AUSTRALIAN PRODUCT INFORMATION – ABILIFY ASIMTUFII® (ARIPIPRAZOLE (AS MONOHYDRATE)) PROLONGED RELEASE SUSPENSION FOR INJECTION

1 NAME OF THE MEDICINE

Aripiprazole (as monohydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Abilify Asimtufii (aripiprazole (as monohydrate)) is a prolonged release suspension for intramuscular injection, supplied in a pre-filled syringe. Abilify Asimtufii (aripiprazole (as monohydrate)) is available in the following presentations:

- 2.4 mL pre-filled syringe containing 720 mg of aripiprazole
- 3.2 mL pre-filled syringe containing 960 mg of aripiprazole

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

White sterile modified release suspension for intramuscular injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the maintenance treatment of schizophrenia in adults.

For maintenance treatment to prevent the recurrence of manic or mixed episodes of bipolar I disorder in adult patients as monotherapy.

4.2 Dose and method of administration

Recommended Dosage and Dosage Adjustment

Abilify Asimtufii is intended for intramuscular injection in the gluteal muscle only, in patients who have been treated with Abilify Maintena in the prior month and whose tolerability to aripiprazole has been established.

Titration of the dose of Abilify Asimtufii is not required.

The recommended Abilify Asimtufii starting dosing regimen is:

Transition from Abilify Maintena:

For patients maintained on Abilify Maintena 400 mg, one injection of Abilify Asimtufii 960 mg should be administered in place of the next scheduled injection of Abilify Maintena 400 mg. Abilify Asimtufii 960 mg should then be dosed once every 2 months.

For patients maintained on Abilify Maintena 300 mg, one injection of Abilify Asimtufii 720 mg should be administered in place of the next scheduled injection of Abilify Maintena 300 mg. Abilify Asimtufii 720 mg should then be dosed once every 2 months.

The first Abilify Asimtufii injection may be administered instead of the second or any later injection of Abilify Maintena.

Dosing interval and dosing adjustments

The recommended maintenance dose is Abilify Asimtufii 960 mg. Inject Abilify Asimtufii 960 mg once every two months as a single injection. Patients may be given the injection up to 2 weeks before or 2 weeks after the scheduled 2-month dose.

If there are adverse reactions with the Abilify Asimtufii 960 mg dose, reduction to Abilify Asimtufii 720 mg once every two months should be considered at the time of the next scheduled injection.

Discontinuation of Abilify Asimtufii

If Abilify Asimtufii is discontinued, its prolonged-release characteristics must be considered.

Missed doses

Table 1 Management of missed doses

	Missed doses
Timing of Missed Dose	**Action**
> 8 weeks and < 14 weeks	If more than 8 weeks and less than 14 weeks have elapsed since the last injection, administer the next dose of Abilify Asimtufii as soon as possible. The once every 2-month schedule should be resumed.
> 14 weeks	If more than 14 weeks have elapsed since the last injection, resume with 10 mg to 20 mg oral aripiprazole per day for 14 days with the next administered injection of Abilify Asimtufii. The once every two-month schedule should be resumed.

Dosage in Special Populations

Elderly Population

The safety and efficacy of Abilify Asimtufii in the treatment of patients with schizophrenia or bipolar I disorder 65 years of age or older has not been established (see section 4.4 Special warnings and precautions for use). No recommendations on dosing can be made.

Renal Impairment

No dosage adjustment of Abilify Asimtufii is required for patients with renal impairment. See 5.2 Pharmacokinetic properties - Special Populations.

Hepatic Impairment

Based on oral data no dosage adjustment of Abilify Asimtufii is required for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish dosage recommendations. In these patients dosing should be managed cautiously; use of oral aripiprazole should be considered. See 5.2 Pharmacokinetic properties - Special Populations.

Other Special Populations

No dosage adjustment of Abilify Asimtufii is recommended based on gender, race or smoking status.

Known CYP2D6 Poor Metabolisers

In patients who are known to be CYP2D6 poor metabolisers and who are already established on Abilify Maintena 300 mg, the starting dose should be one injection of Abilify Asimtufii 720 mg. Thereafter, a maintenance dose of Abilify Asimtufii 720 mg should be administered once every two months as a single injection.

Maintenance dose adjustments due to interactions with CYP2D6 and/or CYP3A4 inhibitors and/or CYP3A4 inducers

Maintenance dose adjustments should be made in patients taking concomitant strong CYP3A4 inhibitors or strong CYP2D6 inhibitors for more than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the dose may need to be increased to the previous dose (see section 4.5 Interactions with other medicines and other forms of interactions). In case of adverse reactions despite dose adjustments of Abilify Asimtufii, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

Table 2 Dose Adjustments of Abilify Asimtufii in Patients who are known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers for Greater than 14 days

Factors	**Adjusted Dose**
CYP2D6 Poor Metabolizers	
Known CYP2D6 Poor Metabolizers	720 mg once every 2 months
Known CYP2D6 Poor Metabolizers taking concomitant CYP3A4 inhibitors	Avoid use
Patients Taking 960 mg of Abilify Asimtufii	
Concomitant use of Abilify Asimtufii with Strong CYP2D6 inhibitors	720 mg once every 2 months
Concomitant use of Abilify Asimtufii with Strong CYP3A4 inhibitors	720 mg once every 2 months
Concomitant use of Abilify Asimtufii with CYP2D6 **and** CYP3A4 inhibitors	Avoid use
Concomitant use of Abilify Asimtufii with CYP3A4 inducers	Avoid use

Paediatric Population

The safety and efficacy of Abilify Asimtufii in children and adolescents aged 0-17 years have not been established. No data are available.

Administration

Abilify Asimtufii is presented as a therapeutic kit.

Abilify Asimtufii should be administered by a healthcare professional once every two months as a single injection.

Abilify Asimtufii pre-filled syringe is for single use only.

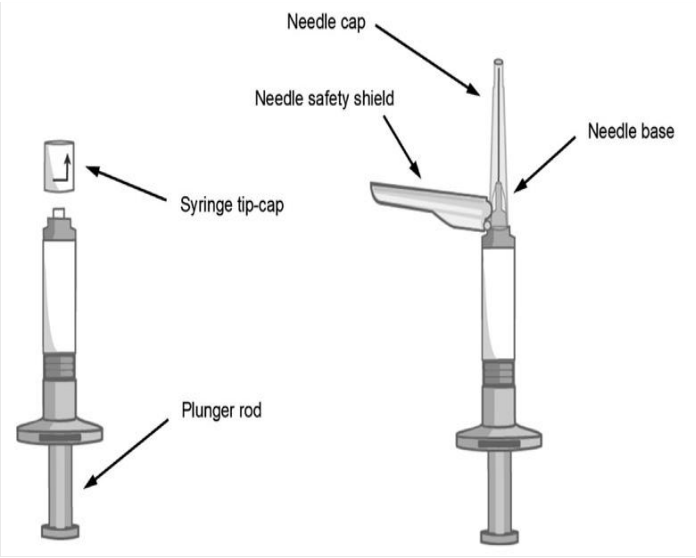
Abilify Asimtufii is for intramuscular use by gluteal injection only. Do not administer by any other route.

Prior to administration, visually inspect Abilify Asimtufii pre-filled syringe for particulate matter and discoloration. The suspension should appear to be a uniform, homogeneous suspension that is opaque and milky-white in colour. Do not use Abilify Asimtufii pre-filled syringe if the suspension is discoloured, or particulate matter is present.

Contents of kit

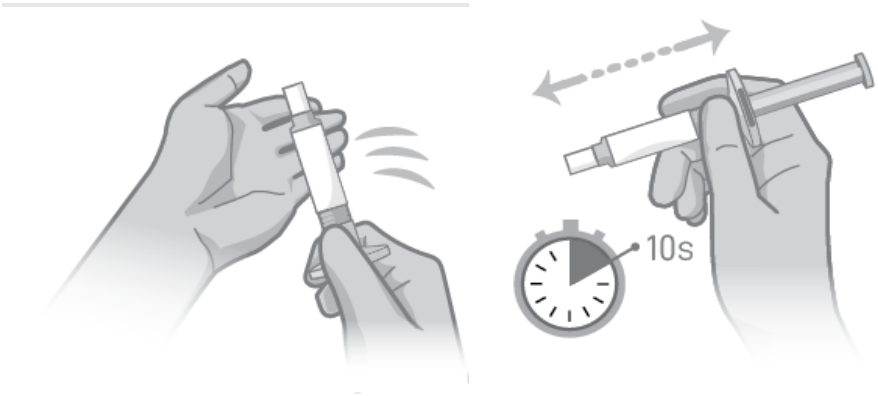
Confirm that components listed below are provided:

- One pre-filled syringe containing either Abilify Asimtufii 960 mg or 720 mg prolonged-release injectable suspension and two safety needles.
- One sterile 38 mm (1.5 inch) 22-gauge needle with black needle hub.
- One sterile 51 mm (2 inch) 21-gauge needle with green needle hub.



Prepare for injection

- Remove the syringe from the package.
- Tap the syringe on your hand at least 10 times.
- After tapping, shake the syringe vigorously for at least 10 seconds until medication is uniform.



Select the appropriate needle

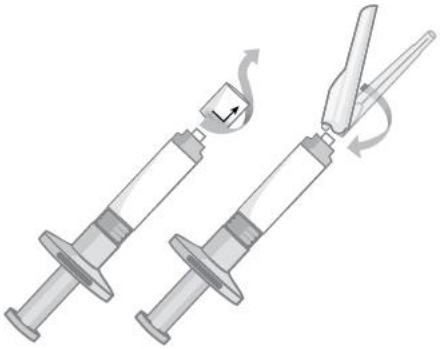
Needle selection is determined by patient body type.

- For gluteal intramuscular administration only.
  - For non-obese patients use the 38 mm (1.5 inch) 22-gauge needle with needle protection device (needle in black packaging)
  - For obese patients use the 51 mm 2 inch) 21-gauge needle with needle protection device (needle in green packaging)

Body Type	Needle Size	Needle packaging
Non-obese (BMI < 28 kg/m^2)	38 mm, 22 gauge	black
Obese (BMI > 28 kg/m^2)	51 mm, 21 gauge	green

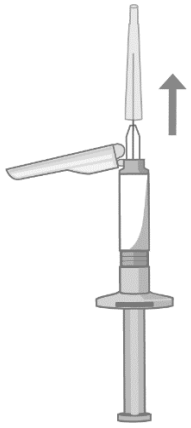
Attach the needle

- Twist and pull off the pre-filled syringe tip-cap.
- While holding the base of the needle, ensure the needle is firmly seated on the safety device with a push. Gently twist clockwise until SECURELY fitted.

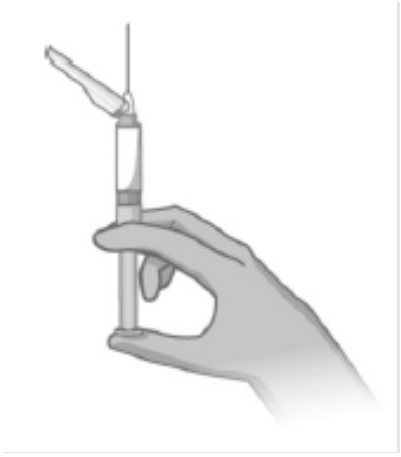


Expel air

- When you are ready to administer the injection, hold the syringe upright and remove the needle cap by pulling straight up. **Do not** twist the needle cap as this may loosen the needle from the syringe.

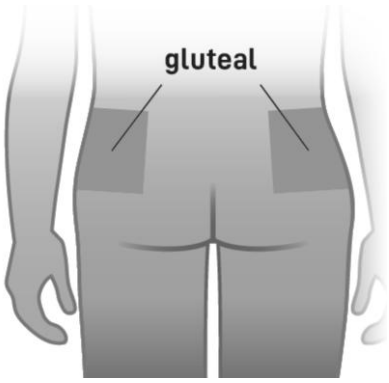


- Slowly advance the plunger rod upward to expel the air and until the suspension fills the needle base.
- Inject immediately after expelling air from syringe.



Inject the dose

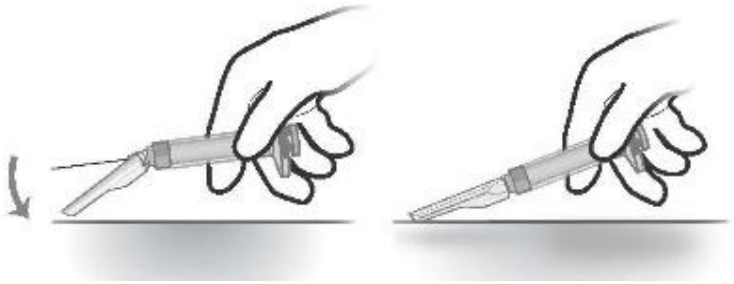
- Slowly inject the entire contents intramuscularly into the gluteal muscle of the patient. **Do not administer by any other route.**
- Do not massage the injection site.



- Remember to rotate sites of injections between the two gluteal muscles.
- Look for signs or symptoms of inadvertent intravenous administration.

Disposal procedure

- After injection, engage the needle safety device by pressing the safety shield on a hard surface to cover and lock shield over the needle.



- Immediately discard used syringe and unused needle in an approved sharps container.
- Unused needle should not be saved for future use.

4.3 Contraindications

Hypersensitivity to aripiprazole or any of the excipients listed in section 6.1 List of Excipients.

4.4 Special warnings and precautions for use

General

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.

Use in patients with acute psychotic states

Abilify Asimtufii should not be used in patients in acute psychotic states.

Elderly patients with dementia-related psychosis

Increased mortality

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs, including aripiprazole, are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g. pneumonia) in nature.

In three placebo-controlled trials with oral aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), patients treated with aripiprazole were at an increased risk of death compared to placebo. The rate of death in the aripiprazole-treated patients was 3.5% compared with 1.7% in the placebo group. Abilify Asimtufii is not indicated for the treatment of patients with dementia-related psychosis.

Cerebrovascular adverse events

In the same three 10-week placebo-controlled trials, cerebrovascular adverse reactions (e.g., stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6% of placebo-treated patients in these trials. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole. The safety and efficacy of aripiprazole on the treatment of patients with psychosis associated with dementia have not been established. Abilify Asimtufii is not indicated for the treatment of patients with dementia-related psychosis.

Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and close supervision of high-risk patients should accompany drug therapy. As Abilify Asimtufii is to be administered by a healthcare professional, suicide due to an overdose is considered unlikely.

Tardive dyskinesia

In clinical trials of one year or less duration, there were uncommon reports of treatment-emergent tardive dyskinesia during treatment with aripiprazole. The risk of tardive dyskinesia

increases with long-term exposure to antipsychotic treatment. If signs and symptoms of tardive dyskinesia appear in a patient on Abilify Asimtufii, dose reduction or discontinuation of treatment should be considered (4.2 Dose and method of administration). These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Neuroleptic malignant syndrome

Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including aripiprazole, must be discontinued.

Seizure

In clinical trials, uncommon cases of seizures were experienced during treatment with aripiprazole. As with other antipsychotic drugs, Abilify Asimtufii should be used cautiously in patients who have a history of seizure disorder or have conditions associated with seizures.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. In clinical trials, the observed differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values between Abilify Maintena (<1%) and placebo (0%) could be considered as of no major clinical concern.

Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including aripiprazole, should be monitored regularly for worsening of glucose control. All patients who are starting treatment with atypical antipsychotics, including aripiprazole, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including aripiprazole, should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued;

however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

In patients with significant treatment-emergent hyperglycaemia, discontinuation of Abilify Asimtufii should be considered.

No specific studies have been conducted with Abilify Asimtufii in patients with hyperglycaemia or diabetes mellitus, however overall findings in clinical trials have been similar to Abilify Maintena and oral aripiprazole.

Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (e.g., dehydration, hypovolaemia, and treatment with antihypertensive medications) or hypertension, including accelerated or malignant. Patients with a history of clinically significant cardiovascular disorders were excluded from clinical trials.

QT interval

In clinical trials of treatment with Abilify Maintena and oral aripiprazole, the incidence of QT prolongation was uncommon. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation. See also 4.8 Adverse effects (Undesirable effects) - QT Interval.

Orthostatic hypotension

Aripiprazole may be associated with orthostatic hypotension, potentially due to its α1-adrenergic receptor antagonism. Aripiprazole may induce orthostatic hypotension, tachycardia, dizziness and sometimes syncope, especially at the initiation of treatment. In the double-blind controlled phase of the long-term clinical trials, orthostasis-related events were reported in 2/534 (0.4%) patients treated with Abilify Maintena. In the 12-week clinical trial in acutely relapsed patients, orthostasis-related events were reported in 1/167 (0.6%) patient treated with Abilify Maintena, while syncope and orthostatic hypotension each occurred and in 2/172 (1.2%) patients treated with placebo.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Abilify Asimtufii and preventive measures undertaken.

Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including aripiprazole, which may lead to falls. Caution should be taken when treating patients with diseases, conditions, or who are taking medications that could exacerbate these effects.

Body temperature regulation

Disruption of the body's ability to increase or reduce core body temperature has been attributed to antipsychotic agents, including aripiprazole. Appropriate care is advised when prescribing Abilify Asimtufii for patients who will be experiencing conditions which may contribute to an

elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity or being subject to dehydration.

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic drug use, including aripiprazole. Abilify Asimtufii and other antipsychotic drugs should be used cautiously in patients at risk of aspiration pneumonia (e.g., elderly patients).

Akathisia

Class effect: The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena (such as pacing, swinging of the legs while seated, rocking from foot to foot), or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Leukopenia, neutropenia and agranulocytosis

Class Effect: In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including aripiprazole. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood cell (CBC) monitored frequently during the first few months of therapy, and discontinuation of Abilify Asimtufii should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly, if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue Abilify Asimtufii and have their WBC followed until recovery. See 4.8 Adverse effects (Undesirable effects) - Laboratory Tests.

Pathological gambling and impulse-control disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges reported include: increased sexual urges, compulsive spending, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive spending, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases urges were reported to have stopped when the dose was reduced or the medication was discontinued. Impulse control disorders may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole. See 4.8 Adverse effects (Undesirable effects).

Weight gain

Antipsychotic drugs have been associated with metabolic changes, including weight gain. In an open-label, multiple-dose, randomised study in adult patients with schizophrenia and bipolar I disorder, in which the highest dose of Abilify Asimtufii (960 mg) was evaluated against Abilify Maintena (400 mg), the overall incidence of weight gain (≥7%) from baseline was comparable between Abilify Asimtufii and Abilify Maintena.

All patients should have baseline and periodic monitoring of body weight, and other cardiometabolic parameters, including fasting glucose, full lipid profile and blood pressure, during treatment with any atypical antipsychotic including Abilify Asimtufii.

Paediatric use

The safety and efficacy of Abilify Asimtufii in children and adolescents aged 0-17 years have not been established. No data are available.

Use in the elderly

The safety and efficacy of Abilify Asimtufii in patients ≥ 65 years of age have not been established. Caution should be used when treating elderly patients.

Effects on laboratory tests

Drug interaction with laboratory tests has not been established.

4.5 Interactions with other medicines and other forms of interactions

While no specific drug interaction studies have been performed with Abilify Asimtufii, the effects of co-administration of inhibitors of CYP2D6 and CYP3A4 were modelled as part of a population pharmacokinetic study but with no data accrued. The information below is therefore obtained from studies with oral aripiprazole.

Potential for other medicinal products to affect aripiprazole

Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes.

Inhibitors and inducers of CYP2D6 and CYP3A4

Quinidine or other strong CYP2D6 inhibitors

In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) decreased oral clearance of aripiprazole by 52%, increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%, respectively. Other strong inhibitors of CYP2D6, such as fluoxetine, paroxetine, and bupropion may be expected to have similar effects and similar dose reduction should, therefore, be applied. See 4.2 Dose and method of administration, Dosage in Special Populations - Dosage in Special Populations.

Ketoconazole or other strong CYP3A4 inhibitors

In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) decreased oral clearance of aripiprazole by 38%, increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77% and 43%, respectively. Other strong inhibitors of CYP3A4, such as itraconazole and

HIV protease inhibitors may be expected to have similar effects and similar dose reductions should, therefore, be applied (see 4.2 Dose and method of administration, Dosage in Special Populations - Dosage in Special Populations). When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with Abilify Asimtufii, potential benefits should outweigh the potential risks to the patient.

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dose of aripiprazole may need to be increased to the dose prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g., diltiazem) or CYP2D6 (e.g., escitalopram) are used concomitantly with aripiprazole, modest increases in plasma aripiprazole concentrations may be expected.

Carbamazepine or other CYP3A4 or CYP2D6 inducers

In a clinical study in patients with schizophrenia or schizo-affective disorder, co-administration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, with aripiprazole (30 mg daily) resulted in an approximate 70% decrease in AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. Concomitant administration of Abilify Asimtufii and other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) or potent inducers of CYP2D6 may be expected to have similar effects.

Valproate and lithium

When either valproate or lithium was administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations.

Inhibitors and inducers of CYP1A1, CYP1A2, CYP2C9 and CYP2C19

Aripiprazole is not metabolised by CYP1A1, CYP1A2, CYP2C9 and CYP2C19 *in vitro*, suggesting that interactions with medications or other factors (e.g., smoking), which are inhibitors or inducers of these enzymes, are unlikely.

Potential for aripiprazole to affect other medicinal products

CNS drugs (including alcohol)

Given the primary CNS effects of aripiprazole, caution should be used when Abilify Asimtufii is administered in combination with alcohol or other CNS drugs with overlapping adverse reactions, such as sedation. See 4.8 Adverse effects (Undesirable effects).

Patients should be advised to avoid alcohol while on Abilify Asimtufii.

When aripiprazole was administered concomitantly with valproate, lithium, lamotrigine, dextromethorphan, warfarin, omeprazole, escitalopram, venlafaxine or desvenlafaxine there was no clinically important change in concentrations of these drugs.

Effects of aripiprazole on substrates for CYP2D6, CYP2C9, CYP2C19, CYP3A4 and CYP1A2

In clinical studies, oral doses of 10-30 mg/day of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), 2C9 (warfarin), 2C19 (omeprazole), and 3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, Abilify Asimtufii is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

Antihypertensive agents

Due to its α_1-adrenergic receptor antagonistic activity, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Medicines which cause QT prolongation or electrolyte imbalance

If aripiprazole is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance, caution should be used.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Reproductive toxicity studies have not been performed on Abilify Asimtufii. The following information is taken from studies performed on oral aripiprazole, which showed that aripiprazole did not impair fertility in reproductive toxicity studies.

Aripiprazole had no effect on fertility in female rats treated orally with 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the oral maximum recommended human dose (MRHD) of 30 mg/day based on mg/m^2) for 2 weeks prior to mating through gestation day 7. Drug-related effects (persistent dioestrus, and increased mating time, pre-implantation losses, and corpora lutea) observed at all doses were considered the result of perturbed oestrous cyclicity secondary to drug-mediated hyperprolactinaemia.

Aripiprazole had no effect on fertility in male rats treated with oral doses of 20, 40, and 60 mg/kg/day (6, 12, and 18 times the oral MRHD of 30 mg/day based on mg/m^2) for 9 weeks prior to mating through mating. Disturbances of spermatogenesis were seen at 60 mg/kg/day and prostatic atrophy was seen at 40 and 60 mg/kg/day.

Women of childbearing potential

Plasma exposure to aripiprazole after a single dose of Abilify Asimtufii is expected to remain for up to 34 weeks (see section 5.2). This should be taken into account when initiating treatment in women of childbearing potential, considering a possible future pregnancy or breast-feeding. Abilify Asimtufii should only be used in women planning to become pregnant if clearly necessary.

Use in pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of aripiprazole in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Patients must be advised to notify their doctors if they become pregnant or intend to become pregnant during treatment with aripiprazole.

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits. Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 9 times the oral Maximum Recommended Human Dose [MRHD] of 30 mg/day on a mg/m^2 basis) of aripiprazole during the period of organogenesis. At 30 mg/kg in the rat, treatment was associated with slightly prolonged gestation, and a slight delay in fetal development, as evidenced by decreased fetal weight, undescended testes, and delayed skeletal ossification. There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights, and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for

these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses and increased post implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2-, 3-, and 11-times human exposure at the oral MRHD of 30 mg/day based on AUC) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 100 mg/kg), and minor skeletal variations (100 mg/kg).

Rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 9 times the oral MRHD of 30 mg/day on a mg/m^2 basis) of aripiprazole from late gestation through weaning. At 30 mg/kg, maternal toxicity, slightly prolonged gestation, an increase in stillbirths, poor postnatal care/nursing, and decreases in pup weight (persisting into adulthood) and survival were seen.

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including aripiprazole) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-marketing reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited; in other cases neonates have required additional medical treatment or monitoring.

Abilify Asimtufii should be used during pregnancy only if the anticipated benefit to the mother outweighs the potential risk to the fetus and the administered dose and duration of treatment should be as low and as short as possible.

Use in labour and delivery

The effect of aripiprazole on labour and delivery in humans is unknown.

Use in lactation

Aripiprazole has been found in human breast milk. Patients should be advised not to breastfeed if they are taking Abilify Asimtufii.

In rats, there were adverse effects in dams and offspring following daily oral administration of aripiprazole from late gestation through weaning. See 4.6 Fertility, pregnancy and lactation - Use in pregnancy.

4.7 Effects on ability to drive and use machines

Abilify Asimtufii, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that Abilify Asimtufii therapy does not affect them adversely.

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (Undesirable effects)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/safety/reporting-problems.

In a 32-week open-label study of Abilify Asimtufii in adult patients with schizophrenia or bipolar I disorder, 266 patients were randomised to receive either Abilify Asimtufii 960 mg (132 patients) or Abilify Maintena 400 mg (134 patients). A total of 132 patients received at least one injection of Abilify Asimtufii, a total of 114 patients received at least two consecutive injections (4 months treatment) of Abilify Asimtufii, and a total of 104 patients received at least four consecutive injections (8 months treatment) of Abilify Asimtufii. Of the total 266 patients receiving Abilify Asimtufii 960 mg or Abilify Maintena 400 mg, 185 had schizophrenia and 81 had bipolar I disorder.

The most frequently observed treatment-emergent adverse events (TEAEs) reported in patients with schizophrenia and bipolar I disorder treated with Abilify Asimtufii during clinical studies were weight increased (22.7%), injection site pain (18.2%), akathisia (9.8%), anxiety (8.3%), headache (7.6%), insomnia (7.6%), and constipation (6.1%).

The incidences of the TEAEs associated with Abilify Asimtufii and Abilify Maintena are tabulated below (Table 3). The table is based on total number of TEAEs reported during the open-label study at a frequency of ≥2% of patients.

Table 3 Incidence of Treatment-Emergent Adverse Events Occurring in Greater Than or Equal to 2% of Total Number of Subjects in Either Product Group, by SOC and MedDRA Preferred Term

System Organ Class MedDRA Preferred Term	Aripiprazole 2M LAI 960 mg			Aripiprazole IM depot 400 mg		
	Schizophrenia (N=92)	Bipolar I Disorder (N=40)	Total (N=132)	Schizophrenia (N=93)	Bipolar I Disorder (N=41)	Total (N=134)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal Disorder						
Abdominal discomfort	1 (1.1)	2 (5.0)	3 (2.3)	3 (3.2)	2 (4.9)	5 (3.7)
Constipation	4 (4.3)	4 (10.0)	8 (6.1)	5 (5.4)	3 (7.3)	8 (6.0)
Diarrhea	1 (1.1)	5 (12.5)	6 (4.5)	0 (0.0)	1 (2.4)	1 (0.7)
Dyspepsia	2 (2.2)	1 (2.5)	3 (2.3)	3 (3.2)	0 (0.0)	3 (2.2)
Nausea	2 (2.2)	2 (5.0)	4 (3.0)	0 (0.0)	1 (2.4)	1 (0.7)
Toothache	0 (0.0)	2 (5.0)	2 (1.5)	4 (4.3)	6 (14.6)	10 (7.5)
Vomiting	2 (2.2)	1 (2.5)	3 (2.3)	1 (1.1)	0 (0.0)	1 (0.7)
General Disorders and Administration Site Conditions						

Influenza like illness	2 (2.2)	1 (2.5)	3 (2.3)	0 (0.0)	2 (4.9)	2 (1.5)
Injection site pain	14 (15.2)	10 (25.0)	24 (18.2)	9 (9.7)	3 (7.3)	12 (9.0)
Infections and Infestations						
Nasopharyngitis	1 (1.1)	1 (2.5)	2 (1.5)	2 (2.2)	2 (4.9)	4 (3.0)
Sinusitis	1 (1.1)	2 (5.0)	3 (2.3)	2 (2.2)	0 (0.0)	2 (1.5)
Upper respiratory tract infection	5 (5.4)	1 (2.5)	6 (4.5)	2 (2.2)	0 (0.0)	2 (1.5)
Investigations						
Blood creatinine phosphokinase increased	3 (3.3)	0 (0.0)	3 (2.3)	1 (1.1)	1 (2.4)	2 (1.5)
Weight decreased	2 (2.2)	0 (0.0)	2 (1.5)	1 (1.1)	2 (4.9)	3 (2.2)
Weight increased	20 (21.7)	10 (25.0)	30 (22.7)	17 (18.3)	11 (26.8)	28 (20.9)
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	2 (2.2)	1 (2.5)	3 (2.3)	0 (0.0)	1 (2.4)	1 (0.7)
Back pain	3 (3.3)	2 (5.0)	5 (3.8)	3 (3.2)	1 (2.4)	4 (3.0)
Muscle spasms	2 (2.2)	1 (2.5)	3 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal pain	3 (3.3)	0 (0.0)	3 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders						
Akathisia	8 (8.7)	5 (12.5)	13 (9.8)	7 (7.5)	5 (12.2)	12 (9.0)
Dyskinesia	1 (1.1)	3 (7.5)	4 (3.0)	1 (1.1)	1 (2.4)	2 (1.5)
Headache	6 (6.5)	4 (10.0)	10 (7.6)	2 (2.2)	3 (7.3)	5 (3.7)
Somnolence	3 (3.3)	3 (7.5)	6 (4.5)	4 (4.3)	0 (0.0)	4 (3.0)
Tremor	0 (0.0)	1 (2.5)	1 (0.8)	3 (3.2)	1 (2.4)	4 (3.0)
Psychiatric Disorders						
Anxiety	6 (6.5)	5 (12.5)	11 (8.3)	5 (5.4)	5 (12.2)	10 (7.5)
Insomnia	8 (8.7)	2 (5.0)	10 (7.6)	8 (8.6)	3 (7.3)	11 (8.2)
Restlessness	2 (2.2)	1 (2.5)	3 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Schizophrenia	5 (5.4)	0 (0.0)	5 (3.8)	2 (2.2)	0 (0.0)	2 (1.5)
Vascular Disorders						
Hypertension	2 (2.2)	0 (0.0)	2 (1.5)	5 (5.4)	1 (2.4)	6 (4.5)

33In addition to the evaluation of safety for Abilify Asimtufii, Abilify Maintena administered once monthly has been evaluated for safety in 3,453 adult patients in clinical trials in schizophrenia and bipolar I disorder. Of the 3,453 adult patients exposed to Abilify Maintena, 2,567 patients have been treated with Abilify Maintena 400 mg/300 mg. Of the 3,453 patients

exposed to Abilify Maintena 1,226 patients have received at least 13 injections Abilify Maintena 400 mg/300 mg injections (i.e., have been treated for at least 12 months).

Prior to these studies Abilify has been evaluated for safety in 1,3543 patients who participated in multiple-dose clinical trials across all approved indications including schizophrenia and bipolar I disorder, and who had approximately 7,619 patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole short acting injection. A total of 3,390 patients were treated with oral aripiprazole for at least 180 days and 1,933 patients treated with oral aripiprazole had at least 1 year of exposure.

Adult patients with Schizophrenia

Abilify Maintena administered once monthly has been evaluated for safety in clinical trials in adult patients with schizophrenia. Of the 2,649 adult patients exposed to aripiprazole long-acting injectable, 2,567 patients have been treated with Abilify Maintena 400/300 mg.

The most frequently observed treatment-emergent adverse events (TEAEs) reported in ≥5% of patients treated with Abilify Maintena 300-400 mg in the two double-blind long-term clinical trials were insomnia (10.9%), weight increased (9.4%), akathisia (8.1%), headache (7.9%), anxiety (6.6%), decreased weight (6.6%), nasopharyngitis (5.8%), and injection site pain (5.2%). Overall, treatment emergent adverse events (TEAEs) were similar to placebo and the majority were mild to moderate in severity. The TEAEs that occurred in the two double-blind long-term clinical trials with Abilify Maintena at a frequency of ≥2% are listed in **Table 4**.

Table 4 Treatment–emergent Adverse Events (TEAE) Reported for ≥2% of Patients with Schizophrenia in Both Placebo- and Active-controlled Long-term Clinical Trials

System Organ Class MedDRA Preferred Term	ABILIFY MAINTENA™ 400 mg/300 mg (N = 534)	Oral Aripiprazole 10-30 mg (N = 266)	Aripiprazole IM Depot 50 mg/25 mg (N = 131)	Placebo (N = 134)
	n (%)	n (%)	n (%)	n (%)
Any TEAE	**389 (72.8)**	**213 (80.1)**	**106 (80.9)**	**83 (61.9)**
Gastrointestinal Disorders				
Abdominal pain upper	4 (0.7)	4 (1.5)	3 (2.3)	0 (0.0)
Diarrhea	15 (2.8)	9 (3.4)	6 (4.6)	3 (2.2)
Nausea	10 (1.9)	4 (1.5)	3 (2.3)	2 (1.5)
Toothache	14 (2.6)	13 (4.9)	3 (2.3)	3 (2.2)
Vomiting	12 (2.2)	4 (1.5)	1 (0.8)	3 (2.2)
General Disorders and Administration Site Conditions				
Fatigue	11 (2.1)	9 (3.4)	2 (1.5)	1 (0.7)

System Organ Class MedDRA Preferred Term	ABILIFY MAINTENA™ 400 mg/300 mg (N = 534)	Oral Aripiprazole 10-30 mg (N = 266)	Aripiprazole IM Depot 50 mg/25 mg (N = 131)	Placebo (N = 134)
	n (%)	n (%)	n (%)	n (%)
Any TEAE	**389 (72.8)**	**213 (80.1)**	**106 (80.9)**	**83 (61.9)**
Injection site pain	28 (5.2)	6 (2.3)	1 (0.8)	5 (3.7)
Oedema peripheral	4 (0.7)	3 (1.1)	3 (2.3)	3 (2.2)
Infections and Infestations				
Bronchitis	7 (1.3)	5 (1.9)	5 (3.8)	2 (1.5)
Influenza	16 (3.0)	11 (4.1)	7 (5.3)	2 (1.5)
Nasopharyngitis	31 (5.8)	25 (9.4)	9 (6.9)	7 (5.2)
Pharyngitis	5 (0.9)	0 (0.0)	3 (2.3)	1 (0.7)
Upper respiratory tract infection	25 (4.7)	11 (4.1)	5 (3.8)	3 (2.2)
Investigations				
Blood creatine phosphokinase increased	10 (1.9)	6 (2.3)	5 (3.8)	2 (1.5)
Blood pressure increased	6 (1.1)	1 (0.4)	0 (0.0)	3 (2.2)
Weight decreased	35 (6.6)	16 (6.0)	12 (9.2)	4 (3.0)
Weight increased	50 (9.4)	35 (13.2)	7 (5.3)	13 (9.7)
Metabolism and Nutrition Disorders				
Decreased appetite	6 (1.1)	1 (0.4)	3 (2.3)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	15 (2.8)	4 (1.5)	0 (0.0)	1 (0.7)
Back pain	16 (3.0)	14 (5.3)	15 (11.5)	3 (2.2)
Pain in extremity	11 (2.1)	7 (2.6)	2 (1.5)	6 (4.5)
Nervous System Disorders				
Akathisia	43 (8.1)	18 (6.8)	11 (8.4)	8 (6.0)
Dizziness	14 (2.6)	6 (2.3)	2 (1.5)	4 (3.0)
Headache	42 (7.9)	30 (11.3)	7 (5.3)	7 (5.2)
Sedation	13 (2.4)	3 (1.1)	1 (0.8)	1 (0.7)
Somnolence	14 (2.6)	12 (4.5)	2 (1.5)	1 (0.7)

System Organ Class MedDRA Preferred Term	ABILIFY MAINTENA™ 400 mg/300 mg (N = 534)	Oral Aripiprazole 10-30 mg (N = 266)	Aripiprazole IM Depot 50 mg/25 mg (N = 131)	Placebo (N = 134)
	n (%)	n (%)	n (%)	n (%)
Any TEAE	**389 (72.8)**	**213 (80.1)**	**106 (80.9)**	**83 (61.9)**
Tremor	24 (4.5)	9 (3.4)	6 (4.6)	2 (1.5)
Psychiatric Disorders				
Agitation	9 (1.7)	2 (0.8)	0 (0.0)	3 (2.2)
Anxiety	35 (6.6)	13 (4.9)	10 (7.6)	10 (7.5)
Depression	7 (1.3)	3 (1.1)	0 (0.0)	3 (2.2)
Insomnia	58 (10.9)	37 (13.9)	18 (13.7)	12 (9.0)
Psychotic disorder	16 (3.0)	8 (3.0)	8 (6.1)	9 (6.7)
Restlessness	16 (3.0)	4 (1.5)	4 (3.1)	3 (2.2)
Schizophrenia	10 (1.9)	5 (1.9)	10 (7.6)	5 (3.7)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	14 (2.6)	7 (2.6)	5 (3.8)	4 (3.0)
Nasal congestion	3 (0.6)	1 (0.4)	1 (0.8)	3 (2.2)
Vascular Disorders				
Rash	2 (0.4)	4 (1.5)	4 (3.1)	1 (0.7)
Hypertension	7 (1.3)	4 (1.5)	4 (3.1)	3 (2.2)

Adult patients with Bipolar I Disorder

Abilify Maintena administered once monthly has been evaluated for safety in clinical trials in 804 adult patients with bipolar I disorder.

In a double-blind, placebo-controlled, randomized withdrawal (maintenance) study, the most frequently observed TEAEs that were reported in ≥ 5 % of patients receiving Abilify Maintena and with a greater frequency than in the placebo group were weight increased (23.5%), akathisia (21.2%), insomnia (7.6%) and anxiety (6.8%).

Table 5 Incidence of Treatment–emergent Adverse Events Occurring in ≥ 2% of Aripiprazole IM Depot Patients and Greater than Placebo in the Placebo-controlled Phase of the Double-blind Trial in Adult Patients with Bipolar I Disorder

System Organ Class MedDRA Preferred Term	Aripiprazole IM Depot (N=132) n (%)	Placebo (N=133) n (%)
Subject With Any Treatment Emergent Adverse Events	101 (76.5)	107 (80.5)

System Organ Class MedDRA Preferred Term	Aripiprazole IM Depot (N=132) n (%)	Placebo (N=133) n (%)
Blood and Lymphatic System Disorders		
Anaemia	3 (2.3)	0 (0.0)
Eye Disorders		
Vision Blurred	3 (2.3)	0 (0.0)
Gastrointestinal Disorders		
Constipation	4 (3.0)	4 (3.0)
Dry Mouth	4 (3.0)	3 (2.3)
Salivary Hypersecretion	3 (2.3)	3 (2.3)
Infections and Infestations		
Bronchitis	3 (2.3)	2 (1.5)
Influenza	3 (2.3)	2 (1.5)
Sinusitis	5 (3.8)	1 (0.8)
Urinary Tract Infection	4 (3.0)	2 (1.5)
Injury, Poisoning and Procedural Complications		
Procedural Pain	4 (3.0)	1 (0.8)
Investigations		
Blood Creatine Phosphokinase Increased	3 (2.3)	1 (0.8)
Weight Increased	31 (23.5)	24 (18.0)
Metabolism and Nutrition Disorders		
Increased Appetite	4 (3.0)	1 (0.8)
Nervous System Disorders		
Akathisia	28 (21.2)	17 (12.8)
Somnolence	6 (4.5)	1 (0.8)
Tremor	3 (2.3)	2 (1.5)
Psychiatric Disorders		
Anxiety	9 (6.8)	6 (4.5)
Bipolar Disorder	5 (3.8)	5 (3.8)
Depression	4 (3.0)	3 (2.3)
Insomnia	10 (7.6)	10 (7.5)
Libido Decreased	3 (2.3)	2 (1.5)
Restlessness	6 (4.5)	5 (3.8)

Injection Site Adverse Events

The percentage of patients in the open-label study reporting any injection site-related adverse reaction (all reported as injection site pain) was 18.2 % for patients treated with Abilify Asimtufii 960 mg and 9.0 % for patients treated with Abilify Maintena 400 mg. In both treatment groups, the majority of the reported injection site pain occurred with the first injection of Abilify Asimtufii 960 mg patients (21 of 24 patients) or Abilify Maintena 400 mg (7 of

12 patients), resolved within 5 days, and were reported with decreasing frequency and severity upon subsequent injections. The overall mean site visual analogue scale scores (0 = no pain to 100 = unbearably painful) for patient reported rating of pain were similar in both treatment groups at the last injection: 0.8 pre-dose and 1.4 post-dose for the Abilify Asimtufii 960 mg group compared to 0.9 pre-dose and 1.3 post-dose for the Abilify Maintena 400 mg group.

Leukopenia

Neutropenia was reported in the clinical program with Abilify Maintena and typically started around day 16 after first injection and lasted a median of 18 days.

Extrapyramidal Symptoms (EPS)

Data from the open-label study of patients treated with Abilify Asimtufii, showed minimal change from baseline in EPS scores, as assessed by the Simpson-Angus Rating scale (SAS), the Abnormal Involuntary Movement Scale (AIMS) and the Barnes Akathisia Rating Scale (BARS). The incidence of reported EPS-related events for patients treated with Abilify Asimtufii was 18.2 % compared to the incidence of patients treated with Abilify Maintena, which was 13.4 %.

In trials in stable patients with schizophrenia, Abilify Maintena was associated with a higher frequency of EPS symptoms (18.4 %) than oral aripiprazole treatment (11.7 %). Akathisia was the most frequently observed symptom (8.2 %) and typically started around Day 10 after first injection and lasted a median of 56 days. Subjects with akathisia typically received anti-cholinergic medicines as treatment, primarily benzatropine mesilate and trihexyphenidyl. Less often substances such as propranolol and benzodiazepines (clonazepam and diazepam) were administered to control akathisia. Parkinsonism events followed at frequencies of 6.9 % for Abilify Maintena, 4.1 % for oral aripiprazole 10 mg to 30 mg tablets and 3.0% for placebo, respectively.

During the double-blind, placebo-controlled phase of the bipolar I disorder trial, 36/132 (27.3%) Abilify Maintena-treated subjects and 22/133 (16.5%) placebo-treated subjects had treatment-emergent EPS and EPS-related AEs. In the Abilify Maintena (vs. placebo) group, EPS and EPS-related events reported by ≥ 2% of subjects were akathisia and psychomotor hyperactivity events (22.0% vs 12.8%), parkinsonism events (5.3% vs 3.8%), dyskinetic (2.3% vs 1.5%), and dystonic events (2.3% vs 0.0%).

The most frequently reported treatment-emergent EPS and EPS-related AE was akathisia with 28/132 (21.2%) Abilify Maintena-treated subjects and 17/133 (12.8%) placebo-treated subjects experiencing an event. One Abilify Maintena-treated and no placebo-treated subjects experienced an SAE of akathisia and 2 Abilify Maintena-treated subjects were discontinued due to akathisia. There were no other EPS-related SAEs and no other TEAEs leading to discontinuation reported.

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with

high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Weight

In an open-label, multiple-dose, randomised study in adult patients with schizophrenia (and bipolar I disorder) in which the highest dose of Abilify Asimtufii 960 mg was evaluated against Abilify Maintena 400 mg, the overall incidence of weight gain ≥ 7 % from baseline (start of study) to end of study was comparable between Abilify Asimtufii *(*40.6 %) and Abilify Maintena *(*42.9 %). The mean change in body weight from baseline to last visit was 3.6 kg for Abilify Asimtufii 960 mg and 3.0 kg for Abilify Maintena 400 mg.

During the double-blind, active-controlled phase of the 38-week long-term relapse prevention trial, the incidence of weight gain of ≥ 7 % from baseline (randomisation) to last visit was 9.5 % for Abilify Maintena and 11.7 % for the oral aripiprazole tablets 10 mg to 30 mg. The incidence of weight loss of ≥ 7 % from baseline to last visit was 10.2 % for Abilify Maintena and 4.5 % for oral aripiprazole tablets 10 mg to 30 mg. During the double-blind, placebo-controlled phase of the 52-week long-term trial, the incidence of weight gain of ≥ 7 % from baseline to last visit was 6.4 % for Abilify Maintena and 5.2 % for placebo. The incidence of weight loss of ≥ 7 % from baseline to last visit was 6.4 % for Abilify Maintena and 6.7 % for placebo. During double-blind treatment, mean change in body weight from baseline to last visit was −0.2 kg for Abilify Maintena and −0.4 kg for placebo (p = 0.812).

During the double-blind, placebo-controlled phase of the bipolar I disorder trial, the incidence of weight gain ≥ 7% at any time was 18.0% in the Abilify Maintena group and 12.9% for the placebo group; the incidence of weight loss ≥ 7% at any time was 9.4% in the Abilify Maintena group and 12.1% in the placebo group. At the last visit, the incidence of potentially clinically relevant weight gain was 13.3% in the Abilify Maintena group and 12.1% in the placebo group; the incidence of weight loss ≥ 7% at last visit was 5.5% in the Abilify Maintena group and 10.6% in the placebo group. The mean change (SD) from baseline at Week 52 was 1.3 (5.9) kg for the Abilify Maintena group and 1.5 (6.1) kg for the placebo group; at the last visit, the mean change from baseline was 0.9 (5.3) kg for the Abilify Maintena group and 0.0 (5.9) kg for the placebo group.

Patients should have baseline and periodic monitoring of body weight, and other cardiometabolic parameters, including fasting glucose, full lipid profile and blood pressure, during treatment with any atypical antipsychotic including Abilify Maintena.

Laboratory Tests

No clinically relevant mean changes from baseline in serum chemistry, haematology, urinalysis or other laboratory test (e.g., insulin, fasting insulin) results were observed during the acute or long-term clinical trials with Abilify Maintena.

Comparisons between oral aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters revealed no medically important differences. Elevations of CPK (creatine phosphokinase), generally transient and asymptomatic, were observed in 3.5% of patients treated with oral aripiprazole as compared to 2.0% of patients treated with placebo.

QT Interval

During double-blind treatment in the long-term trials, 1/534 (0.2%) Abilify Maintena subject had a treatment-emergent adverse event related to QT interval change (prolonged ECG QT).

Prolactin

In clinical trials for the approved indications and in post-marketing data of Abilify Maintena, both increase and decrease in serum prolactin as compared to baseline was observed with aripiprazole (section 5.1 Pharmacodynamic properties).

In the double-blind, active-controlled phase of the 38-week trial, from baseline to last visit there was a mean decrease in prolactin levels in the Abilify Maintena group (−0.33 ng/mL) compared with a mean increase in the oral aripiprazole tablets 10-30 mg group (0.79 ng/mL; $p<0.01$). The incidence for Abilify Maintena patients with prolactin levels >1 time the upper limit of normal (ULN) range at any assessment was 5.4% compared with 3.5% of oral aripiprazole tablets 10-30 mg, with a higher incidence in male patients than female patients in each treatment group.

In the double-blind, placebo-controlled phase of the 52-week trial in schizophrenia, from baseline to last visit, there was a mean decrease in prolactin levels in the Abilify Maintena group (−0.38 ng/mL) compared with a mean increase in the placebo group (1.67 ng/mL). The incidence of Abilify Maintena patients with prolactin levels >1 time the ULN was 1.9% compared to 7.1% for placebo patients.

Of note, differences in the mean (± SD) change from the double-blind treatment phase baseline to the last visit of the double-blind treatment phase in prolactin were negligible between the Abilify Maintena and placebo groups and of little if any clinical relevance, indicating no implications for adverse effects on prolactin.

In the double-blind, placebo-controlled phase of the bipolar I disorder trial, the mean changes from baseline to last visit in prolactin were minimal in the Abilify Maintena 400 mg/300 mg group (0.15 ng/mL) compared to placebo (3.00 ng/mL) and none of the changes were considered to be clinically meaningful. There were no clinically meaningful differences in the incidence of prolactin levels above the ULN between treatment groups and no incidence of > 3 × ULN reported during the double-blind, phase of this trial. No clinically meaningful differences in shifts in prolactin between treatment groups or gender were reported. During the double-blind phase, no Abilify Maintena-treated and 0.8% of placebo-treated subjects experienced the prolactin-related TEAE of hyperprolactinaemia.

Lipid Parameters

In the two double-blind studies of 38 and 52 weeks' duration, the differences in the mean change from baseline (double-blind treatment phase) to the last visit in fasting lipid parameter values (total cholesterol, triglycerides, HDL, and LDL) were negligible between the Abilify Maintena 400 mg/300 mg group compared with oral aripiprazole tablets 10-30 mg group, aripiprazole IM depot 50 mg/25 mg group or placebo groups and could be considered as of no major clinical concern.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Abilify Maintena

All reported events in the Abilify Maintena group during the randomisation phase of the clinical trials, reported by less than 2% of subjects, and at least as frequently as in the placebo group are listed below.

Blood and Lymphatic System Disorders

Anaemia, bicytopenia, leukopenia, lymphadenopathy, neutropenia, thrombocytopenia.

Cardiac Disorders

Acute myocardial infarction, atrial fibrillation, bradycardia, cardio-respiratory arrest, first degree atrioventricular blocks, cardiac failure congestive, ventricular extrasystoles.

Ear and Labyrinth disorders

Deafness, tinnitus, vertigo.

Eye Disorders

Conjunctivitis allergic, eye irritation, eye pain, eyelid ptosis, oculogyric crisis, photophobia, vision blurred.

Gastrointestinal disorders

Abdominal distension, abdominal pain, abdominal pain upper, anorectal discomfort, aphthous stomatitis, colitis, constipation, dental caries, diverticulum, dry mouth, dyspepsia, dysphagia, food poisoning, frequent bowel movements, gastritis, gastroesophageal reflux disease, gingival oedema, gingival pain, gingivitis, haemorrhoidal haemorrhage, haemorrhoids, inguinal hernia, loose tooth, nausea, oral discomfort, periodontitis, poor dental condition, salivary hypersecretion, tongue disorder, tooth impacted, tooth loss, vomiting.

General disorders and administration site conditions

Asthenia, chest discomfort, gait disturbance, influenza-like illness, infusion site haematoma, infusion site swelling, injection related reaction, injection site discomfort, injection site pruritus, injection site induration, injection site pain, injection site reaction, injection site swelling, lethargy, night sweats, oedema peripheral, pain, sluggishness, suprapubic pain, swollen tongue, thirst, vessel puncture site haematoma, vessel puncture site pain.

Hepatobiliary disorders

Cholecystitis chronic, cholelithiasis, hepatic cirrhosis, hepatic steatosis, hepatosplenomegaly.

Immune System Disorders

Drug hypersensitivity.

Infections and Infestations

Acarodermatitis, anal abscess, appendicitis perforated, breast cellulitis, chlamydial infection, cellulitis, cystitis, dermatitis, ear infection, Escherichia UTI, folliculitis, fungal infection, fungal skin infection, furuncle, gastroenteritis, gastroenteritis viral, herpes virus infection, herpes zoster, hordeoleum, impetigo, laryngitis, lice infestation, localised infection, mastitis, oral candidiasis, oropharyngitis fungal, otitis externa, otitis media, pharyngitis, pharyngitis streptococcal, pilonidal cyst, pneumonia, respiratory tract infection, sycosis barbae, trichomoniasis, viral rhinitis, subcutaneous abscess, tinea pedis, tooth abscess, tooth infection, urinary tract infections, vaginal infection, varicella, viral infection, viral upper respiratory tract infection, vulvovaginal mycotic infection.

Injury, poisoning and procedural complications
Accident, ankle fracture, arthropod bite, carbon monoxide poisoning, chest injury, contusion, drug toxicity, excoriation, face injury, fall, foot fracture, gunshot wound, injury, joint dislocation, joint sprain, laceration, multiple injuries, muscle injury, muscle oedema, muscle strain, procedural pain, radius fracture, skeletal injury, skin laceration, spinal column injury, thermal burn, tooth fracture, wound.

Investigations
Alkaline phosphatase increased, bilirubin increased, blood creatinine phosphokinase increased, blood insulin increased, cholesterol decreased, glucose decreased, glucose increased, lactate dehydrogenase increased, triglycerides decreased, triglycerides increased, electrocardiogram abnormal, electrocardiogram QT prolonged, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, electrocardiogram T wave inversion, gamma-glutamyltransferase increased, glucose urine present, glycosylated haemoglobin increased, heart rate decreased, hepatic enzyme increased, liver function test abnormal, liver function test increased, neutrophil count decreased, protein urine, waist circumference increased, white blood cell count decreased, white blood cells urine.

Metabolism and nutrition disorders
Appetite disorder, decreased appetite, diabetes mellitus, gout, hypercholesterolaemia, hyperglycaemia, hyperinsulinaemia, hyperlipidaemia, hypertriglyceridaemia, hyperuricaemia, hypoglycaemia, increased appetite, overweight, type 2 diabetes mellitus.

Musculoskeletal and connective tissue disorders
Arthritis, joint swelling, muscle rigidity, muscle haemorrhage, muscle spasm, muscle tightness, muscle twitching, musculoskeletal pain, myalgia, neck pain, nuchal rigidity, rotator cuff syndrome, sciatica, trismus.

Neoplasms benign malignant and unspecified
Basal cell carcinoma, breast fibroma, pancreatic carcinoma.

Nervous system disorders
Bradykinesia, brain injury, cogwheel rigidity, disturbance in attention, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypersomnia, hypoaesthesia, migraine, movement disorder, paraesthesia, parkinsonism, parosmia, poor quality sleep, post-traumatic neck syndrome, psychomotor hyperactivity, restless leg syndrome, sedation, sinus headache, syncope, tardive dyskinesia, tension headache, dizziness, transient ischaemic attack.

Psychiatric Disorders
Abnormal dreams, affect lability, apathy, bruxism, bulimia nervosa, delusion, dysphemia, dysphoria, hallucination auditory, hypersexuality, hypomania, hyposomnia, initial insomnia, irritability, libido decreased, middle insomnia, mood altered, nightmare, panic attack, panic reaction, psychomotor retardation, sleep disorder, social avoidant behaviour, somnambulism, suicidal ideation, suicide attempt, tension.

Renal and Urinary Disorders
Asymptomatic bacteriuria, glycosuria, hypertonic bladder, micturition urgency, nephrolithiasis, pollakiuria.

Reproductive system and breast disorders
Adnexa uteri pain, breast mass, breast tenderness, ejaculation delayed, erectile dysfunction, galactorrhoea, gynaecomastia, menorrhagia, ovarian cyst, sexual dysfunction, vulvovaginal dryness.

Respiratory Thoracic and Mediastinal disorders
Allergic sinusitis, acute respiratory distress syndrome, asthma, dysphonia, dyspnoea, epistaxis, nasal septum deviation, non-cardiac chest pain oropharyngeal pain, paranasal sinus hypersecretion, respiratory failure, respiratory tract congestion, rhinalgia, rhinitis allergic, sinus congestion, wheezing, hiccups.

Skin and Subcutaneous tissue disorders
Acne, blister, dermatitis contact, dry skin, eczema, erythema, hyperkeratosis, pityriasis, pruritus, psoriasis, rash, rash macula, rosacea, skin induration, skin lesion, skin striae, urticaria.

Social circumstances
Poor personal hygiene.

Vascular Disorders
Orthostatic hypertension.

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported during post-marketing surveillance with aripiprazole. The frequency of these reactions cannot be estimated from available post-marketing data and the causal relationship to the drug cannot be definitely established in the post-marketing scenario.

Blood and lymphatic system disorders

Leukopenia, neutropenia, thrombocytopenia, blood prolactin decrease.

Endocrine disorders

Hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma.

Metabolism and nutrition disorders

Anorexia, hyponatraemia.

Psychiatric disorders

Agitation, hypersexuality, pathological gambling, impulse-control disorders, obsessive-compulsive disorder, eating disorder.

Nervous system disorders

Speech disorder, grand mal convulsion.

Eye disorders

Diplopia.

Vascular disorders

Syncope, hypertension.

Respiratory, thoracic and mediastinal disorders

Aspiration pneumonia, hiccups.

Gastrointestinal disorders

Pancreatitis, dysphagia, diarrhoea.

Hepato-biliary disorders

Jaundice, hepatitis.

Skin and subcutaneous tissue disorders

Allergic reaction (e.g. anaphylactic reaction, angioedema, pruritus, or urticaria, rash, laryngospasm), hyperhidrosis, alopecia, drug reaction with eosinophilia and systemic symptoms (DRESS).

Musculoskeletal and connective tissue disorders

Rhabdomyolysis, myalgia, musculoskeletal stiffness.

Renal and urinary disorders

Urinary incontinence, urinary retention.

Reproductive system and breast disorders

Priapism.

General disorders and administration site conditions

Temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain.

Investigations

Blood creatine phosphokinase increased, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased, weight increased, weight decreased, Alanine Aminotransferase increased, Aspartate Aminotransferase increased, Gamma-glutamyltransferase increased.

Although a causal relationship has not been established, cases of suicide attempt, suicidal ideation, and completed suicide, have been reported post marketing.

Undesirable effects known to be associated with antipsychotic medication which have also been reported in association with aripiprazole are Neuroleptic Malignant Syndrome, tardive dyskinesia, and seizure.

Uncommon occurrences of depression and tachycardia have also been reported in association with aripiprazole.

4.9 Overdose

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

No cases of overdose associated with adverse reactions were reported in clinical studies with aripiprazole. Care must be taken to avoid inadvertent injection of this medicinal product into a blood vessel. Following any confirmed or suspected accidental overdose/inadvertent intravenous administration with aripiprazole, close observation of the patient is needed and if any potential medically serious sign or symptom develops, monitoring, which should include continuous eletrocardiographic monitoring is required. The medical supervision and monitoring should continue until the patient recovers.

The potential for inadvertent intravenous administration has been evaluated by simulation of aripiprazole plasma concentrations after an Abilify Asimtufii 960 mg dose is entirely absorbed in the systemic circulation. Based on the results of the simulation, if inadvertent intravenous administration would occur, aripiprazole concentrations may reach up to 13.5 times the concentrations that are achieved by a therapeutic dose of Abilify Asimtufii without inadvertent intravenous administration. Furthermore, aripiprazole concentrations following inadvertent intravenous administration would decline within 5 days to concentrations normally observed following the administration of Abilify Asimtufii 960 mg.

Signs and symptoms

In clinical trials and post-marketing experience, accidental or intentional acute overdose of aripiprazole alone was identified in adult patients with reported estimated doses up to 1,260 mg (42 times higher than the recommended daily aripiprazole dose, 30 mg) with no fatalities.

The potentially medically significant signs and symptoms observed in overdose included lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting and diarrhoea. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence, transient loss of consciousness and extrapyramidal symptoms.

Management of overdose

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation, and ventilation and management of symptoms. The possibility of multiple medicinal product involvement should be considered. Therefore, cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

Haemodialysis

Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management, since aripiprazole is highly bound to plasma proteins.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

The mechanism of action of aripiprazole, as well as other drugs having efficacy in schizophrenia and bipolar disorder, is unknown. It has been proposed that aripiprazole's

efficacy is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors.

Abilify Asimtufii activity is primarily due to the parent drug, aripiprazole. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.3, 0.8, 1.7, and 3.4 nM, respectively), and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, α1-adrenergic, and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61 nM, respectively). Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site (K_i value of 98 nM) but no appreciable affinity for muscarinic receptors (IC_{50}>1000 nM).

The predominant metabolite in human plasma, dehydro-aripiprazole, has been shown to have a similar affinity for dopamine D_2 and D_3 receptors (K_i values 0.4 and 0.5 nM, respectively) as the parent compound and a much lower affinity for the other receptor subtypes (serotonergic, noradrenergic and histaminergic receptors).

Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole oral doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of 11C-raclopride, a D_2 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical trials

Maintenance treatment of schizophrenia and bipolar I disorder in adults

The efficacy of Abilify Asimtufii administered once every 2 months, was established in part, on the basis of pharmacokinetic bridging through an open-label, multiple-dose, randomised, parallel-arm multi-centre bioequivalence study. The study demonstrated that Abilify Asimtufii 960 mg (n=132) provides similar aripiprazole concentrations, to Abilify Maintena 400 mg (n=134) over the dosing interval (see section 5.2).

The similarity of aripiprazole plasma concentrations between Abilify Asimtufii 960 mg to Abilify Maintena 400 mg are presented in Table 6.

Table 6 Geometric Mean Ratio and Confidence Interval Following the Fourth Administration of Abilify Asimtufii 960 mg or the Seventh and Eighth Administration of Abilify Maintena 400 mg in the Open-Label Study

Parameter	**Ratio** (Abilify Asimtufii 960 mg/ Abilify Maintena 400 mg)	**90% CI**
AUC_{0-56}*	1.006‡	0.851 - 1.190
C_{56}/C_{28}†	1.011§	0.893 - 1.145
C_{max} †	1.071‡	0.903 - 1.270

*****AUC_{0-56} following the fourth administration of Abilify Asimtufii 960 mg or the sum of AUC_{0-28} following the seventh and eighth administration of Abilify Maintena 400 mg.

†Aripiprazole plasma concentrations following the fourth administration of Abilify Asimtufii 960 mg (C_{56}) or the eighth administration of Abilify Maintena 400 mg (C_{28}).

‡Abilify Asimtufii 960 mg (n=34), Abilify Maintena 400 mg (n=32)

§Abilify Asimtufii 960 mg (n=96), Abilify Maintena 400 mg (n=82).

The effectiveness of Abilify Asimtufii in the treatment of schizophrenia and bipolar I disorder is further supported by the established effectiveness of Abilify Maintena, as summarized below:

Efficacy of Abilify Maintena

Schizophrenia

The efficacy and safety of Abilify Maintena in the treatment of adult patients with schizophrenia was established in one pivotal short-term, randomised, double-blind, placebo-controlled trial in acutely relapsed patients and one pivotal long-term, randomised, double-blind, placebo-controlled trial.

Clinical Efficacy in the Acute Phase of Schizophrenia

The efficacy of Abilify Maintena in adult patients in the acute phase of schizophrenia was established in one short-term (12 weeks), randomised, double-blind, placebo-controlled trial. Patients included in this trial met DSM-IV-TR criteria for schizophrenia and must have experienced an acute psychotic episode as defined by both a PANSS total score ≥80 and a PANSS score >4 on each of four specific psychotic symptoms (conceptual disorganisation, hallucinatory behaviour, suspiciousness/persecution, unusual thought content) at baseline. Patients experiencing their first psychotic episode and those considered treatment resistant were excluded. Patients had a mean PANSS Total Score of 103 (range 82 to 144) and a CGI-S score of 5.2 (markedly to severely ill) at entry.

In this study patients were administered Abilify Maintena (n=167) or IM placebo (n=172) on Days 0, 28, and 56. The dose could be adjusted down and up within the range of 400 mg to 300 mg on a one-time basis. Patients who had not taken aripiprazole previously had tolerability with oral aripiprazole (10 mg daily for 3 days) established prior to initiating treatment with Abilify Maintena or placebo. Patients randomised to Abilify Maintena also received concomitant oral aripiprazole, 10 to 20 mg/day, for the first two weeks of the study.

In the Abilify Maintena group, for 96.4% of patients, there was no difference between the starting dose and ending dose of Abilify Maintena (400 mg).

The primary endpoint was the change from baseline to Week 10 in PANSS Total Score. Abilify Maintena was superior to placebo in improving the PANSS total score, with Week 10 scores of -26.8 and -11.7, respectively (see Table 7).

Table 7 Change from Baseline in PANSS Total Score at Week 10 in Acute Phase Schizophrenia Study

Treatment Group	Primary Efficacy Measure: PANSS Total Score[a]		
	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Treatment Difference[b] (95% CI)
Abilify Maintena 400 mg/300 mg	102.4 (11.4) N=162	-26.8 (1.6) N=99	-15.1 (-19.4, -10.8) p<0.0001
Placebo	103.4 (11.1) N=167	-11.7 (1.6) N=81	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a]Data were analysed using a mixed model for repeated measurements (MMRM) approach. The analysis included only patients who were randomly assigned to treatment, given at least one injection, had baseline and at least one post-baseline efficacy assessment.
[b]Difference (Abilify Maintena minus placebo) in LS mean change from baseline.

A statistically significant difference ($p \leq 0.0001$) was seen at each measured time point beginning at Week 1 and continuing through to study completion. The adjusted mean change in PANSS Total Score over time is shown in Figure 1.

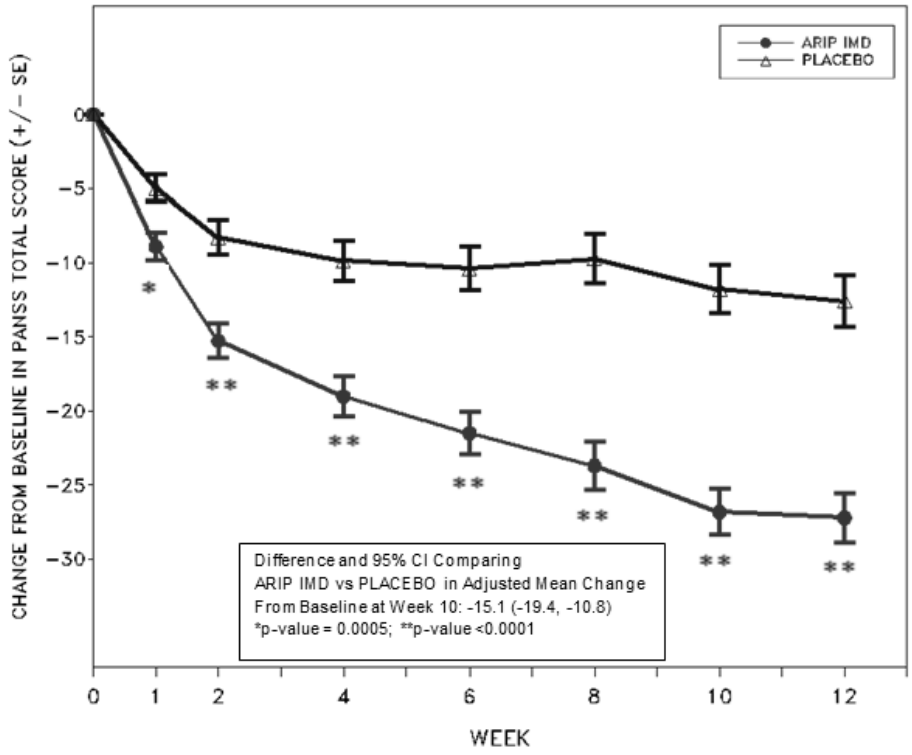


Figure 1 Adjusted Mean Change from Baseline in PANSS Total Score (MMRM)

For the key secondary endpoint, the change from baseline to Week 10 in CGI-S score, the treatment difference between the Abilify Maintena group (LS mean change −1.4) and the

placebo group (LS mean change −0.6) was −0.8 (95% CI: −1.1, −0.6), which was statistically significant (p<0.0001).

Response was defined as a ≥30% reduction from baseline in PANSS total score. The responder rate was numerically higher in the Abilify Maintena group at all post-baseline time points; the treatment differences were statistically significant (p≤0.0013) from Week 8 to Week 12 (see Figure 2). At Week 10, the responder rate was 37.0% in the Abilify Maintena group compared to 14.4% in the placebo group; the treatment difference was 22.7% (95% CI 12.9%, 32.4%).

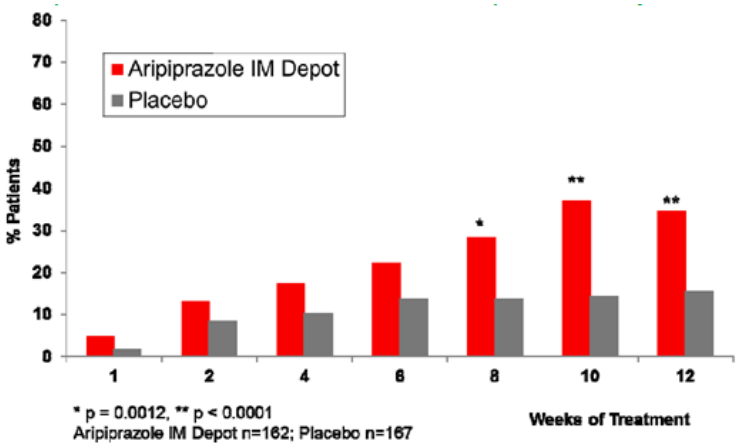


Figure 2 Responder Rate in the Acute Phase Schizophrenia Study

Clinical Efficacy in the Maintenance Phase of Schizophrenia

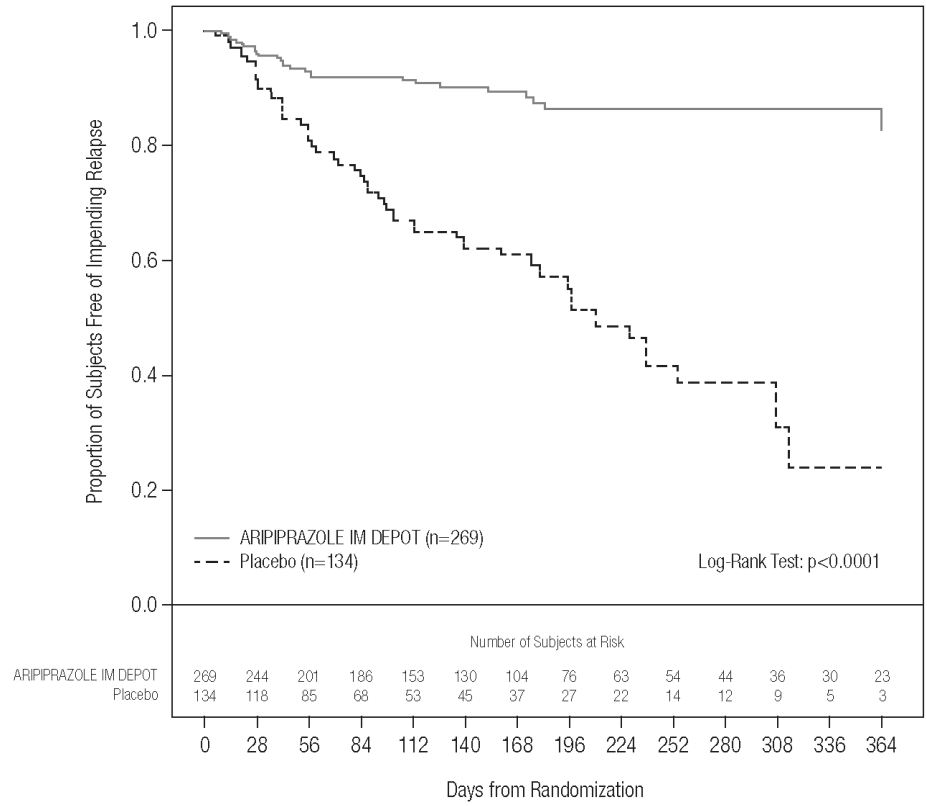
The pivotal trial was a 52-week, randomised, double-blind, placebo-controlled trial conducted in adult patients with a current diagnosis of schizophrenia. This trial consisted of a screening phase and four treatment phases: Conversion, Oral Stabilisation, Abilify Maintena Stabilisation, and Double-blind Placebo-controlled. Patients eligible for the double-blind, placebo-controlled phase were randomly assigned in a 2:1 ratio to double-blind treatment with Abilify Maintena 400 mg (with an option to decrease to 300 mg for tolerability reasons) or placebo, respectively. The trial was completed early as a consequence of the positive pre-specified interim analysis and therefore only 26 patients completed 52 weeks of treatment. Eighty-seven per cent (87%) of subjects randomised to the 400 mg dose remained on this dose until either completing the trial duration or withdrawing from the trial.

The final efficacy analysis included 403 randomised patients and 80 exacerbations of psychotic symptoms/impending relapse events. The trial was terminated early because efficacy was demonstrated by the pre-specified interim analysis. The hazard ratio from the Cox proportional hazard model for the placebo to Abilify Maintena comparison was 5.029 (95% CI: 3.154, 8.018), thus patients in the placebo group had a 5-fold greater risk of experiencing impending relapse than patients in the Abilify Maintena group. The trial results support the efficacy for Abilify Maintena over 52 weeks of treatment.

The Kaplan-Meier curves of the time from randomisation to impending relapse during the 52-week, double-blind treatment phase for Abilify Maintena and placebo groups are shown in Figure 3.

The percentage of patients meeting the impending relapse criteria was significantly lower (p<0.0001) in the Abilify Maintena group (10.0%) than in the placebo group (39.6%).

The time to impending relapse was significantly shorter (p<0.0001) for subjects in the placebo group compared with subjects in the Abilify Maintena group.



IM = Intramuscular

Figure 3 Kaplan-Meier Product Limit Plot of Time to Impending Relapse (Double-blind, Placebo-controlled Phase Efficacy Sample)

Further, the superiority of Abilify Maintena compared to placebo is supported by the results of the analysis of PANSS total score, PANSS Positive and Negative Subscales, CGI-S, CGI-I. During the double-blind phase, significant differences in mean PANSS total and CGI-S scores were observed.

Bipolar I Disorder

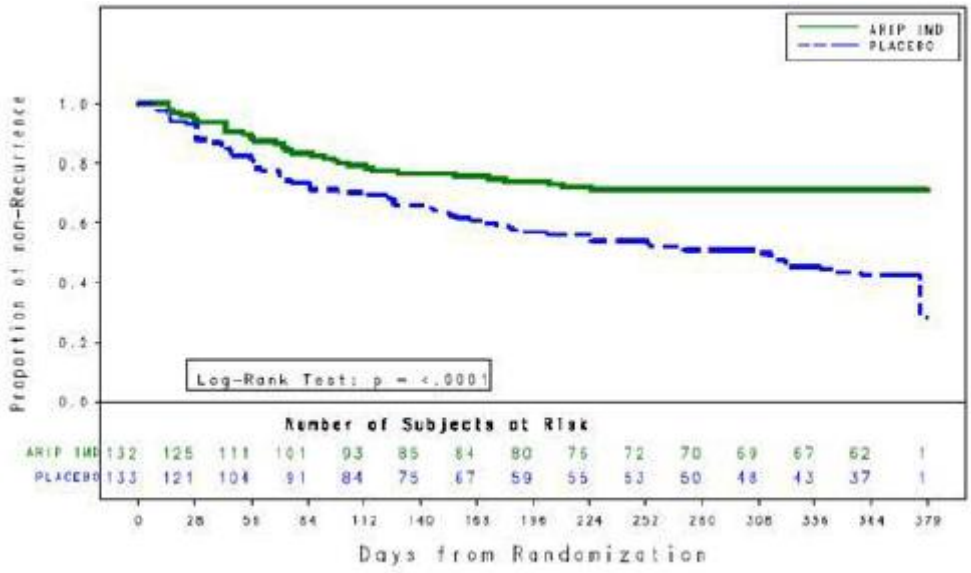
Clinical Efficacy in Prevention of Recurrence of Manic or Mixed Episodes of Bipolar 1 Disorder

The efficacy and safety of Abilify Maintena as treatment in adults aged 18 to 65 years was demonstrated in a 52-week, double-blind, placebo-controlled randomised withdrawal trial in patients who met DSM-IV-TR criteria for bipolar I disorder and who were experiencing a manic episode at trial entry. This trial consisted of a screening phase and 4 treatment phases: oral conversion, oral stabilization, Abilify Maintena stabilization, and a randomised, double-blind, placebo-controlled withdrawal phase.

Patients currently receiving oral treatment for their bipolar I disorder with medications other than aripiprazole monotherapy entered the oral conversion phase. In this phase, patients discontinued other treatments, such as mood stabilizers, antidepressants, or other antipsychotics over a period of 4 to 6 weeks and converted to aripiprazole monotherapy. Patients already treated with oral aripiprazole monotherapy at the time of trial entry and those subjects converted to oral aripiprazole monotherapy in the oral conversion phase proceeded to

the oral stabilization phase. Patients fulfilling the stabilization requirement were assigned to receive, in a single-blind fashion, Abilify Maintena 400 mg and began an IM depot stabilization phase for a minimum of 12 weeks and a maximum of 28 weeks. Patients who demonstrated stability for 8 consecutive weeks were randomised into the 52-week double-blind, placebo-controlled treatment phase. Of the 731 subjects who entered the trial, 466 subjects entered the conversion phase, 632 subjects entered the oral stabilization phase (including 265 subjects who entered the oral stabilization phase directly), and 425 subjects entered the IM depot stabilization phase. Stability was defined as: having achieved or maintained outpatient status; Young-Mania Rating Scale (YMRS) total score ≤ 12; Montgomery Asberg Depression Rating Scale (MADRS) total score ≤ 12 and no active suicidality; with active suicidality defined as a score of 4 or more on the MADRS Item 10 or an answer of "yes" on Question 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS).

The final efficacy analysis included 265 patients and the primary efficacy endpoint is shown in the Kaplan-Meier curves of the cumulative proportion of patients with recurrence of any mood episode (manic, mixed or depressive) during the 52-week, double-blind treatment phase for Abilify Maintena and placebo treatment groups (Figure 4). A total of 103 patients with recurrence of any mood episode were observed during the double-blind treatment phase: 35 occurred during Abilify Maintena treatment and 68 occurred during placebo treatment. The hazard ratio from the Cox proportional hazard model for the placebo to Abilify Maintena comparison was 2.220 (95% CI: 1.475, 3.340), thus patients receiving placebo had a 2.2-fold greater risk of experiencing a recurrence of a mood episode than patients receiving Abilify Maintena. These results support efficacy for Abilify Maintena over 52 weeks of treatment.



ARIP IMD= Aripiprazole IM depot

Figure 4 Kaplan-Meier Curves of Time to Recurrence for Any Mood Episode

For the key secondary endpoint, the percentage of patients meeting the criteria for recurrence of any mood episode (manic, mixed, depressive) was significantly lower (Fisher's exact test $p < 0.0001$) in the Abilify Maintena group (26.5%) compared with placebo (51.1%). The times to recurrence of manic, mixed, and mixed/manic mood episodes were statistically significantly delayed in the aripiprazole IM depot group compared with the placebo group, with the log-rank test p-values of < 0.0001, 0.0237, and < 0.0001, respectively. The time to recurrence of a

depressive mood episode showed no difference between the aripiprazole IM depot and placebo groups (p = 0.8247) (Table 8).

Table 8 Analysis of Time to Recurrence of a Manic, Depressive, or Mixed Mood Episode (Double-blind, Placebo-controlled Phase Efficacy Sample)

Mood Episode	Number of Subjects Treated	Number of Subjects With Recurrence	Recurrence Rate (%)	Median Time to Recurrence (Days)	Hazard Ratio[a]	95% CI	P-value[b]
Manic							
Aripiprazole IM Depot	132	12	9.1	NE	0.259[c]	(0.136, 0.495)	<0.0001
Placebo	133	40	30.1	377	3.856[d]	(2.020, 7.358)	
Depressive							
Aripiprazole IM Depot	132	20	15.2	NE	0.932[c]	(0.497, 1.747)	0.8247
Placebo	133	19	14.3	NE	1.073[d]	(0.572, 2.013)	
Mixed[e]							
Aripiprazole IM Depot	132	2	1.5	NE	0.202[c]	(0.044, 0.939)	0.0237
Placebo	133	9	6.8	NE	4.939[d]	(1.065, 22.904)	
Mixed/Manic[e]							
Aripiprazole IM Depot	132	14	10.6	NE	0.249[c]	(0.137, 0.451)	<0.0001
Placebo	133	49	36.8	377	4.017[d]	(2.216, 7.282)	

[a]The HR was derived from the Cox proportional hazard model with treatment as term.
[b]The p-value was derived from the log-rank test.
[c]HR < 1 is in favor of aripiprazole IM depot 400/300 mg group.
[d]HR > 1 is in favor of aripiprazole IM depot 400/300 mg group.
[e]Time to recurrence of a mixed mood or a mixed/manic mood episode are exploratory endpoints.

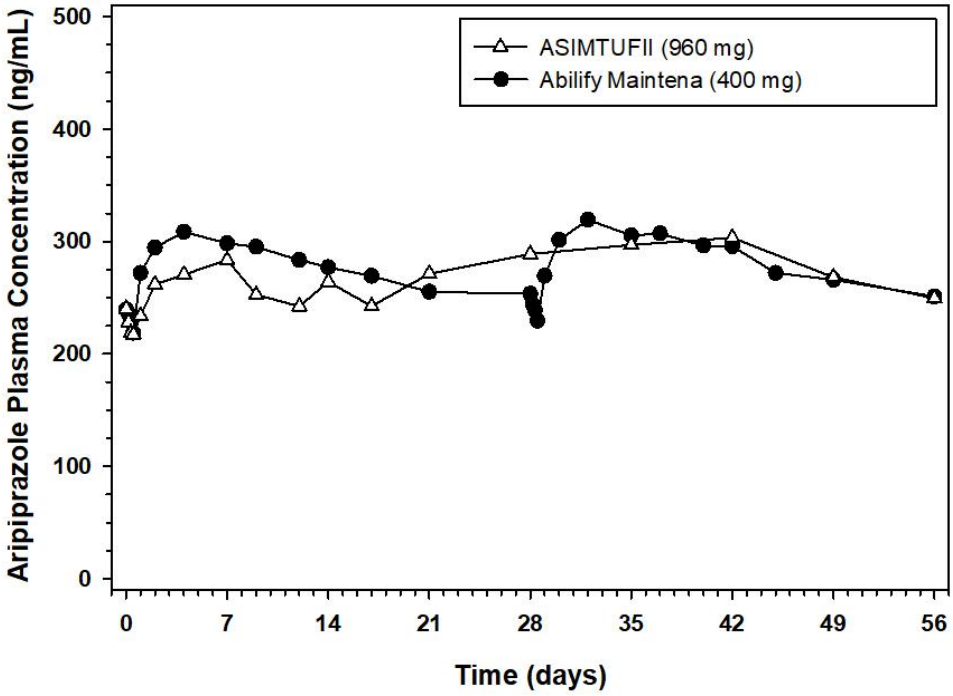
5.2 Pharmacokinetic properties

The pharmacokinetics of aripiprazole after administration of Abilify Asimtufii, presented below, are based on gluteal administration.

Abilify Asimtufii delivers aripiprazole over a 2-month period, compared to 1 month for Abilify Maintena. Abilify Asimtufii doses of 960 mg and 720 mg, administered in the gluteal muscle, result in aripiprazole total exposure ranges that are encompassed within the exposure range corresponding to 400 mg and 300 mg doses of Abilify Maintena (dosed once a month), respectively. Additionally, mean observed maximum plasma concentrations (C_{max}) and plasma concentrations of aripiprazole at the end of the dosing interval were similar for Abilify Asimtufii as compared to corresponding doses of Abilify Maintena (see section 5.1).

The mean aripiprazole plasma concentration compared to the time profiles following the fourth administration of Abilify Asimtufii 960 mg (n = 102) or the seventh and eighth administration of Abilify Maintena 400 mg (n = 93) in the gluteal muscle of patients with schizophrenia (and bipolar I disorder) are shown in Figure 5.

Figure 5 **Mean Aripiprazole plasma concentration vs. time profile following the fourth administration of Abilify Asimtufii 960 mg or the seventh and eighth administration of Abilify Maintena 400 mg***



Absorption

Aripiprazole absorption into the systemic circulation is slow and prolonged following Abilify Asimtufii administration due to the low solubility of aripiprazole particles.

The release profile of aripiprazole from Abilify Asimtufii results in sustained plasma concentrations over 2 months following gluteal injection(s). The release of the active substance after a single dose of 2-monthly aripiprazole injectable starts Day 1 and lasts for as long as 34 weeks. Following multiple doses, the median peak:trough ratio for aripiprazole following an Abilify Asimtufii dose is 1.3, resulting in a flat plasma concentration profile with T_{max} ranging between 1 to 49 days following multiple gluteal administrations of 960 mg.

Distribution

Based on results from trials with oral administration of aripiprazole, aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole is highly bound (88-97% to >99%, as determined by polydimethylsiloxane-glass bead and equilibrium dialysis assays, respectively) to serum proteins, primarily albumin, *in vitro*. Aripiprazole did not alter the pharmacokinetics and pharmacodynamics of highly protein-bound warfarin, suggesting that protein displacement of warfarin did not occur.

Metabolism

Aripiprazole undergoes minimal pre-systemic metabolism at the site of injection. Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are primarily responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant drug moiety in systemic circulation. After multiple dose administration of Abilify Asimtufii, dehydro-aripiprazole, the active metabolite represents approximately 30% of aripiprazole AUC in plasma.

Excretion

After administration of multiple doses of Abilify Asimtufii 960 mg or 720 mg, the estimated median aripiprazole terminal elimination half-life is 29.4 days, for both strengths.

Following a single oral dose of [^{14}C]-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged oral aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

Special Populations

No specific studies have been performed with Abilify Asimtufii in special patient groups.

CYP2D6 Poor Metabolisers

Based on population pharmacokinetic evaluation of Abilify Maintena, the total body clearance of aripiprazole was 3.71 L/h in extensive metabolisers of CYP2D6 (EMs) and approximately 1.88 L/h (approximately 50% lower) in poor metabolisers of CYP2D6 (PMs). For dose recommendations see 4.2 Dose and method of administration, Dosage in Special Populations - Known CYP2D6 Poor Metabolisers. Subjects were entered into clinical studies without knowledge of their metaboliser status and, therefore, the safety profile reflects experience in both EMs and PMs.

Elderly Patients

After oral administration of aripiprazole, there are no clinically relevant differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adults. Similarly, there was no detectable effect of age (18-61 year age range) in a population pharmacokinetic analysis of aripiprazole clinical trials in patients with schizophrenia.

Gender

After oral administration of aripiprazole, there are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects when differences in body weight are considered. Population pharmacokinetic analysis of aripiprazole revealed a difference in the predicted mean half-lives between men (24 days) and women (32 days) as well as a gender dependent absorption rate. At steady state (model predicted) however, the parameters of C_{min}, C_{max}, and $AUC_{o\text{-}tau}$ did not exhibit any trends towards gender.

Smoking

Population pharmacokinetic evaluation of oral aripiprazole has revealed no evidence of clinically relevant effects from smoking on the pharmacokinetics of aripiprazole.

Race

Population pharmacokinetic evaluation showed no evidence of race-related differences in the pharmacokinetics of aripiprazole.

Renal Impairment

In a single-dose study with oral administration of aripiprazole, the pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to those in young healthy subjects.

In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole.

Hepatic Impairment

A single-dose study with oral administration of aripiprazole to subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole. The AUC of aripiprazole, compared to healthy subjects, increased 31% in mild hepatic impairment, increased 8% in moderate hepatic impairment, and decreased 20% in severe hepatic impairment. None of these differences would require dose adjustment, but the study included only three patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity

5.3 Preclinical safety data

Animal toxicology

The toxicological profile for aripiprazole administered to experimental animals by intramuscular injection is generally similar to that seen following oral administration at comparable plasma levels of the drug. With intramuscular injection, however, injection-site tissue reactions are observed that consist of localised inflammation, swelling, scabbing and foreign-body reactions to deposited drug. In dogs, repeated intramuscular dosing of the 2-month aripiprazole prolonged- release injectable suspension over a period of 52 weeks produced no clinical evidence of significant local irritation, and resulted in slight foreign-body type of localized granulomatous inflammatory reaction to deposited drug at the injection site. These effects gradually resolved with discontinuation of dosing.

Choleliths observed in the bile of monkeys given aripiprazole orally at doses of 25 to 125 mg/kg/day for 4 to 52 weeks (1-3 times the oral MRHD of 30 mg/day based on plasma AUC and 15-76 times the oral MRHD based on mg/m^2) have been attributed to precipitation of sulfate conjugates of hydroxy metabolites, which exceeded their solubility limits in bile. Human biliary concentrations of these sulfate conjugates after repeated daily administration of the oral MRHD are substantially lower (0.2-14% of their in vitro solubility limits).

Bilateral retinal degeneration was observed in albino rats given oral aripiprazole for 6 months or 2 years at exposures of 6-13 times the clinical exposure at the oral MRHD of 30 mg/day (based on plasma AUC). The exposure at the no-effect dose was 3 times that at the MRHD. A subsequent 18-month study reported this finding in albino but not pigmented rats, possibly due to lack of photoprotective ocular melanin in the albino rats, although it is unknown whether

pigmentation prevented or merely delayed retinal degeneration in the pigmented rats. The clinical relevance of this finding is uncertain.

Genotoxicity

Aripiprazole was tested for genotoxic potential in a standard range of assays for gene mutation, chromosomal damage, and DNA damage and repair. Aripiprazole was nongenotoxic in the *in vitro* bacterial reverse mutation assay, in vitro forward gene mutation assay in mouse lymphoma cells, *in vitro* bacterial DNA repair assay, and the unscheduled DNA synthesis assay in rat hepatocytes. However, aripiprazole and its minor metabolite 2,3-DCPP were clastogenic in the *in vitro* chromosomal aberration assay in Chinese hamster lung cells with and without metabolic activation. A positive response in 1 of 6 *in vivo* mouse micronucleus tests was likely due to a mechanism not relevant to humans.

Carcinogenicity

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and Fischer (F344) rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the oral maximum recommended human dose [MRHD] of 30 mg/day based on mg/m^2, respectively). SD rats were dosed orally by gavage for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 18 times the MRHD based on mg/m^2). There was no evidence of tumorigenesis in male mice. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenocanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times the MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (<0.1 times the MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral gavage dose of 60 mg/kg/day (10 times the MRHD based on AUC and 18 times the MRHD based on mg/m^2). In male rats, the incidences of benign and combined benign/malignant phaeochromocytomas were also increased at an oral gavage dose of 60 mg/kg/day (10 times the MRHD based on AUC and 18 times the MRHD based on mg/m^2).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. At the doses associated with mammary and/or pituitary tumours, hyperprolactinaemia was observed in female mice in a 13-week dietary study but not in female rats in 4- and 13-week dietary studies. Hyperprolactinaemia was observed in female rats after 5 and 13 weeks of oral administration at doses up to that associated with adrenocortical tumours, but serum prolactin was decreased at this dose in male rats. The relationship between tumourigenic findings with aripiprazole and prolactin is unclear and the relevance for human risk of prolactin-mediated endocrine tumours is unknown. The adrenocortical response in female rats is considered a consequence of increased adrenocortical cell proliferation secondary to chronic drug-related adrenocortical cytotoxicity; the no-effect exposure (plasma AUC) was about 7 times clinical exposure at the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose sodium
Macrogol 400
Povidone
Sodium chloride
monobasic sodium phosphate monohydrate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products. In addition, refer to 4.5 Interactions with other medicines and other forms of interactions.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store in the original packaging below 25°C. Do not freeze.

For single use in only one patient. Discard any unused solution.

6.5 Nature and contents of container

Pre-filled syringe (cyclic-olefin-copolymer) with bromobutyl plunger stopper and bromobutyl tip-cap and polypropylene plunger rod and finger grip.

Pack size

Abilify Asimtufii 960 mg prolonged-release suspension for injection in pre-filled syringe

Each 960 mg pack contains one pre-filled syringe, and two sterile safety needles: one 38 mm (1.5 inch) 22 gauge and one 51 mm (2 inch) 21 gauge.

Abilify Asimtufii 720 mg prolonged-release suspension for injection in pre-filled syringe

Each 720 mg pack contains one pre-filled syringe, and two sterile safety needles: one 38 mm (1.5 inch) 22 gauge and one 51 mm (2 inch) 21 gauge.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

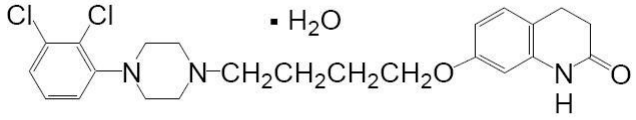
6.7 Physicochemical properties

Aripiprazole is present in Abilify Asimtufii as aripiprazole monohydrate. The chemical name of aripiprazole monohydrate is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-carbostyril monohydrate. The molecular formula is $C_{23}H_{27}Cl_2N_3O_2.H_2O$ and its

molecular weight is 466.40. Aripiprazole monohydrate is a white-to-off-white crystalline powder. Aripiprazole monohydrate is practically insoluble in water.

Chemical structure

Aripiprazole monohydrate has the structural formula:



CAS number

851220-85-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

Abilify Asimtufii is sponsored by Lundbeck Australia:

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Abilify Asimtufii is co-marketed by Lundbeck Australia and Otsuka Australia Pharmaceutical.

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9 DATE OF FIRST APPROVAL

05 February 2025

10 DATE OF REVISION

N/A

Abilify Asimtufii is a registered trademark of Otsuka Pharmaceutical Company.

Summary table of changes

Section changed	Summary of new information
	New Product Information