# London Medicines Evaluation Network Review

**Aripiprazole (Abilify Maintena®) Prolonged release IM (depot) injection for maintenance treatment of patients with schizophrenia stabilised on oral aripiprazole**

**June 2014**

## 1. Background and introduction

Aripiprazole (Abilify Maintena) is the fourth long-acting injectable formulation of a second-generation antipsychotic to be licensed in the UK. It is licensed for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole. Dose titration is not required and the recommended starting and maintenance dose is 400 mg once a month. The Scottish Medicines Consortium recently accepted it for use within NHS Scotland.

## 2. Proposed place in therapy

As per licensed indication (for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole).

**Starting criteria:** Patients who have demonstrated both tolerability and response to oral aripiprazole.

**Stopping criteria:** Patients unwilling to continue treatment.

## 3. Evidence selected for inclusion

### 3.1 Randomised Controlled Trials

(see appendix for full details of trials reviewed in SMC guidance and by NICE evidence summary)

The key evidence supporting use of this new formulation comes from two clinical studies in patients whose condition had been stabilised on oral aripiprazole: one comparing it with oral aripiprazole and the other with placebo.

The active comparator study was a 38 week non-inferiority study of aripiprazole 400mg (could be reduced to 300mg if required for tolerability) prolonged release (PR) injection every 4 weeks (n=265), oral aripiprazole (10 to 30mg daily, n=266) or aripiprazole 50mg PR injection (‘pseudo-placebo’ to test assay sensitivity for non-inferiority design) every 4 weeks (n=131). 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 which occurred in 7.1% of the aripiprazole 400mg/300mg PR injection group, 7.8% of the oral aripiprazole 10 to 30mg group and 21.8% 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% CI; -5.26 to 3.99, p=0.787] thus meeting the non-inferiority criteria (i.e. 95% CI for difference in estimated proportion of participants experiencing impending relapse by end of week 26 excluded predefined noninferiority margin of 11.5%). There were also 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.

The study of aripiprazole 400mg/300mg PR injection (n=269) or placebo injection (n=134) planned for 52 weeks was terminated early because efficacy was demonstrated by the preplanned interim analysis (conducted after 64 events). Time to impending relapse (primary endpoint) was significantly delayed with aripiprazole compared with placebo in both the interim analysis and the final analysis (p<00001). The hazard ratio (placebo/aripiprazole) at final analysis was 5.03 (95% CI, 3.15-8.02). The rate of impending relapse was significantly lower with aripiprazole than placebo at endpoint (final analysis, 10.0% [n = 27/269] vs. 39.6% [n = 53/134]). These findings are limited by early stopping resulting in fewer patients than planned being treated for 52 weeks.
No quality of life data were collected during these studies.\(^2\)

### 3.2 Safety

A pooled analysis of safety data from the two studies included 534 aripiprazole 400mg/300mg patients, 266 oral aripiprazole patients, and 134 placebo patients (data omitted for ‘pseudo-placebo’ aripiprazole group). During the double-blind phase of the studies:\(^2\)

- Adverse events were reported in 73%, 80%, and 62% of patients respectively.
- Serious adverse events were reported in 4.9%, 5.6%, and 6.7% patients, respectively.
- The most frequently reported adverse events were insomnia (11%, 14%, and 9.0%, respectively), akathisia (8.1%, 6.8%, and 6.0%), headache (7.9%, 11%, and 5.2%), weight increase (9.4%, 13%, and 9.7%), weight decrease (6.6%, 6.0%, and 3.0%), nasopharyngitis (5.8%, 9.4%, and 5.2%), injection site pain (5.2%, 2.3%, and 3.7%) and anxiety (6.6%, 4.9%, and 7.5%).
- Extrapyramidal symptoms (EPS) and extrapyrdimal-related adverse events were reported in 18% aripiprazole 400mg/300mg patients, 12% oral aripiprazole patients, and 9.7% placebo patients.
- The most frequently reported extrapyramidal events in the aripiprazole 400mg/300mg group were akathisia (8.2%) and parkinsonism (6.9%).
- There was no significant difference between aripiprazole 400mg/300mg and oral aripiprazole in terms of suicide-related adverse events (1.1% vs. 0.4%).

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]). In addition, a clinically relevant increase in weight (\(\geq 7\%\) from baseline) was reported during the double-blind phase in 16% aripiprazole 400mg/300mg patients and 16% oral aripiprazole patients. In the placebo-controlled study, a clinically relevant increase in weight was reported in 10% aripiprazole 400mg/300mg patients and 7.5% placebo patients.\(^4\)

### 4. Critical evaluation

#### 4.1. Clinical application

The majority of research showing that depot formulations of antipsychotics were more effective in reducing relapse rates than oral formulations was based on studies that involved the use of first-generation antipsychotic agents.\(^4\) NICE recommends offering depot/long-acting injectable antipsychotic medication to people with psychosis or schizophrenia, who would prefer such treatment after an acute episode 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, NICE recommends taking into account the service user's preferences and attitudes towards the mode of administration (regular intramuscular injections) and organisational procedures (e.g. home visits and location of clinics), as well as the same criteria recommended for the use of oral antipsychotic medication, particularly in relation to the risks (e.g. weight gain and diabetes, extrapyramidal, cardiovascular, and hormonal effects) and benefits of the drug regimen.\(^5\) Despite the cost differential, NICE did not distinguish between the types of long-acting injectable antipsychotics available.\(^4\)

It is not known how aripiprazole PR injection compares with other long-acting antipsychotic injections or oral antipsychotics and the proposed benefits of this treatment is extrapolated from data on the oral formulation. A recent Cochrane review conducted of 174 RCTs comparing oral aripiprazole with: clozapine, quetiapine, risperidone, ziprasidone and olanzapine in 17,244 patients with schizophrenia or schizophrenia-like psychoses found no significant differences between aripiprazole and these agents in global state assessments. There was a higher incidence of general EPS in participants receiving risperidone vs. aripiprazole. When compared with ziprasidone, weight gain was significantly greater in
people receiving aripiprazole. Significantly more people on olanzapine gained weight vs. aripiprazole. It was noted that information on all comparisons was of limited quality, incomplete and problematic to apply clinically. Overall, the quality of the evidence was considered low or very low, and long-term data were sparse.⁶

A 28-week, randomised open-label study (QUALIFY) comparing the effectiveness of aripiprazole 400 mg or 300 mg once monthly with paliperidone palmitate 50–150 mg once monthly in people with schizophrenia is currently ongoing. Long-term safety data for the PR formulation of aripiprazole are currently limited; an ongoing open-label safety study should provide more data. A post-authorisation safety study has been requested to further investigate EPS.³

### 4.2. Potential advantages over existing technologies

- Aripiprazole PR injection has a less frequent dosing schedule (4-weekly, like olanzapine and paliperidone) than risperidone (2-weekly).¹,⁷⁻⁹
- Overall adverse event profile of aripiprazole prolonged-release injection is similar to that of oral aripiprazole, apart from injection-site reactions.²,³

### Potential disadvantages over existing technologies

- While depot antipsychotic injections are often recommended to address adherence problems, evidence on the comparative effectiveness of depot versus oral antipsychotics is inconsistent.¹⁰
- Aripiprazole PR injection is only licensed for use after stabilisation with same drug in oral form, whereas risperidone is licensed for use in patients stabilised with any oral antipsychotic, and paliperidone is licensed for use in patients stabilised with oral paliperidone or oral risperidone.¹,⁷,⁹
- The evidence base for aripiprazole PR injection is limited to one placebo-controlled study and one unpublished comparison with oral aripiprazole.²,³
- Aripiprazole PR injection has not been compared with other atypical antipsychotics depot injections.
- Aripiprazole PR injection is more expensive compared to 25 mg dose of risperidone PR and lower doses of paliperidone PR.

### 4.2.1. Healthcare resource utilisation

Administration of injection by CPNs.

### 4.2.2. Suitability for shared care

Are there already shared care arrangements in place for depot antipsychotics???

### 4.2.3. Drug cost & likely budgetary impact of depot injections

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maintenance dose</th>
<th>Cost per year (excl VAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>400mg monthly</td>
<td>£2645</td>
</tr>
<tr>
<td>Risperidone</td>
<td>25-50mg every 2 weeks</td>
<td>£2072 to 3712</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>25-150mg monthly</td>
<td>£2207* to 4711</td>
</tr>
<tr>
<td>Olanzapine pamoate monohydrate</td>
<td>150-300mg every 2 weeks or 300-405mg every 4 weeks</td>
<td>£2894 to 5789</td>
</tr>
</tbody>
</table>

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*25mg same price as 50mg as lowest strength of injection available is 50mg single use syringe*

The current annual cost of aripiprazole tablets (15-30mg/day) is £1152- 2302 but this will come down with the advent of generic versions following expiry of the patent in October 2014\(^1\) which will result in a bigger cost difference in comparison to the depot injection. The current annual cost of generic risperidone tablets is about £54 for maximum daily dose of 16mg.\(^12\)

**Estimated usage**

The manufacturer estimates that 15,245 people in England are currently receiving a second-generation prolonged-release antipsychotic for maintenance treatment for schizophrenia. They predict that 4% of those eligible for treatment with these drugs will receive aripiprazole prolonged-release in year 1 rising to 8% in year 2 and 12% in year 3.\(^3\). Based on population in SE London of 1.8 million, this would equate to 20 people receiving aripiprazole in the first year rising to 40 in year 2 and 60 in year 3.

**5. Health Economics**

In its submission to the SMC, the company provided a cost-minimisation analysis comparing aripiprazole PR with risperidone PR and paliperidone palmitate PR injections for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole. The SMC noted that aripiprazole PR has lower drug acquisition costs than paliperidone PR and fewer administrations than risperidone PR, and was cost saving versus the comparators therefore the economic case had been demonstrated.\(^2\)

**6.Likely commissioning and funding pathway**

CCG commissioned but funding pathway remains to be determined.

**7.Suggested place in therapy**

Aripiprazole PR injection is the fourth second generation atypical antipsychotic depot to be licensed in the UK. It has been shown in two studies to be non-inferior to oral aripiprazole and superior to placebo. It has not been compared with other antipsychotic depot injections. It is licensed only for use in patients stabilised on oral aripiprazole whereas risperidone can be used in patients stabilised on any oral antipsychotic. Aripiprazole has a less frequent administration schedule than risperidone, but is more expensive compared to 25 mg dose of risperidone and to lower doses of paliperidone. The case for use over currently available depot injections is based on evidence for the oral formulation, which suggests a better metabolic profile for aripiprazole. However these findings are based on low quality evidence and there is a paucity of long term data. It should be borne in mind that the evidence for the other second-generation antipsychotic depot injections is also limited to a relatively small number of short-term studies mainly designed to demonstrate non-inferiority to their oral counterparts. The case for using antipsychotic depot injections would need to take into account their considerable cost and the inconsistent evidence base on their effectiveness compared with oral antipsychotics, of which most are now available as generics. The patent for aripiprazole expires later this year and the advent of generic aripiprazole tablets will result in a significant cost differential between the oral and depot formulations. These factors highlight the need to ensure that depot injections are used only in patients who have been properly assessed as not being suitable for oral therapy.
References

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   http://www.scottishmedicines.org.uk/SMC_Advice/Advice/962_14_aripiprazole_Abilify_Maintena/aripiprazole_Abilify


7. Janssen-Cilag Ltd. Risperdal Consta 25, 37.5 and 50 mg powder and solvent for prolonged-release suspension for intramuscular injection. SPC (date of revision of text November 2013).
   http://www.medicines.org.uk/emc/medicine/9939/SPC/RISPERDAL+CONSTA+25%2c+50%2c+50+mg+powder+and+solvent+for+prolonged-release+suspension+for+injection/

8. Eli Lilly and Company Limited. Zypadhera 210 mg, 300 mg, and 405 mg, powder and solvent for prolonged release suspension for injection. SPC (date of revision of text 25 April 2014)
   http://www.medicines.org.uk/emc/medicine/21361/SPC/ZYPADHERA+210+mg%2c+300+mg%2c+405+mg%2c+powder+and+solvent+for+prolonged-release+suspension+for+injection/#INDICATIONS

9. Janssen-Cilag Ltd. Xeplion 50 mg, 75 mg, 100 mg and 150 mg prolonged release suspension for injection. SPC (date of revision of the text 03 December 2013).
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11. UKMI patents database accessed 09 June 2014

12. Drug tariff accessed online 10 June 2014

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