Licensed Indications
Aripiprazole is indicated¹ for the;
1. Treatment of schizophrenia (adults and adolescents 15 years and older).
   Aripiprazole long-acting injection (Maintena)² is indicated for maintenance treatment of schizophrenia in adult patients who have been stabilised with oral aripiprazole.
2. The treatment of moderate to severe manic episodes in Bipolar I Disorder (adults and adolescents aged 13 years and older)
3. For the prevention of a new manic episode in adult patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Any Exclusions
Aripiprazole is not licensed for the treatment of behavioural problems in dementia or dementia-related psychosis⁷.

Therapeutic Summary
NICE guidance for schizophrenia³ does not specifically recommend an antipsychotic class or individual antipsychotic as first-line treatment for schizophrenia but instead emphasises the importance of patient choice (taking into account adverse effects, and carer views where possible). NICE guidance for bipolar disorder⁴ does not make any specific reference to the use of aripiprazole in adult bipolar disorder but does refer to the NICE technology appraisal guidance (TAG)⁵ on aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder.

Aripiprazole is a second generation antipsychotic which is a partial agonist at the D2 and serotonin 5HT1a receptors, and an antagonist at serotonin 5HT2a receptors. It has no appreciable affinity for muscarinic receptors.

Medicines Initiation
Aripiprazole should not be started in primary care unless in consultation with a specialist. Monitoring is the responsibility of the secondary care team for at least the first 12 months or until the person’s condition has stabilised.

Products Available
Currently available as tablets in strengths of 5mg, 10mg, 15mg, 30mg tablets, and orodispersible tablets in strengths of 10mg and 15mg. A 1mg/1ml oral solution is also available but is very expensive and should be reserved only for initial dose titration in adolescents. Oro-dispersible tablets may be helpful for patients with swallowing difficulties. There is a 400mg strength aripiprazole (Maintena) long-acting depot injection and a short-acting 7.5mg/ml injection used in hospitals for rapid tranquillisation.
Dosages and Route of Administration

- **Schizophrenia (Adult)** initial starting dose: 10–15mg once daily, with a maintenance dose of 15mg once daily. Sometimes a starting dose of 5mg can help minimise initial side-effects.

- Aripiprazole is effective in a dose range of 10 to 30mg daily. Enhanced efficacy at doses above 15mg/day has not been demonstrated although individual patients may benefit from a higher dose. The maximum dose should not exceed 30mg/day.

- The recommended starting and maintenance dose of aripiprazole Maintena long-acting injection is 400mg every calendar month\(^2\). After the first injection, treatment with oral aripiprazole should be continued for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy.

- **Manic episode in bipolar I disorder (Adult)** initial starting dose: 15mg once daily. Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30mg daily.

- **Recurrence prevention of manic episodes in Bipolar I Disorder (Adult)** for those receiving therapy, continue therapy at the same dose. Dose adjustments, including dose reductions, should be considered on the basis of clinical status.

- **Elderly**: effectiveness not established in patients over 65 years. Consider lower starting dose (e.g. 5mg once daily) when clinical factors warrant.

- **Adolescents**:
  - Schizophrenia (aged 15 years and over) – initially 2mg (using oral solution 1mg/1ml) daily for 2 days, then 5mg daily for 2 days, then 10mg daily. Enhanced efficacy at doses higher than 10mg/day has not been demonstrated and there is a higher incidence of side-effects e.g. EPSE, somnolence, fatigue and weight gain.
  - Manic episode in bipolar I disorder (aged 13 years and older) – initially 2mg (using oral solution 1mg/1ml) daily for 2 days, then 5mg daily for 2 days, then 10mg daily. Enhanced efficacy at doses higher than 10mg/day has not been demonstrated and there is a higher incidence of side-effects e.g. EPSE, somnolence, fatigue and weight gain. Treatment should not exceed 12 weeks duration.
  - The safety and efficacy of aripiprazole for irritability associated with autistic disorder and tics associated with Tourette’s disorder has not yet been established in those below the age of 18 years.

- **Renal impairment** requires no dose adjustment although experience is limited.

- **Mild/moderate hepatic impairment** requires no dose adjustment. In severe hepatic impairment use with caution - limited experience.

- The orodispersible tablet should be taken immediately after removal from the blister and placed on the tongue, where it will rapidly disperse in saliva. It may be taken with or without liquid. It may also be dispersed in water.

- The aripiprazole orodispersible tablets are bioequivalent to the aripiprazole tablets.

- Combinations of aripiprazole with other antipsychotics have not been fully studied. However, when switching over to aripiprazole it is recommended that the previous antipsychotic is continued at the same dose for 2 weeks and then gradually discontinued (i.e. an overlap and taper). The mean half life for aripiprazole may vary from 75 hours to 146 hours.
Duration of Treatment
As stated in NICE guidance, following the treatment of an acute episode of schizophrenia, the risk of relapse is high if antipsychotic medication is stopped within 1 to 2 years. For bipolar disorder treatment should be reviewed within 4 weeks of resolution of manic symptoms and if continued, reviewed every 3-6 months.

Monitoring Requirements and Responsibilities
During antipsychotic treatment, improvement in the patient’s clinical condition may take several days to some weeks. During this period the patient should be closely monitored. Please note that the occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders, and in some cases has been reported early after initiation or switch of antipsychotic therapy. High risk patients should be closely supervised during treatment.

General Monitoring Requirements
Ask about compliance and side effects at every consultation.

All patients should be offered an annual physical health check by their GP (more often if clinically indicated). A copy should be sent to the care coordinator and psychiatrist and put in the secondary care notes.

Particular attention should be given to:

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
<th>Smoking, alcohol, substance misuse, diet, level of physical exercise, sexual health, contraceptive advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to treatment</td>
<td>Including changes in symptoms and behaviour</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td>Blood pressure and lipids</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Hyperglycaemia/diabetes and hyperprolactinaemia</td>
</tr>
<tr>
<td>Other side-effects</td>
<td>Such as weight gain (monitor BMI, waist circumference), sexual dysfunction, lethargy, emergence of extrapyramidal movement disorder side-effects (including tardive dyskinesia)</td>
</tr>
</tbody>
</table>

Schedule for Physical Monitoring

<table>
<thead>
<tr>
<th>Initial Baseline Health Check &amp; during first year by secondary care</th>
<th>Annual Health Check By GP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(frequency may increase if clinically indicated)</td>
</tr>
<tr>
<td>Thyroid Function</td>
<td>✓</td>
</tr>
<tr>
<td>Liver Function</td>
<td>✓</td>
</tr>
<tr>
<td>Renal Function</td>
<td>✓</td>
</tr>
<tr>
<td>Full Blood Count</td>
<td>✓</td>
</tr>
<tr>
<td>E.C.G. (if indicated)</td>
<td>✓</td>
</tr>
<tr>
<td>Fasting Blood Plasma Glucose and HbA1c</td>
<td>✓ (repeat at 3 months and 12 months)</td>
</tr>
<tr>
<td>Weight / Height (B.M.I.) (plotted on chart)</td>
<td>✓ (weekly for 6 weeks then at 3 months and 12 months)</td>
</tr>
<tr>
<td>Waist circumference (plotted on chart)</td>
<td>✓</td>
</tr>
</tbody>
</table>
Explicit Criteria for Review and Discontinuation of Aripiprazole

Acute withdrawal symptoms have been described after abrupt discontinuation of high doses of antipsychotics. The long half-life of aripiprazole will minimise the likelihood however it is recommended that aripiprazole is discontinued gradually – ideally over a 3-4 week period – and that signs and symptoms of relapse are monitored for at least 2 years after discontinuation.3,4

### SIDE EFFECTS

<table>
<thead>
<tr>
<th>ACTION</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common (≥1/100 to &lt;1/10)</strong></td>
<td><strong>ACTION</strong></td>
</tr>
<tr>
<td>Insomnia, restlessness, anxiety</td>
<td>Give as a single morning dose. Consider temporary dose reduction or short-term benzodiazepine.</td>
</tr>
<tr>
<td>Extrapyramidal disorder e.g. tremor, rigidity</td>
<td>Consider a dose reduction. An anticholinergic (e.g. procyclidine) may be helpful for symptoms of stiffness, tremor and dystonia.</td>
</tr>
<tr>
<td>Akathisia</td>
<td>A reduction in dose or change to an alternative antipsychotic may be required. Refer to Consultant.</td>
</tr>
<tr>
<td>Sedation, fatigue, somnolence (more likely at 30mg /day)</td>
<td>Give as a single night-time dose. Consider temporary dose reduction. Advise patients not to drive/operate machinery if affected.</td>
</tr>
<tr>
<td>Headache</td>
<td>Try paracetamol. Consider decreasing dose.</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Advise patient to take time to stand up. Initiate slowly. Consider temporary dose reduction.</td>
</tr>
<tr>
<td>Vomiting, nausea</td>
<td>A transient early side-effect likely to be as a result of the partial dopamine agonist activity of aripiprazole. Consider temporary dose-reduction</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Consider an antacid.</td>
</tr>
<tr>
<td>Constipation</td>
<td>Recommend high fibre diet, good fluid intake and regular exercise. Consider a bulk-forming laxative.</td>
</tr>
<tr>
<td>Salivary hypersecretion</td>
<td>Consider decreasing dose. If persists consider prescribing treatment to manage adverse effect - seek advice from consultant / specialist psychiatric pharmacist.</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>Consider decreasing dose.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Uncommon (≥1/1,000 to &lt;1/100)</strong></th>
<th><strong>ACTION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic hypotension / tachycardia</td>
<td>See Dizziness above.</td>
</tr>
<tr>
<td>Depression</td>
<td>Refer to Consultant.</td>
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</tbody>
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Author: John Lawton  
REVIEW DATE: January 2018  
DATE APPROVED BY THE NOTTINGHAMSHIRE APC: January 2015  
aripiprazole info sheet 01.2015 v2
### Tardive dyskinesia
Refer to Consultant. A reduction in dose or change to an alternative atypical antipsychotic maybe required. Review use of anticholinergics as these can worsen Tardive Dyskinesia. Please note that these symptoms can temporarily deteriorate or can even arise after discontinuation of treatment.

### Neuroleptic malignant syndrome (NMS) - hyperthermia, muscle rigidity, autonomic instability, altered consciousness, elevated CPK levels
Discontinue ALL antipsychotic(s).
If suspected immediate referral to a hospital is required.

### Weight gain
Encourage a healthy balanced diet and regular exercise.
Monitor and refer to a dietician and/or Consultant if appropriate

### Elevated glucose levels
Manage according to local diabetes guidelines. Refer to Consultant if appropriate.

### Seizures
Refer to Consultant.

### Pathological gambling
Monitor and refer to Consultant.

## Contraindications
Patients with a known hypersensitivity to any ingredient. See SPC for further information.

## Precautions
- Pregnancy / Breastfeeding - Refer to Consultant.
- Patients with known cardiovascular disease, cerebrovascular disease, conditions pre-disposing to hypotension or hypotension, or those with a family history of QT prolongation.
- Patients with diabetes mellitus or risk factors for diabetes mellitus should be monitored regularly for worsening glucose control. Antipsychotics may cause hyperglycaemia so all patients should be observed for signs and symptoms.
- Patients at risk for aspiration pneumonia – antipsychotics have been associated with oesophageal dysmotility and aspiration.
- Elderly patients with dementia – increased mortality risk (cardiovascular, cerebrovascular, pneumonia).
- Severe hepatic impairment.
- Patients with a history of seizures or conditions associated with seizures.
- Antipsychotic use may be associated with an increased risk of venous thromboembolic events (VTE). All possible risk factors for VTE should be identified before and during antipsychotic treatment and preventative measures undertaken.

## Clinically Relevant Medicine Interactions and their Management
- Alcohol and sedative drugs may potentiate CNS effects of aripiprazole.
- May potentiate effect of antihypertensive drugs due to alpha1-adrenergic antagonism.
- Use with caution with drugs known to cause QT prolongation or electrolyte imbalance.
- Potent CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, HIV protease inhibitors) can
significantly increase AUC and Cmax aripiprazole therefore **halve dose** of aripiprazole. If CYP2D6 / 3A4 inhibitor is then discontinued raise dose of aripiprazole.

- Potent CYP3A4 inducers (e.g. carbamazepine, rifampicin, phenytoin, rifabutin, phenobarbital, primidone, efavirenz, nevirapine, St Johns Wort) can significantly lower AUC and Cmax aripiprazole therefore **double dose** of aripiprazole. If CYP3A4 inducer is then discontinued reduce dose of aripiprazole.
- Please note - no dosage adjustment is required for smokers.

Please consult the manufacturers Summary of Product Characteristics (SPC) for further information.

**References**

2. SPC Abilify Maintena Injection. Last updated April 2014
3. NICE Clinical Guideline 178, Psychosis and schizophrenia in adults. February 2014
4. NICE Clinical Guideline 185, Bipolar disorder. September 2014
5. NICE TAG 292, 2013
7. NAPC Managing Behavioural and Psychological Problems in Patients with Diagnosed or Suspected Dementia. January 2012 (under review).