Aripiprazole prescribing changes: Special Authority approval no longer required, new sole-subsidised brand

**KEY MESSAGES:**

- From 1 June, 2018, aripiprazole (Aripiprazole Sandoz brand only) can be prescribed in primary care without the need for Special Authority approval; patients no longer need to trial other antipsychotics before receiving subsidised treatment.
- The Aripiprazole Sandoz brand will be fully subsidised via a Sole Supply arrangement from June 1, 2018, and it will have sole supply status from November 1, 2018.
- Patients currently taking the Abilify brand of aripiprazole will need to switch to Aripiprazole Sandoz to continue to receive subsidised treatment.
- The Abilify brand of aripiprazole will be delisted on 1 November, 2018.
- Aripiprazole is approved in New Zealand for the treatment of patients with schizophrenia or mania; it provides an alternative for patients who have experienced unacceptable weight gain, other intolerable adverse effects or a sub-optimal response with other antipsychotics, e.g. risperidone, quetiapine.
- Aripiprazole is used to manage aggressive behaviours in some people with autism spectrum disorder (unapproved indication).
- Aripiprazole is typically associated with fewer adverse effects than other antipsychotic medicines, e.g. weight gain and sedation.

From 1 June, 2018, aripiprazole can be prescribed without Special Authority approval, making access easier for patients who require an alternative to other antipsychotics such as risperidone or quetiapine. Patients currently taking aripiprazole will need to switch brands in order to continue to receive subsidised treatment.

**Aripiprazole is an atypical antipsychotic with a different profile of adverse effects**

Aripiprazole is an atypical, or second-generation, antipsychotic like risperidone, quetiapine, olanzapine or clozapine. However, it has a different mechanism of action than other atypical antipsychotics in that it acts as a partial agonist at sub types of dopamine D2 receptors. This property is thought to allow aripiprazole to block pathways where excess dopamine is causing psychosis, while at the same time stimulating areas where dopamine reduction could produce adverse effects. In addition, aripiprazole acts as a partial agonist at 5-HT1a receptors as well as an antagonist at 5-HT2a receptors.

Aripiprazole is approved for the treatment of patients with schizophrenia or mania. Aripiprazole is sometimes used to manage aggressive behaviours or irritability associated with autism spectrum disorder in children, vocal and motor tics.
Schizophrenia and mania are the approved indications for aripiprazole

In patients with schizophrenia, the main advantage of aripiprazole is that it is less likely to cause severe adverse effects than other atypical antipsychotics including clozapine, olanzapine or risperidone. Prescribers who are managing patients with schizophrenia or bipolar disorder who are taking other antipsychotics, may consider a switch to aripiprazole for patients who are gaining significant amounts of weight and/or have developed hyperglycaemia or hyperlipidaemia (see below).

The dose of aripiprazole for adults with schizophrenia is:³

- 10–15 mg, once daily, with a maintenance dose of 15 mg, once daily. Occasionally higher doses may be trialled with a maximum dose of 30 mg, once daily.

The dose of aripiprazole for adults with mania is:³

- 15 mg, once daily. Occasionally higher doses may be trialled with a maximum dose of 30 mg, once daily.

Switching patients to the subsidised brand of aripiprazole

Switching brands of antipsychotics may cause anxiety for some patients; primary care prescribers and community pharmacists have an important role in helping patients navigate this change. Lack of communication about the change can be the most significant issue for patients rather than any perceived adverse effects caused by the change.

Patients can be reassured that Medsafe evaluates the information on the safety and effectiveness of all medicines prior to registration in New Zealand. The Aripiprazole Sandoz brand has been demonstrated to be bioequivalent to other brands, indicating that it has the same therapeutic and adverse effects. The Aripiprazole Sandoz brand and the Abilify brand also have the same excipients, although this is not always the case with different brands of medicine. The available dose formulations and colour of the two brands are the same and the appearance is similar - the only difference patients may notice is that the Aripiprazole Sandoz tablets have “SZ” written on one side and a three digit number on the other.⁷ ⁸

Patients who may require additional support through an aripiprazole brand change include those who:

- Have been stabilised on the previous brand for a long time
- Have had a previous negative experience with a brand change
- Have a condition which may make them more vulnerable to change, e.g. obsessive compulsive disorder, anxiety disorder, autism spectrum disorder

Further information on engaging with people with autism spectrum disorder is available from the Ministry of Health: www.health.govt.nz search for “engaging autism”
Behavioural problems in autism spectrum disorders is an unapproved indication

Aripiprazole may be initiated in some situations, generally by a paediatrician or psychiatrist, to treat behavioural problems in children with autism spectrum disorder, e.g. aggression or uncontrollable temper, however, the possibility of adverse effects needs to be considered.\(^*\) Evidence suggests that aripiprazole is best used only as a short term intervention for this indication, e.g. for three to six months.\(^*\) Doses of aripiprazole used in studies vary from 2–15 mg per day.\(^*\)

\(^*\) Previously aripiprazole was subsided for use in autism spectrum disorder only on application from a paediatrician or psychiatrist

Aripiprazole is not approved for use in patients with dementia-related psychosis

The only antipsychotic that is approved for use in people with behavioural and psychological symptoms of dementia is risperidone, however, other antipsychotics are sometimes used as an unapproved indication. Antipsychotics are a short-term, second-line treatment to non-pharmacological approaches if aggression, agitation or psychotic symptoms are causing severe distress or an immediate risk of harm to the patient or others. Aripiprazole may be considered if other choices such as risperidone, quetiapine or olanzapine are not appropriate due to intolerable adverse effects or they have not been effective. As with other antipsychotics, aripiprazole should be considered cautiously in older patients who have an increased cardiovascular risk or personal or family history of cerebrovascular events.


Adverse effect profile of aripiprazole

The range of adverse effects associated with aripiprazole is similar to that of the other atypical antipsychotics, but in many instances, these adverse effects are less pronounced. Aripiprazole is associated with a superior adverse effect profile compared to other atypical antipsychotics in terms of weight gain (weight loss has been reported), sedation, QT prolongation and hyperprolactinaemia. It is also associated with less hyperglycaemia and hyperlipidaemia than most other antipsychotics (Table 1).\(^4\)

Impulse-control deficits are a rare adverse effect of aripiprazole, which are not associated with other antipsychotics.\(^10\) Uncontrollable gambling is the most frequent impulse-control issue reported with aripiprazole, however, a range of compulsive behaviours may occur, e.g. compulsive spending, binge eating or increased sexual urges.\(^5,10\) Patients and caregivers should be made aware of this risk before aripiprazole is initiated and should be specifically asked about the development of any such urges during the course of treatment. The exact incidence of this adverse effect

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Aripiprazole</th>
<th>Clozapine</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
<th>Amisulpride</th>
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<tbody>
<tr>
<td>Anticholinergic</td>
<td>–/1</td>
<td>3</td>
<td>3</td>
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<td>2</td>
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<td>–</td>
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<tr>
<td>Dyslipidaemia</td>
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<td>3</td>
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<td>2</td>
<td>2</td>
<td>?</td>
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<tr>
<td>Extrapyramidal</td>
<td>1</td>
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<td>–/3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Hyperglycaemia</td>
<td>–</td>
<td>3</td>
<td>3</td>
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<td>2</td>
<td>2</td>
<td>–</td>
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<tr>
<td>Hyperprolactinaemia</td>
<td>–</td>
<td>–/1</td>
<td>1</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Orthostatic</td>
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<tr>
<td>Hypotension</td>
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<td>3</td>
<td>3</td>
<td>–</td>
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<tr>
<td>QT prolongation</td>
<td>–</td>
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<tr>
<td>Sedation</td>
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<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Weight gain</td>
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<td>3</td>
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<td>2</td>
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</tbody>
</table>

– Absent or negligible, 1 infrequent, 2 Moderately frequent, 3 Frequent

Table 1: Approximate relative frequency of adverse effects associated with second generation antipsychotics, adapted from Galletly et al (2016) and Taylor et al (2015)\(^4,11\)
is unknown; a literature review in 2016 identified 184 case reports of impulse-control deficits associated with the use of aripiprazole.\textsuperscript{10}

For further information, see: www.medsafe.govt.nz/profs/PUArticles/September2017/Aripiprazole.htm

**Changes in subsidy may mean more patients are prescribed aripiprazole**

Changes to how aripiprazole is subsidised:\textsuperscript{12}

- From 1 June, 2018, the Aripiprazole Sandoz brand can be prescribed without Special Authority approval\textsuperscript{12}
- The Aripiprazole Sandoz brand will be fully subsidised via a Sole Supply arrangement from June 1, 2018, and it will have sole supply status from November 1, 2018
- The Abilify brand will be reference priced to the price and subsidy of Aripiprazole Sandoz from 1 August, 2018, and will be delisted from November 1, 2018
- A Brand Switch Fee for pharmacies will be added to dispensings of aripiprazole from 1 November, 2018, for three months

Previously, aripiprazole was only subsidised for patients with schizophrenia who had trialled risperidone or quetiapine, or for patients with autism spectrum disorder aged less than 18 years with severe irritability who had trialled risperidone and the application was from a paediatrician or psychiatrist

As Special Authority approval is no longer required to prescribe aripiprazole, it is now available to a larger group of patients, including patients who have experienced adverse effects while taking antipsychotics other than risperidone or quetiapine, e.g. clozapine.

**Switching patients to aripiprazole from another antipsychotic**

If patients already taking an antipsychotic are changed to aripiprazole, a slow crossover is recommended to reduce adverse effects. Cholinergic rebound is a potential concern when patients are switched from a medicine with a high affinity for the muscarinic M1 receptor, e.g. clozapine, to aripiprazole which has a low affinity for the receptor (Table 1).\textsuperscript{1} Patients who develop cholinergic rebound may experience flu-like symptoms as well as malaise, agitation, anxiety, insomnia, nausea and diarrhoea.\textsuperscript{4} In addition to a slow crossover, short-term use of an anticholinergic medicine, e.g. benzotropine, may also be required.\textsuperscript{4}

Rebound insomnia may occur when a patient is switched from a medicine with heavily sedating properties, e.g. clozapine or olanzapine (Table 1), to aripiprazole.\textsuperscript{4} Taking aripiprazole in the morning may reduce rebound insomnia; short-term use of a hypnotic medicine, e.g. zopiclone or temazepam, may be required if the insomnia is severe.\textsuperscript{4}

A suggested protocol for switching to aripiprazole from another antipsychotic involves three steps over approximately eight weeks:\textsuperscript{13}

1. Initiate aripiprazole
2. Overlap between the first antipsychotic and aripiprazole
3. Withdrawal of the first antipsychotic once treatment of aripiprazole at the target dose has been established

The target dose of aripiprazole is 15 mg, daily, which is approximately equivalent to clozapine 300 mg, daily, olanzapine 10 mg, daily, or risperidone, 5 mg, daily, according to defined daily doses.\textsuperscript{14}

**Contraception may need to be discussed with females**

A number of antipsychotics can cause hyperprolactinaemia, e.g. risperidone (Table 1), which reduces fertility.\textsuperscript{4} When a female is switched from a medicine that increases prolactin, to aripiprazole, which does not affect prolactin levels, fertility may be restored and there may be a risk of an unplanned pregnancy, therefore appropriate contraception should be discussed.\textsuperscript{4}

**Monitoring patients taking aripiprazole**

As with any antipsychotic medicine, patients require close monitoring in the first weeks of treatment with aripiprazole for onset of adverse effects.\textsuperscript{4}

**Compulsive behaviours:** Close monitoring for impulse-control deficits is recommended for patients with a personal or family history of obsessive-compulsive disorder, impulse-control disorder, bipolar disorder, alcohol misuse, drug use or other addictive behaviours.\textsuperscript{10} Impulse-control disorders associated with aripiprazole can be expected to resolve once the medicine has been withdrawn or the dose reduced.\textsuperscript{10}

**Cardiovascular risk:** Although aripiprazole is associated with less metabolic adverse effects than many other antipsychotics, the cardiovascular health of adults taking aripiprazole should still be regularly monitored. Cardiovascular risk assessments are recommended in primary care from age 25 years in patients with schizophrenia or bipolar disorder, with repeat assessments every two years, unless the five-year cardiovascular risk is 15 percent or more, in which case it should be repeated annually.\textsuperscript{15} Patients who have changed to aripiprazole from another antipsychotic with more significant metabolic adverse effects may require further support to reduce their cardiovascular risk. Alongside lifestyle modification, this may include initiating metformin, a statin or an antihypertensive with regular monitoring of blood glucose levels, blood pressure and lipid profile.\textsuperscript{4}

**Leukopenia and neutropenia:** A baseline white blood cell count should be considered before initiating aripiprazole as...
there is an increased risk of leukopenia and/or neutropenia in patients with a low white blood cell count or a history of medicine-induced leukopenia. Patients should be advised to report symptoms of systemic infection, e.g. fever, sore throat.

A patient medicine leaflet for aripiprazole is available from: www.medsafe.govt.nz/consumers/cmi/a/Abilifytab.pdf

Medicines that may interact with aripiprazole
Aripiprazole is metabolised by the CYP3A4 and CYP2D6 pathways, therefore medicines that inhibit these enzymes (e.g. clarithromycin, itraconazole, erythromycin, paroxetine) can increase the blood concentration of aripiprazole and the effects can be difficult to predict. Medicines that induce the CYP3A4 pathway, e.g. carbamazepine, can significantly reduce the blood concentration of aripiprazole and a dose increase may be required.

In general, medicines that interact with aripiprazole should be avoided and a different medicine from that class selected, e.g. citalopram rather than paroxetine. If an interaction is unavoidable then the dose of aripiprazole may need to be adjusted and discussion with a clinician with significant experience in prescribing aripiprazole may be helpful.

The NZF provides details of medicines that interact with aripiprazole and the clinical significance of these interactions, available from: http://nzf.org.nz

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N.B. Expert reviewers are not responsible for the final content of the article.

References