Aripiprazole Long-Acting Injection (LAI)

(Abilify Maintena®)

Guidance for Prescribing

Purpose of this guidance

From 1 January 2024, aripiprazole long-acting injection (Abilify Maintena) will be available as a second line depot antipsychotic treatment option, to help mitigate the current supply issues with olanzapine long acting injection (Zyprexa Relprevv). This guidance informs appropriate use of aripiprazole LAI while navigating the olanzapine LAI shortage.

Abilify Maintena unapproved product

Aripiprazole LAI is funded for maintenance of clinical improvement in the treatment of schizophrenia in New Zealand. The product that will be available initially is an Australian product that is approved for use in Australia however is unapproved in New Zealand. While a New Zealand datasheet is not currently available for Abilify Maintena, the Australian datasheet for Abilify Maintena issued by the Therapeutics Goods Administration (TGA) can also be referred to for prescribing guidance.

Clinical evidence for Abilify Maintena

During its development, the pivotal Phase III study (n=662), a randomised double-blind double dummy non-inferiority trial, reported that aripiprazole LAI was non-inferior to oral aripiprazole for the prevention of relapse of schizophrenia over 26 weeks. A second trial, comparing aripiprazole 400mg LAI to placebo, reported that it was superior to placebo for the same outcome (Canadian Agency for Drugs and Technology, 2017).

The authors of the pivotal trial highlighted that efficacy analysis was conducted in people already stabilised on oral aripiprazole, and its results cannot be extrapolated to people taking other oral antipsychotics.

Characteristics of Aripiprazole

Aripiprazole is an atypical antipsychotic, thought to act as a partial agonist at dopamine D2 receptors and serotonin 5HT1A receptors, and as an antagonist at serotonin 5HT2A receptors. As such, aripiprazole is different from the other antipsychotics available in New Zealand. These differences must be considered when deciding if aripiprazole is appropriate for a person considered for treatment.

Aripiprazole has the highest affinity for dopamine D2 receptors of all antipsychotics available in New Zealand. Approximately 10mg/day of oral aripiprazole is enough to saturate the D2 receptors and prevent any other antipsychotic from binding. This characteristic of aripiprazole can have a significant impact if aripiprazole is insufficiently effective and a new antipsychotic is required.

Most oral antipsychotics have half-lives of approximately 24 hours and reach steady state within a week. Aripiprazole has a particularly long half-life, ranging from 32 to 157 hours when taken orally and can take up to a month to reach steady state. Assessing for response must therefore be done later than with other antipsychotics, and approximately eight weeks of oral treatment might be needed to reasonably trial effectiveness.

Abilify Maintena has a mean elimination half-life of 46.5 days for the 400mg dose and could take up to seven months to clear from the body completely if discontinued. This prolonged clearance time, combined with dopamine D2 receptor affinity, means that if Abilify Maintena is insufficiently effective and needs to be switched to a different antipsychotic, the action of the new antipsychotic may be hindered for a considerable period.

Patient Selection

It is important to ensure good patient selection prior to starting aripiprazole LAI.

Abilify Maintena is approved in New Zealand for maintenance of clinical improvement in the treatment of schizophrenia. Evidence suggests aripiprazole is most effective when used early in schizophrenia.

From 1 January 2024, Abilify Maintena will be funded for people meeting the following special authority criteria:

> ***Both:***
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> 1. *Patient has a current Special Authority approval for olanzapine depot injection, risperidone depot injection or paliperidone depot injection; and*
> 2. ***Either:***
>
>   1. *Patient has tried but has experienced an inadequate response to, or has experienced intolerable side effects from, prior therapy with olanzapine depot injection, risperidone depot injection or paliperidone depot injection; or*
>
>   2. *Patient has been unable to access olanzapine depot injection due to supply issues with olanzapine depot injection, or otherwise would have been initiated on olanzapine depot injection but has been unable to due to supply issues with olanzapine depot injection.*

People who are most likely to do well on aripiprazole LAI who meet the above criteria include:

(please note this is not a complete list)

- those who responded to oral aripiprazole previously but were switched to an atypical antipsychotic long acting injection due to difficulty adhering with oral treatment.
- those who would have otherwise trialled aripiprazole if a long acting injectable formulation had been available.
- those who are currently prescribed olanzapine LAI because risperidone, paliperidone, or typical antipsychotics were not tolerable.

If somebody has already experienced failure of adequate trials of two or more antipsychotics, i.e. if their disease is considered treatment resistant, clozapine is indicated and should be considered.

If clozapine is not able to be used and a depot long-acting injection is indicated, consider the merits of all available depot options, including the typical antipsychotics.

Prescribing Abilify Maintena

For people who have never taken aripiprazole, it is important to establish tolerability with oral aripiprazole prior to starting Abilify Maintena. Due to the long half-life of oral aripiprazole, it may take up to two weeks to fully assess tolerability. The trial of oral aripiprazole should be long enough to establish a clear clinical response prior to starting Abilify Maintena.

For people who have previously trialled and benefitted from aripiprazole, Abilify Maintena can be considered. See below for advice on switching from other antipsychotics.

Abilify Maintena is administered once monthly into the deltoid or gluteal muscle. After the first injection, it is recommended that oral aripiprazole is continued for 14 days to maintain plasma concentrations, although anecdotal reports from the United Kingdom suggest this may not always be required. See below for advice on switching from other antipsychotics.

Prescribing Abilify Maintena under Section 29 of the Medicines Act 1981

Prescribing and supplying unapproved medicines under Section 29 of the Medicines Act 1981 requires sending patient information to the importer/manufacturer of the medicine and the Ministry of Health and obtaining patient consent for this information to be shared. Further information regarding the requirements for prescribing and supplying unapproved medicines under Section 29 of the Medicines Act 1981 is available here.

Prescribing Abilify Maintena under the Mental Health (Compulsory Assessment and Treatment) Act 1992

For people considered for treatment with Abilify Maintena who are treated under the Mental Health Act 1992 and unable or unwilling to provide informed consent, the processes and requirement for a second clinical opinion under section 59 of the Mental Health Act would apply. As Abilify Maintena will be unapproved initially, the Director of Mental Health has advised that a second opinion in such circumstances, must be demonstrably robust. In particular all of the clinical risks and benefits would need to be considered along with any expressed views of the patient and their family. As part of that process there should be disclosure around the status of the medication. Further guidance on this process can be found in section 10 of the Guidelines to the Mental Health (Compulsory Assessment and Treatment) Act 1992.

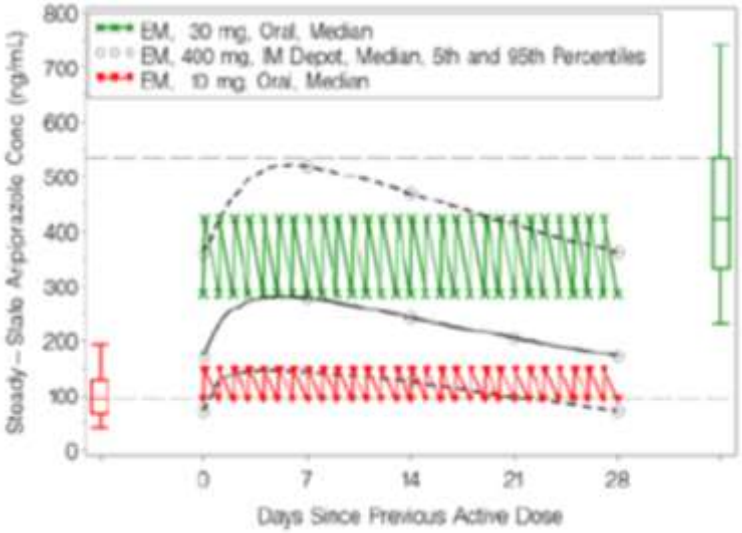
Dose Selection

The recommended starting and maintenance dose of Abilify Maintena is 400mg once a month. Titration of the dose is not required. If there are adverse reactions with the 400mg dose, consider reducing the dose to 300mg once monthly.

In patients who are known to be CYP2D6 poor metabolisers, the starting and maintenance dose should be 300mg. If Abilify Maintena is taken concomitantly with strong CYP3A4 inhibitors, the dose should be reduced to 200mg.

Abilify Maintena 400mg monthly is approximately equivalent to 15mg per day orally. While there is little trial data to support it, if somebody is stabilised on oral aripiprazole at a dose lower than 15mg per day, it would be reasonable to consider a reduced dose of Abilify Maintena. The package insert includes reconstitution and administration instructions for doses of 400mg, 300mg, 200mg and 160mg.

Figure 1 shows a simulation of median aripiprazole concentration and its estimated fifth and 95th percentiles after administration of 400 mg IM aripiprazole depot at dose initiation and at steady-state and comparison to that of 10 and 30 mg oral aripiprazole.



Switching to Abilify Maintena from another depot or long acting injection

If switching directly from another long acting injection to Abilify Maintena, the initial dose of Abilify Maintena can be administered on the day the previous injection would have been due.

However, please note, switching to aripiprazole is often poorly tolerated. Aripiprazole binds strongly to dopamine receptors, displacing other antipsychotics and stimulating receptors to about 30% activity. This abrupt change from minimal dopamine activity (i.e. when blocked by the other antipsychotic) to 30% activity can be acutely distressing and aversive. Please keep this in mind when assessing a patient's response to aripiprazole.

A cross taper is most likely to be successful when switching from another long acting injection. For example, introduce aripiprazole orally at a maximum of 5mg daily when the next injection would have been due. Increase the dose stepwise and switch to Abilify Maintena only once the oral dose is stable and tolerated.

Safety

Safety and efficacy studies have included adults aged 18-60 years. The safety and efficacy of Abilify Maintena in younger or older people have not been established.

In adults, no new safety concerns have been identified with Abilify Maintena when compared with other aripiprazole formulations. Overall, the adverse event profile of Abilify Maintena was similar to that of oral aripiprazole, apart from injection site reactions.

In both long-term trials, injection site reactions were observed to be mild to moderate in severity and resolved over time. Injection site pain (incidence 5.2 %), has a median onset on day two after the injection and a median duration of four days.

In the acute phase trial, injection site pain (incidence 5.4%) was reported to be mild in severity and resolved over time.

Extrapyramidal side effects were more common with the 400mg LAI than with oral aripiprazole (18.4% vs 11.7%). The incidence also increased with time. This likely reflects the higher equivalent dose of the LAI and the long half-life, and suggests EPSEs may be less common with a lower dose of LAI.

Guidance for Administration

Abilify Maintena is available as a therapeutic kit containing a vial of powdered drug, a vial of water for injections, syringes and needles, similar to the other long acting injections. There are two strengths, 300mg and 400mg. Abilify Maintena is administered once a month into the deltoid or gluteal muscle.

Reconstitution and preparing the injection

Instructions for reconstitution and administration are detailed in the package insert.

If the injection is not administered immediately after reconstitution, keep the vial below 25°C for up to 4 hours and shake the vial vigorously for at least 60 seconds to resuspend prior to injection.

Do not store the reconstituted suspension in the syringe.

Injection site reactions

In both long-term trials, injection site reactions were observed to be generally mild to moderate in severity and resolved over time. Injection site pain had a median onset on day 2 after the injection and a median duration of 4 days.

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Guidance prepared by Mental Health Pharmacist Group in conjunction with Pharmac.