534]).<sup>1</sup>

During the two studies, there was no relevant difference between aripiprazole 400mg/300mg and oral aripiprazole in terms of suicide-related adverse events (including completed suicide, suicidal ideation and suicide attempt: 1.1% [6/534] versus 0.4% [1/266]).<sup>1</sup>

In the comparative study with oral aripiprazole, there was a higher incidence of neutropenia in the aripiprazole 400mg/300mg group (2.3% [6/260]) than the oral aripiprazole group (0.8% [2/258]). Cases of neutropenia typically started around day 16 after first injection and lasted a median of 18 days.<sup>1</sup>

In addition, this comparative study reported a clinically relevant increase in weight ( $\geq 7\%$  from baseline) during the double-blind phase in 16% (42/265) aripiprazole 400mg/300mg patients, 16% (43/266) oral aripiprazole patients and 6.1% (8/131) aripiprazole 50mg/25mg patients. Clinically relevant decreases in weight ( $\geq 7\%$  from baseline) were reported in 15% (40/265), 10% (27/266) and 14% (18/131) patients respectively.<sup>1</sup> In the placebo-controlled study, a clinically relevant increase in weight was reported in 10% (27/269) aripiprazole 400mg/300mg patients and 7.5% (10/134) placebo patients and a clinically relevant decrease in weight in 8.2% (22/269) and 8.2% (11/134) patients respectively.<sup>2</sup>

## Summary of clinical effectiveness issues

Schizophrenia is a chronic psychiatric disorder and, once stabilised, the aim of treatment is to prevent further relapses. Clinical experts consulted by SMC considered that there is an unmet need in the therapeutic area, namely treatment options with improved tolerability. This new formulation of aripiprazole would allow monthly administration of this atypical antipsychotic which may improve compliance and reduce relapse in patients who have difficulty taking daily oral formulations. There is evidence demonstrating that aripiprazole PR injection is as effective as oral aripiprazole and superior to placebo in reducing the risk of impending relapse. This outcome has been accepted by the European Medicines Agency for assessing the efficacy of depot antipsychotics and may be more sensitive than rating scales only.<sup>3</sup> Results from the study comparing aripiprazole PR injection with placebo are limited by early stopping, resulting in fewer patients than planned treated for 52 weeks.<sup>2</sup>

In both studies, patients were required to be stabilised on oral or oral and intramuscular aripiprazole before being eligible for randomisation into the double-blind randomised phase of the studies.<sup>1,2</sup> This may have introduced selection bias, since only patients responding to and tolerating aripiprazole would be randomised. However, since the Summary of Product Characteristics for aripiprazole states that it is licensed for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole, this should reflect the patient population treated in clinical practice.

The main additional safety issue with this new formulation was local injection site reactions, particularly injection site pain. There was also a higher incidence of neutropenia in patients treated with aripiprazole 400mg/300mg PR injection compared with oral aripiprazole.

There are no comparative data with other depot antipsychotic agents. Therefore, to allow comparison with risperidone and paliperidone PR injections, the company presented results of a mixed treatment comparison (MTC) using a Bayesian competing risk model. Data from six studies were used to estimate relative efficacy outcomes (relapse, discontinuation due to adverse events and discontinuation due to other reasons) and from five studies for relative safety outcomes (clinically significant weight gain and incidence of extrapyramidal symptoms). The submitting company concluded that there were no important clinical differences between aripiprazole, paliperidone and risperidone PR injections. The MTC found small numerical, non-significant advantages for aripiprazole in terms of discontinuation due to adverse events, discontinuation due to reasons other than adverse events, weight gain ( $\geq 7\%$ ) and extrapyramidal symptoms. However, the MTC had several limitations, including notable differences in the risperidone study population (who were acutely symptomatic), differences in definitions of relapse and different durations of follow-up, three studies stopping early thereby limiting results, pooling of results for dosing groups and the assumption that very low dose of active drug was equivalent to placebo, and a lack of similar results in the placebo group of each study. These limitations may affect the validity of the MTC results, particularly the comparison with risperidone.

The introduction of aripiprazole PR injection would offer a long acting injectable form of this atypical antipsychotic for patients who are stabilised on the oral form and may benefit from improved compliance. Since paliperidone is the active metabolite of risperidone, aripiprazole also offers a different chemical entity. Clinical experts consulted by SMC considered that aripiprazole PR injection is a therapeutic advancement offering an alternative long acting injectable with improved tolerability.

## Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing aripiprazole PR compared with risperidone PR and paliperidone palmitate PR injections for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole. The submitting company justified the comparators on the basis that both treatments have been accepted by SMC for use or restricted use in the indication being considered for aripiprazole PR. The base case analysis used a one year time horizon with a five year time horizon explored in the sensitivity analysis.

The data to support comparable efficacy were based on the MTC of aripiprazole PR, risperidone PR and paliperidone PR injections described above. The submitting company used a random effects model for the analysis of efficacy and a fixed effects model for the analysis of safety outcomes. The results of the MTC showed that there were no significant differences between aripiprazole PR, risperidone PR and paliperidone PR in terms of efficacy and safety. This was used to support the assumption of comparable efficacy which underpins the cost-minimisation analysis. However, as noted above there were some weaknesses with the MTC.

The cost analysis consisted of three different cost components for aripiprazole PR and the comparators: overall drug acquisition costs for the initiation phase, acquisition costs for maintenance treatment and administration costs. The initiation phase was included separately as this phase is more expensive than maintenance. The treatments require to be administered by a healthcare professional and cannot be self-administered, thus staff time costs were included. No associated adverse events costs were included. When specific drug strengths are required and not available in a single vial, the required amount is administered and the remaining assumed to be discarded. The results of the base case analysis were:

Including initiation phase

Treatment	Total cost	Incremental cost versus aripiprazole PR in year 1
Aripiprazole PR	£2,997	-
Risperidone PR	£3,633	£636
Paliperidone PR	£4,174	£1,177

Excluding initiation phase

Treatment	Total cost	Incremental cost versus aripiprazole PR from year 2 onwards
Aripiprazole PR	£2,949	-
Risperidone PR	£3,632	£638
Paliperidone PR	£3,807	£858

When the time horizon was increased in the sensitivity analysis to five years, aripiprazole PR remained cost-saving with the cost savings increasing to £3,146 versus risperidone PR and £4,328 versus paliperidone PR. Based on drug costs alone, the savings were £280 and £1,208 for the comparisons with risperidone and paliperidone respectively.

The key weaknesses with the submission are:

- There is a lack of direct comparative data comparing aripiprazole PR with the relevant comparators and therefore a MTC was conducted. As noted above, there are some weaknesses with the MTC, in particular the comparison with risperidone PR which is likely to be the main comparator used in clinical practice.
- The company was asked to provide analysis assuming administration in an inpatient setting as the base case analysis assumed administration would occur in a community setting only. The company subsequently provided the analysis in two scenarios with hospital based nurse administration included but not inpatient hospitalisation costs. However, the administration setting would not be expected to differ between aripiprazole PR and the comparators, so the conclusion remained unchanged.
- The sensitivity analysis revealed that cost-savings are very sensitive to changes in doses. When lower doses are used the savings fall considerably and, in some cases, aripiprazole PR is no longer cost saving compared with the comparators. However, according to Scottish Prescribing Cost Analysis data, lower doses are not thought to be prescribed as frequently and the analyses based on the doses most commonly prescribed result in cost-savings for aripiprazole.

Aripiprazole PR has lower drug acquisition costs than paliperidone PR and fewer administrations than risperidone PR, and thus aripiprazole PR is cost saving versus the comparators. Therefore, the economic case has been demonstrated.

## Summary of patient and public involvement

A Patient Interest Group Submission was not made.

## Additional information: guidelines and protocols

NICE published clinical guideline number 178 on psychosis and schizophrenia in adults: treatment and management in February 2014.<sup>4</sup> This recommends considering offering depot or long-acting injectable antipsychotic medication to people with psychosis or schizophrenia who would prefer such treatment after an acute episode or where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan. When initiating depot/long-acting injectable antipsychotic medication take into account the service user's preferences and attitudes towards mode of administration (regular intramuscular injections) and organisational procedures (for example, home visits and location of clinics); take into account the same criteria recommended for the use of oral antipsychotic medication within these guidelines (i.e. the relative potential of individual antipsychotic drugs to cause extrapyramidal,, metabolic, cardiovascular, hormonal and other side effects), particularly in relation to the risks and benefits of the drug regimen and initially use a small test dose as set out in the British National Formulary (BNF) or Summary of Product Characteristics (SPC). The guideline does not include specific guidance on choice of depot or long-acting injectable antipsychotic medication.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 131, management of schizophrenia, in March 2013.<sup>5</sup> This recommends that individuals with schizophrenia which is in remission should be offered maintenance treatment with an antipsychotic medication for a minimum of 2 years and that prescribers should consider amisulpride, olanzapine or risperidone as the preferred medications with chlorpromazine and other low-potency first-generation antipsychotics providing suitable alternatives. The guideline also recommends that individuals with schizophrenia who request depot and those with medication adherence difficulties should be offered maintenance treatment with depot antipsychotic medication. The guideline does not include specific guidance on choice of depot or long-acting injectable antipsychotic medication and predates the availability of aripiprazole PR injection.

## Additional information: comparators

Other atypical antipsychotic PR injections.

## Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Aripiprazole	400mg by intramuscular injection every month	2,865
Paliperidone palmitate	25mg to 150mg by intramuscular injection every month	2,391 to 5,104
Risperidone	25mg to 50mg by intramuscular injection every 2 weeks	2,072 to 3,712
Olanzapine*	150mg to 300mg by intramuscular injection every 2 weeks or 300mg to 405mg every 4 weeks	2,894 to 5,789
Aripiprazole	10 to 30mg orally daily	1,249 to 2,497

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27 January 2014. The cost per year is based on monthly injections being administered every 4 weeks i.e. 13 doses per year.

\*Olanzapine PR injection was not recommended by SMC for the treatment of schizophrenia.

## Additional information: budget impact

The submitting company estimated the population eligible for the treatment to be 37 in year 1 and 186 in year 5 with an estimated uptake rate of 4% in year 1 and 20% in year 5.

The gross impact on the medicines budget including the initiation phase was estimated to be £100k in year 1 and £494k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be a saving of £23k in year 1 and a saving of £103k 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. European Medicines Agency, European Public Assessment Report for Abilify Maintena® EMEA/H/C/002755/0000 19 September 2013. [www.ema.europa.eu](http://www.ema.europa.eu) [accessed 9 January 2014]
2. Kane J, Sanchez R, Perry P et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2012;73:617-24.
3. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia, 20 September 2012. [www.ema.europa.eu](http://www.ema.europa.eu) [accessed 9 January 2014]
4. National Institute for Health and Care Excellence (NICE). Clinical guideline 178. Psychosis and schizophrenia in adults: treatment and management, February 2014. [www.nice.org](http://www.nice.org) [accessed 20 March 2014]
5. Scottish Intercollegiate Guidelines Network (SIGN). Guideline 131: Management of schizophrenia, March 2013. [www.sign.ac.uk](http://www.sign.ac.uk) [accessed 9 January 2014]

This assessment is based on data submitted by the applicant company up to and including 14 March 2014.

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.*