

1 NAME OF THE MEDICINAL PRODUCT

Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection

Each vial contains 400 mg aripiprazole.

After reconstitution each ml of suspension contains 200 mg aripiprazole.

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

3 PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection

Powder: white to off-white

Solvent: clear solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Schizophrenia

Abilify Maintena is indicated for treatment of schizophrenia in adult patients stabilized with oral aripiprazole. Efficacy has been established in both acute and maintenance phases of schizophrenia.

Bipolar I Disorder

Abilify Maintena is indicated for the maintenance monotherapy treatment of bipolar I disorder in adult patients.

See section 5.1 Pharmacodynamics: further information on clinical trials

4.2 Posology and method of administration

Posology

For patients who have never taken aripiprazole, tolerability with oral aripiprazole must occur prior to initiating treatment with Abilify Maintena.

Titration of the dose of this medicinal product is not required.

The starting dose can be administered by following one of two regimens:

- One injection start: On the day of initiation, administer one injection of 400 mg Abilify Maintena and continue treatment with 10 mg to 20 mg oral aripiprazole per day for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy.
- Two injection start: On the day of initiation, administer two separate injections of 400 mg Abilify Maintena at separate injection sites (see method of administration), along with one 20 mg dose of oral aripiprazole.

After the injection start, the recommended maintenance dose of Abilify Maintena is 400 mg. Abilify Maintena should be administered once monthly as a single injection (no sooner than 26 days after the previous injection). If there are adverse reactions with the 400 mg dosage, reduction of the dose to 300 mg once monthly should be considered.

Missed doses

Missed doses	
Timing of Missed Dose	Action
If 2nd or 3rd dose is missed and time since last injection is:	
> 4 weeks and < 5 weeks	The injection should be administered as soon as possible and then the monthly injection schedule should be resumed.
> 5 weeks	Concomitant oral aripiprazole should be restarted for 14 days with next administered injection or two separate injections given at one time, along with a single dose of 20 mg oral aripiprazole. Monthly injection schedule should then resume.
If 4th or subsequent doses are missed (i.e., after attainment of steady state) and time since last injection is:	
> 4 weeks and < 6 weeks	The injection should be administered as soon as possible and then the monthly injection schedule should be resumed.
> 6 weeks	Concomitant oral aripiprazole should be restarted for 14 days with next administered injection or two separate injections given at one time, along with a single dose of 20 mg oral aripiprazole. Monthly injection schedule should then resume.

Special populations

Elderly

The safety and efficacy of Abilify Maintena in the treatment of schizophrenia in patients 65 years of age or older has not been established (see section 4.4 Special warnings and precautions for use).

Renal impairment

No dosage adjustment is required for patients with renal impairment (see section 5.2 Pharmacokinetic properties).

Hepatic impairment

No dosage adjustment is required for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. Oral formulation should be preferred (see section 5.2 Pharmacokinetic properties).

Known CYP2D6 poor metabolisers

In patients who are known to be CYP2D6 poor metabolisers:

- One injection start: The starting dose should be 300 mg Abilify Maintena and continue treatment with prescribed dose of oral aripiprazole per day for 14 consecutive days.
- Two injection start: The starting dose should be 2 separate injections of 300 mg Abilify Maintena (see section 4.2 Posology and method of administration) along with one single dose of the previous prescribed dose of oral aripiprazole.

In patients who are known to be CYP2D6 poor metabolisers and concomitantly use a strong CYP3A4 inhibitor:

- The one injection start: The starting dose should be reduced to 200 mg (see section 4.5 Interactions with other medicinal products and other forms of interactions) and continue treatment with the prescribed dose of oral aripiprazole per day for 14 consecutive days.
- Two injection start is not to be used in patients who are known to be CYP2D6 poor metabolisers and concomitantly use a strong CYP3A4 inhibitor.

After the injection start, see table below for the recommended maintenance dose of Abilify Maintena. Abilify Maintena should be administered once monthly as a single injection (no sooner than 26 days after the previous injection).

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

Maintenance dosage 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 dosage may need to be increased to the previous dose (see section 4.5 Interactions with other medicinal products and other forms of interactions). In case of adverse reactions despite dose adjustments of Abilify Maintena, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

Concomitant use of CYP3A4 inducers with Abilify Maintena should be avoided for more than 14 days because the blood levels of aripiprazole are decreased and may be below the effective levels (see section 4.5 Interactions with other medicinal products and other forms of interactions).

Maintenance dose adjustments of Abilify Maintena in patients who are taking concomitant strong CYP2D6 inhibitors, strong CYP3A4 inhibitors, and/or CYP3A4 inducers for more than 14 days

	Adjusted dose
Patients taking 400 mg of Abilify Maintena	
Strong CYP2D6 or strong CYP3A4 inhibitors	300 mg
Strong CYP2D6 and strong CYP3A4 inhibitors	200 mg*
CYP3A4 inducers	Avoid use

*200 mg can be achieved via adjustment of the injection volume only by using Abilify Maintena powder and solvent for prolonged-release suspension for injection.

Paediatric population

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

Method of administration

Abilify Maintena is only intended for intramuscular use and should not be administered intravenously or subcutaneously. It should only be administered by a healthcare professional.

The suspension should be injected immediately after reconstitution but can be stored below 25 °C for up to 4 hours in the vial. The suspension should be injected slowly as a single injection (doses must not be divided) into the gluteal or deltoid muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Sites of injections should be rotated between the two gluteal or deltoid muscles.

If initiating with the two injection start, inject into two different sites in two different muscles. DO NOT inject both injections concomitantly into the same deltoid or gluteal muscle. For known CYP2D6 poor metabolisers administer in either two separate deltoid muscles or one deltoid and one gluteal muscle. DO NOT inject into two gluteal muscles.

The recommended needle for gluteal administration is a 38 mm (1.5 inch), 22 gauge hypodermic safety needle. For obese patients (Body mass index > 28 kg/m²), a 51 mm (2 inch), 21 gauge hypodermic safety needle should be used.

The recommended needle for deltoid administration is a 25 mm (1 inch), 23 gauge hypodermic safety needle. For obese patients, a 38 mm (1.5 inch), 22 gauge hypodermic safety needle should be used (see section 6.6 Special precautions for disposal and other handling).

The powder and solvent vials are for single-use only.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 List of excipients .

4.4 Special warnings and precautions for use

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

Suicidality

The occurrence of suicidal behaviour is inherent in psychotic illnesses, and in some cases, has been reported early after initiation or switch of antipsychotic treatment, including treatment with aripiprazole (see section 4.8 Undesirable effects). Close supervision of high risk patients should accompany antipsychotic treatment.

Cardiovascular disorders

Abilify Maintena should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. 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 Maintena and preventive measures undertaken (see section 4.8 Undesirable effects).

QT prolongation

In clinical trials of treatment with oral aripiprazole, the incidence of QT prolongation was comparable to placebo. Aripiprazole should be used with caution in patients with a family history of QT prolongation (see section 4.8 Undesirable effects).

Tardive dyskinesia

In clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on Abilify Maintena, dose reduction or discontinuation of should be considered (see section 4.8 Undesirable effects). These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Neuroleptic Malignant Syndrome (NMS)

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 (see section 4.8 Undesirable effects).

Seizure

In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures (see section 4.8 Undesirable effects).

Elderly patients with dementia-related psychosis

Increased mortality

In three placebo-controlled trials of 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 are at an increased risk of death compared to placebo. The rate of death in oral aripiprazole-treated patients was 3.5 % compared to 1.7 % in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8 Undesirable effects).

Cerebrovascular adverse reactions

In the same trials with oral aripiprazole, 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 oral aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6 % of placebo-treated patients in these trials. This difference was not statistically significant. 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 (see section 4.8 Undesirable effects).

Abilify Maintena is not indicated for the treatment of patients with dementia-related psychosis.

Hyperglycemia and diabetes mellitus

Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics 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 this confounder, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-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 should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved

when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

In schizophrenia clinical trials with Abilify Maintena there have been few reports of hyperglycemia and diabetes, the incidence was 0.6% and 1.1% respectively in the maintenance trials and 0% and 0.6% in the acute trial.

In the bipolar I disorder clinical trial, the incidence of hyperglycemia and diabetes were 0.8% and 0% respectively.

Hypersensitivity

Hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole.

Weight gain

Weight gain is commonly seen in schizophrenic patients due to use of antipsychotics known to cause weight gain, co-morbidities, poorly managed life-style and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed oral aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain (see section 4.8 Undesirable effects).

Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic medicinal product use, including aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

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 shopping, binge or compulsive eating, and other impulsive and compulsive behaviors. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, 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. Patients who are at higher risk for impulse-control problems (e.g. personal or family history of obsessive-compulsive disorder, impulse-control disorders, bipolar disorder, impulsive personality, alcoholism, drug abuse or other addictive behaviours) would require closer monitoring for new or worsening of uncontrollable urges. Impulse control problems 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 section 4.8 Undesirable effects).

Falls

Antipsychotics, including aripiprazole, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α_1 -adrenergic receptor antagonism. Aripiprazole may induce orthostatic hypotension, tachycardia, dizziness, and sometimes syncope, especially at the initiation of treatment.

In the placebo-controlled trial in acute schizophrenia, presyncope occurred in 1/167 (0.6%) of patients treated with Abilify Maintena, while syncope and orthostatic hypotension each occurred in 1/172, (0.6%) of patients treated with placebo. There were no significant orthostatic changes in blood pressure for the Abilify Maintena treated patients or placebo-treated patients (defined as a decrease in systolic blood pressure ≥ 20 mmHg accompanied by an increase in heart rate ≥ 25 when comparing standing to supine values).

In the double-blind controlled phase of the schizophrenia maintenance clinical trials using Abilify Maintena orthostatic related events were reported in 2/534 (0.4%) patients. Orthostasis occurred in 4/576 (0.7%) patients treated with Abilify Maintena during the stabilization phase, including abnormal orthostatic blood pressure (1/576, 0.2%), postural dizziness (1/576, 0.2%), presyncope (1/576, 0.2%) and orthostatic hypotension (1/576, 0.2%). In the stabilization phase, the incidence of significant orthostatic change in blood pressure was 0.2% (1/575).

During the stabilization phase of the maintenance trial in adult patients with bipolar I disorder, syncope was the only orthostatic related adverse event reported in 0.2% of patients treated with Abilify Maintena. Incidence of potential clinically relevant orthostatic hypotension reported during the Abilify Maintena stabilization phase in bipolar I disorder was 0.2% (1/421) and during the double-blind, placebo-controlled phase, there were no differences reported in either treatment group.

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

4.5 Interactions with other medicinal products and other forms of interactions

No specific interaction studies have been performed with Abilify Maintena. The information below is obtained from studies with oral aripiprazole.

Due to its α 1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive medicinal products.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is administered in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as sedation (see section 4.8 Undesirable effects).

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

Potential for other medicinal products to affect Abilify Maintena

Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes, but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

Quinidine and other strong CYP2D6 inhibitors

In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) 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 and paroxetine, may be expected to have similar effects and similar dose reduction should, therefore, be applied (see section 4.2 Posology and method of administration).

Concomitant use of Abilify Maintena with quinidine or other CYP2D6 inhibitors increases the concentrations of aripiprazole after longer-term use (i.e., over 14 days) and reduction of the Abilify Maintena is recommended.

Ketoconazole and other strong CYP3A4 inhibitors

In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) 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. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolisers (see section 4.2 Posology and method of administration).

When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. 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 section 4.2 Posology and method of administration). Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of Abilify Maintena should 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 this medicinal product, modest increases in plasma aripiprazole concentrations may be expected.

Concomitant use of Abilify Maintena with ketoconazole or other CYP3A4 inhibitors for more than 14 days increases the concentrations of aripiprazole and reduction of the Abilify Maintena dose is recommended.

Carbamazepine and other CYP3A4 inducers

Following concomitant administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizoaffective disorder, the geometric means of C_{max} and AUC for aripiprazole were 68 % and 73 % lower, respectively, compared to when oral aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of C_{max} and AUC after carbamazepine co-administration were 69 % and 71 % lower, respectively, than those following treatment with oral aripiprazole alone.

Concomitant administration of Abilify Maintena and other inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects. The concomitant use of CYP3A4 inducers with Abilify Maintena should be avoided because the blood levels of aripiprazole are decreased and may be below the effective levels.

Valproate and lithium

When either valproate or lithium was administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations, and, therefore, no dose adjustment is necessary when either valproate or lithium is administered with Abilify Maintena.

Potential for Abilify Maintena to affect other medicinal products

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 Maintena is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

When aripiprazole was administered concomitantly with lamotrigine, dextromethorphan, warfarin, omeprazole, escitalopram, or venlafaxine there was no clinically important change in concentrations of these medicinal products. Thus, no dosage adjustment of these medicinal products is required when co-administered with Abilify Maintena.

Serotonin syndrome

Cases of serotonin syndrome have been reported in patients taking aripiprazole, and possible signs and symptoms for this condition can occur especially in cases of concomitant use with other serotonergic medicinal products, such as SSRI/SNRI, or with medicinal products that are known to increase aripiprazole concentrations (see section 4.8 Undesirable effects).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3 Preclinical safety data). Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with Abilify Maintena. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

Prescribers need to be aware of the long-acting properties of Abilify Maintena.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been 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 intensive care unit support and prolonged hospitalisation. Consequently, neonates should be monitored carefully (see section 4.8 Undesirable effects).

Abilify Maintena should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

Aripiprazole is excreted in human breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Abilify Maintena therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Aripiprazole did not impair fertility based on data from reproductive toxicity studies.

4.7 Effects on ability to drive and use machines

Abilify Maintena can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia (see section 4.8 Undesirable effects). Therefore, patients should be advised not to drive or operate machines until their individual susceptibility to this medicinal product is known.

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions (ADRs) reported in $\geq 5\%$ of patients in two double-blind controlled clinical trials of Abilify Maintena were weight increased (9.0 %), akathisia (7.9 %), insomnia (5.8 %), and injection site pain (5.1 %).

Tabulated list of adverse reactions

The incidences of the Adverse Drug Reactions (ADRs) associated with aripiprazole therapy are tabulated below. The table is based on adverse events reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ class and frequency; very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known".

	Common	Uncommon	Not known
Blood and lymphatic system disorders		Neutropenia Anaemia Thrombocytopenia Neutrophil count decreased White blood cell count decreased	Leukopenia
Immune system disorders		Hypersensitivity	Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders		Blood prolactin decreased Hyperprolactinaemia	Diabetic hyperosmolar coma Diabetic ketoacidosis
Metabolism and nutrition disorders	Weight increased Diabetes mellitus Weight decreased	Hyperglycaemia Hypercholesterolaemia Hyperinsulinaemia Hyperlipidaemia Hypertriglyceridaemia Appetite disorder	Anorexia Hyponatraemia
Psychiatric disorders	Agitation Anxiety Restlessness Insomnia	Suicidal ideation Psychotic disorder Hallucination Delusion Hypersexuality	Completed suicide Suicide attempt Pathological gambling Nervousness

	Common	Uncommon	Not known
		Panic reaction Depression Affect lability Apathy Dysphoria Sleep disorder Bruxism Libido decreased Mood altered	Aggression Impulse control disorders Binge eating Compulsive shopping Poriomania
Nervous system disorders	Extrapyramidal disorder Akathisia Tremor Dyskinesia Sedation Somnolence Dizziness Headache	Dystonia Tardive dyskinesia Parkinsonism Movement disorder Psychomotor hyperactivity Restless legs syndrome Cogwheel rigidity Hypertonia Bradykinesia Drooling Dysgeusia Parosmia	Neuroleptic malignant syndrome Grand mal convulsion Serotonin syndrome Speech disorder
Eye disorders		Oculogyric crisis Vision blurred Eye pain Diplopia Photophobia	
Cardiac disorders		Ventricular extrasystoles Bradycardia Tachycardia Electrocardiogram T wave amplitude decreased Electrocardiogram abnormal Electrocardiogram T wave inversion	Sudden unexplained death Cardiac arrest Torsades de pointes Ventricular arrhythmias QT prolongation
Vascular disorders		Hypertension Orthostatic hypotension Blood pressure increased	Syncope Venous thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders		Cough Hiccups	Oropharyngeal spasm Laryngospasm Aspiration pneumonia
Gastrointestinal disorders	Dry mouth	Gastroesophageal reflux disease Dyspepsia Vomiting Diarrhoea Nausea	Pancreatitis Dysphagia

	Common	Uncommon	Not known
		Abdominal pain upper Abdominal discomfort Constipation Frequent bowel movement Salivary hypersecretion	
Hepatobiliary disorders		Liver function test abnormal Hepatic enzyme increased Alanine aminotransferase increased Gamma-glutamyl transferase increased Blood bilirubin increased Aspartate aminotransferase increased	Hepatic failure Jaundice Hepatitis Alkaline phosphatase increased
Skin and subcutaneous tissue disorders		Alopecia Acne Rosacea Eczema Skin induration	Rash Photosensitivity reaction Hyperhidrosis Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Musculoskeletal stiffness	Muscle rigidity Muscle spasms Muscle twitching Muscle tightness Myalgia Pain in extremity Arthralgia Back pain Joint range of motion decreased Nuchal rigidity Trismus	Rhabdomyolysis
Renal and urinary disorders		Nephrolithiasis Glycosuria	Urinary retention, Urinary incontinence
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see section 4.6 Fertility, pregnancy and lactation)
Reproductive system and breast disorders	Erectile dysfunction	Galactorrhoea Gynaecomastia Breast tenderness Vulvovaginal dryness	Priapism

	Common	Uncommon	Not known
General disorders and administration site conditions	Injection site pain Injection site induration Fatigue	Pyrexia Asthenia Gait disturbance Chest discomfort Injection site reaction Injection site erythema Injection site swelling Injection site discomfort Injection site pruritus Thirst Sluggishness	Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
Investigations	Blood creatine phosphokinase increased	Blood glucose increased Blood glucose decreased Glycosylated haemoglobin increased Waist circumference increased Blood cholesterol decreased Blood triglycerides decreased	Blood glucose fluctuation

Description of selected adverse reactions

Injection site reactions

During the double-blind, controlled phases of the two trials, injection site reactions were observed; those seen were generally mild to moderate in severity, and resolved over time. Injection site pain (incidence 5.1 %), has a median onset on day 2 after the injection and a median duration of 4 days.

In an open label study comparing bioavailability of Abilify Maintena administered in the deltoid or gluteal muscle, injection site related reactions were slightly more frequent in the deltoid muscle. The majority were mild and improved on subsequent injections. When compared to studies where Abilify Maintena was injected in the gluteal muscle, repeated occurrence of injection site pain is more frequent in the deltoid muscle.

Leukopenia

Neutropenia has been reported in the clinical program with Abilify Maintena and typically starts around day 16 after first injection, and lasts a median of 18 days.

Extrapyramidal Symptoms (EPS)

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 starts around day 10 after first injection, and lasts a median of 56 days.

Subjects with akathisia typically received anti-cholinergic medicines as treatment, primarily benztropine mesilate and trihexyphenidyl. Less often substances such as propranolol and benzodiazepines (clonazepam and diazepam) were administered to control akathisia.

Parkinsonism events followed in frequency (6.9 % Abilify Maintena, 4.15 % oral aripiprazole 10-30 mg tablets group and 3.0 % placebo, respectively).

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 medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

Weight

During the double-blind, active-controlled phase of the 38-week trial, the incidence of weight gain of $\geq 7\%$ from baseline to last visit was 9.5 % for Abilify Maintena group and 11.7 % for the oral aripiprazole tablets 10-30 mg group. The incidence of weight loss of $\geq 7\%$ from baseline to last visit was 10.2 % for Abilify Maintena and 4.5 % for oral aripiprazole tablets 10-30 mg.

During the double-blind, placebo-controlled phase of the 52-week trial, the incidence of weight gain of $\geq 7\%$ from baseline to last visit was 6.4 % for the Abilify Maintena group and 5.2 % for the placebo group.

The incidence of weight loss of $\geq 7\%$ from baseline to last visit was 6.4 % for the Abilify Maintena group and 6.7 % for the placebo group. 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 ($p = 0.812$).

Prolactin

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 of Abilify Maintena patients with prolactin levels > 1 time the upper limit of normal range (ULN) at any assessment was 5.4 % compared with 3.5 % of the patients on oral aripiprazole tablets 10-30 mg. Male patients generally had a higher incidence than female patients in each treatment group.

In the double-blind placebo-controlled phase of the 52-week trial, 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 incidences of Abilify Maintena patients with prolactin levels > 1 time the upper limit of normal range (ULN) was 1.9 % compared to 7.1 % for placebo patients.

Psychiatric disorders

Pathological gambling, hypersexuality, impulse-control problems (see section 4.4 Special warnings and precautions for use).

Sleep Apnea

Atypical antipsychotic drugs, including aripiprazole, have been associated with cases of sleep apnea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnea, aripiprazole should be prescribed with caution.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Clinical trial adverse drug reactions

Adverse Drug Reaction Overview

Abilify Maintena has been evaluated for safety in 804 adult patients in clinical trials in bipolar I disorder, with approximately 530 patient-years of exposure to Abilify Maintena. A total of 419 patients were treated with Abilify Maintena for at least 7 consecutive injections (i.e., have been treated for at least 6 months) and 287 patients treated with Abilify Maintena had at least 13 consecutive injections (i.e., have been treated for at least 12 months).

Clinical trial adverse drug reactions

Adverse Events Associated with Discontinuation of Treatment

In the schizophrenia trials, overall adverse reactions that led to discontinuation were similar for the aripiprazole-treated and placebo-treated patients in both the acute and maintenance phase studies. During double-blind treatment phase of the maintenance trials (Controlled Trials), TEAEs resulting in discontinuation of trial medication were experienced by 40/534 (7.5%) Abilify Maintena 400 mg/300 mg subjects, 19/266 (7.1%) oral aripiprazole tablets 10-30 mg subjects, 24/131 (18.3%) aripiprazole IM depot 50 mg/25 mg subjects, and 18/134 (13.4%) placebo subjects. In the acute schizophrenia trial, there was overall little difference in the incidence of discontinuations due to adverse reactions between Abilify Maintena-treated (4%) and placebo-treated (8%) patients.

During the double-blind, placebo-controlled phase of the bipolar I disorder trial, fewer subjects experienced a TEAE resulting in discontinuation in the Abilify Maintena group (23/132; 17.4%) compared to the placebo group (34/133; 25.6%). The following TEAEs led to discontinuation of IMP in more than 1 subject in either treatment group (Abilify Maintena vs placebo): mania (2.3% vs 8.3%), bipolar I disorder (1.5% vs 6.0%), bipolar disorder (3.8% vs 3.0%), depression (3.0% vs 2.3%), akathisia (1.5% vs 0.0%), affective disorder (0.0% vs 1.5%), and major depression (0.0% vs 1.5%).

Commonly Reported Adverse Events

The adverse event profile was similar across placebo-controlled trials of Abilify Maintena, irrespective of the schizophrenia or bipolar I disorder indications.

In the schizophrenia trials, the most frequently observed adverse events (AEs) reported in $\geq 5\%$ of patients in two double-blind pivotal maintenance clinical studies of Abilify Maintena were insomnia, weight increased, akathisia, headache, anxiety, weight decreased, nasopharyngitis and injection site pain. Overall these adverse events were mild to moderate in severity and were similar to those in the placebo treated patients. Table 1 lists the adverse events in the maintenance clinical trials with Abilify Maintena that occurred at the frequency of 2% or greater.

Based on the placebo-controlled trial of Abilify Maintena in the acute phase of schizophrenia, the most commonly observed adverse events associated with the use of aripiprazole in patients (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were increased weight, akathisia, sedation, and injection site pain. Table 2 presents the Adverse Events that occurred in the acute trials at a rate of 2% or greater.

Table 1 – Adverse Events occurring in 2% or more of subjects with schizophrenia in both placebo and active controlled maintenance 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				
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)
Injection site pain	28 (5.2)	6 (2.3)	1 (0.8)	5 (3.7)
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)
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)
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)
Vascular Disorders				
Hypertension	7 (1.3)	4 (1.5)	4 (3.1)	3 (2.2)

Table 2 - Adverse Events occurring in 2% or more of subjects with schizophrenia in the Acute Phase Placebo controlled clinical trial and greater than placebo.

	Aripiprazole IM Depot 400/300mg (N=167)	Placebo (N=172)
System organ class MedDRA preferred term	n (%)	n (%)
Gastrointestinal disorders		
Abdominal discomfort	4 (2.4)	2 (1.2)
Constipation	16 (9.6)	12 (7.0)
Diarrhoea	5 (3.0)	4 (2.3)
Dry mouth	6 (3.6)	4 (2.3)
Toothache	9 (5.4)	8 (4.7)
Vomiting	5 (3.0)	2 (1.2)
General disorders and administration site conditions		
Fatigue	4 (2.4)	3 (1.7)
Injection site pain	9 (5.4)	1 (0.6)
Infections and infestations		
Upper respiratory tract infection	6 (3.6)	3 (1.7)
Investigations		
Weight decreased	6 (3.6)	4 (2.3)
Weight increased	28 (16.8)	12 (7.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	6 (3.6)	2 (1.2)
Back pain	7 (4.2)	4 (2.3)
Musculoskeletal pain	5 (3.0)	2 (1.2)
Myalgia	6 (3.6)	1 (0.6)
Nervous system disorders		
Akathisia	19 (11.4)	6 (3.5)
Dizziness	6 (3.6)	3 (1.7)
Sedation	9 (5.4)	2 (1.2)
Tremor	5 (3.0)	1 (0.6)
Psychiatric disorders		
Insomnia	8 (4.8)	8 (4.7)
Respiratory, thoracic and mediastinal disorders		
Cough	10 (6.0)	10 (5.8)
Nasal congestion	4 (2.4)	2 (1.2)

In the bipolar I disorder trial of Abilify Maintena, none of the adverse events in the double-blind, placebo-controlled phase were reported at an incidence $\geq 5\%$ of patients AND at least twice the incidence of placebo. Based on the placebo-controlled trial of Abilify Maintena in patients with bipolar I disorder, the most frequently observed adverse events reported in $\geq 5\%$ of Abilify Maintena patients and greater than placebo were weight increased, akathisia, anxiety, restlessness, and somnolence. Table 3 presents the Adverse Events that occurred in the bipolar I disorder trials at a rate of 2% or greater.

Table 3 - Adverse events occurring in 2% or more of subjects with bipolar I disorder in the placebo controlled clinical trial and greater than placebo

	ABILIFY MAINTENA 400/300mg (N=132)	Placebo (N=133)
System organ class MedDRA preferred term	n (%)	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)

4.9 Overdose

No cases of overdose associated with adverse reactions were reported in clinical studies with Abilify Maintena. 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, close observation of the patient is needed and if any potentially medically serious sign or symptom develops, monitoring, which should include continuous electrocardiographic monitoring, is required. The medical supervision and monitoring should continue until the patient recovers.

A simulation of dose dumping showed that the predicted median aripiprazole concentration reaches a peak of 4500 ng/ml or approximately 9 times the upper therapeutic range. In case of dose dumping, aripiprazole concentrations are predicted to descend rapidly to the upper limit of the therapeutic window after approximately 3 days. By the 7th day, the median aripiprazole concentrations further decline to concentrations following an IM depot dose with no dose dumping. While overdose is less likely with parenteral than oral medicinal products, reference information for oral aripiprazole overdose is presented below.

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 (41 times highest recommended daily aripiprazole dose) with no fatalities. The potentially medically important signs and symptoms observed 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

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX12

Mechanism of action

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia or bipolar I disorder is unknown. However, it has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties of dopaminergic hypoactivity. Aripiprazole exhibits high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and has moderate affinity for dopamine D4, serotonin 5-HT_{2C} and 5-HT₇, alpha-1 adrenergic, and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for cholinergic muscarinic 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 ^{11}C -raclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Further information on clinical trials:

Clinical Efficacy in Maintenance treatment of schizophrenia in adults

The efficacy of Abilify Maintena in the maintenance treatment of patients with schizophrenia was established in two randomised, double-blind trials.

The first trial was a 38 week, randomised, double-blind, active-controlled trial designed to establish the efficacy, safety, and tolerability of this medicinal product administered as monthly injections compared to once daily oral aripiprazole tablets 10-30 mg as maintenance treatment in adult patients with schizophrenia. This trial consisted of a screening phase and 3 treatment phases: Conversion Phase, Oral Stabilisation Phase, and Double-Blind, Active-Controlled Phase.

Six-hundred and sixty two patients eligible for the 38-week Double-Blind, Active-Controlled Phase were randomly assigned in a 2:2:1 ratio to double-blind treatment to one of 3 treatment groups: 1) Abilify Maintena 2) the stabilisation dose of oral aripiprazole 10-30 mg, or 3) aripiprazole Long-Acting Injectable 50 mg/25 mg. The aripiprazole Long-Acting Injectable 50 mg/25 mg dose was included as a low dose aripiprazole group to test assay sensitivity for the non-inferiority design.

The results of analysis of the primary efficacy endpoint, the estimated proportion of patients experiencing impending relapse by end of Week 26 of the Double-blind, Active-controlled Phase, showed that Abilify Maintena 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10-30 mg.

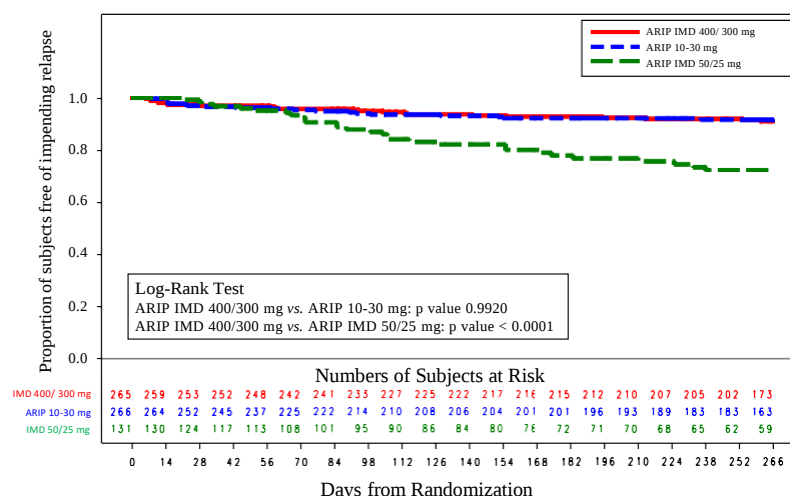
The estimated relapse rate by end of Week 26 was 7.12 % in the Abilify Maintena group, and 7.76 % in the oral aripiprazole tablets 10-30 mg group, a difference of -0.64 %.

The 95 % CI (-5.26, 3.99) for the difference in the estimated proportion of patients experiencing impending relapse by end of Week 26 excluded the predefined non-inferiority margin, 11.5 %. Therefore, Abilify Maintena is non-inferior to the aripiprazole oral tablets 10-30 mg formulation.

The estimated proportion of patients experiencing impending relapse by end of Week 26 for the Abilify Maintena group was 7.12 %, which was statistically significantly lower than in the aripiprazole Long-Acting Injectable 50 mg/25 mg group (21.80 %; $p = 0.0006$). Thus, superiority of Abilify Maintena over the aripiprazole Long-Acting Injectable 50 mg/25 mg was established and the validity of the trial design was confirmed.

The Kaplan-Meier curves of the time from randomisation to impending relapse during the 38-week, double-blind treatment phase for Abilify Maintena, oral aripiprazole 10-30 mg group, and aripiprazole Long-Acting Injectable 50 mg/25 mg groups are shown in Figure 1.

Figure 1 Kaplan-Meier Product Limit Plot for Time to Exacerbation of Psychotic Symptoms/Impending Relapse



NOTE: ARIP IMD 400/300 mg = Abilify Maintena; ARIP 10-30 mg = oral aripiprazole; ARIP IMD 50/25 mg = Long-acting Injectable

Further, the non-inferiority of Abilify Maintena compared to oral aripiprazole 10-30 mg is supported by the results of the analysis of Positive and Negative Syndrome Scale for Schizophrenia (PANSS).

Table 4 PANSS Total Score – Change From Baseline to Week 38-LOCF: Randomised Efficacy Sample ^{a, b}

PANSS Total Score – Change From Baseline to Week 38-LOCF: Randomised Efficacy Sample ^{a, b}			
	Abilify Maintena 400 mg/300 mg (n = 263)	Oral aripiprazole 10-30 mg/day (n = 266)	Aripiprazole Long-Acting Injectable 50 mg/25 mg (n = 131)
Mean baseline (SD)	57.9 (12.94)	56.6 (12.65)	56.1 (12.59)
Mean change (SD)	-1.8 (10.49)	0.7 (11.60)	3.2 (14.45)
P-value	NA	0.0272	0.0002

a: Negative change in score indicates improvement.

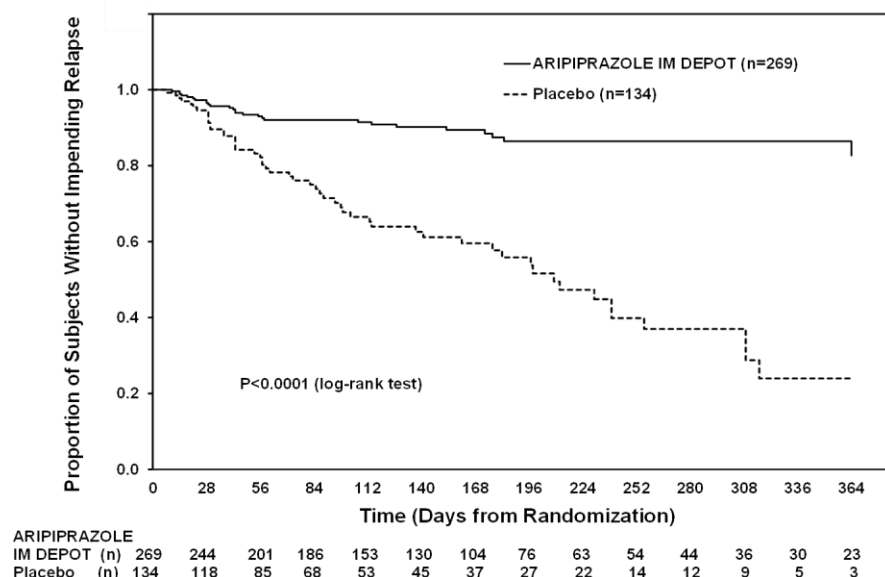
b: Only patients having both baseline and at least one post baseline were included. P-values were derived from comparison for change from baseline within analysis of covariance model with treatment as term and baseline as covariate.

The second trial was a 52-week, randomised, withdrawal, double-blind, trial conducted in adult patients with a current diagnosis of schizophrenia. This trial consisted of a screening phase and 4 treatment phases: Conversion, Oral Stabilisation, Abilify Maintena Stabilisation, and Double-blind Placebo-controlled. Patients fulfilling the oral stabilisation requirement in the Oral Stabilisation Phase were assigned to receive, in a single-blind fashion, Abilify Maintena and began an Abilify Maintena Stabilisation Phase for a minimum of 12 weeks and a maximum of 36 weeks. Patients eligible for the Double-blind, Placebo-controlled Phase were randomly assigned in a 2:1 ratio to double-blind treatment with Abilify Maintena or placebo, respectively. The final efficacy analysis included 403 randomised patients and 80 exacerbations of psychotic symptoms/impending relapse events.

The study 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 5.03-fold greater risk of experiencing impending relapse than patients in the Abilify Maintena group. This results support 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 2.

Figure 2 Kaplan-Meier Product Limit Plot for Time to Exacerbation of Psychotic Symptoms/Impending Relapse



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 %).

Further, the superiority of Abilify Maintena compared to placebo is supported by the results of the analysis of PANSS.

Table 5 PANSS Total Score - Change From Baseline to Week 52- LOCF: Randomised Efficacy Sample ^a

PANSS Total Score - Change From Baseline to Week 52- LOCF: Randomised Efficacy Sample ^a		
	Abilify Maintena 400 mg/300 mg (n = 266)	Placebo (n = 134)
Mean baseline (SD)	54.4 (11.96)	54.4 (11.59)
Mean change (SD)	1.43 (10.82)	11.6 (15.21)
P-value	NA	< 0.0001

a: Only patients having both baseline and at least one post baseline were included. P-values were derived from comparison for change from baseline within analysis of covariance model with treatment as term and baseline as covariate.

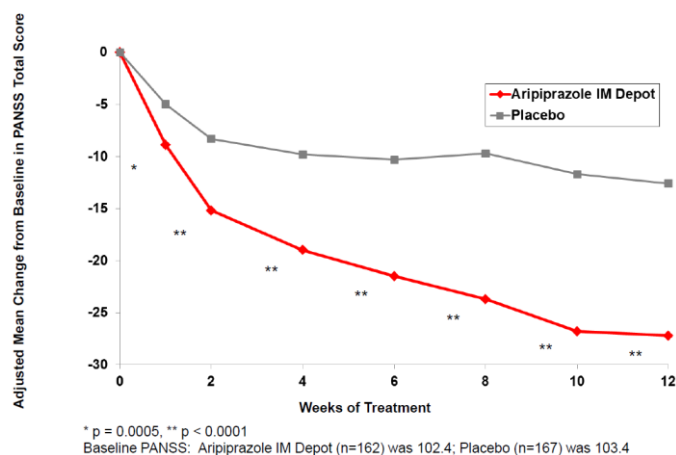
Clinical Efficacy in the Acute Phase of Schizophrenia

The efficacy of Abilify Maintena in adult patients in the acute phase of schizophrenia was established in one short-term (12-week), randomized, double-blind, placebo controlled trial of acutely relapsed adult patients. In this trial, the primary measure used for assessing psychiatric signs and symptoms was the Positive and Negative Syndrome Scale (PANSS). The primary endpoint was the change from baseline to week 10 in PANSS total score. The key secondary endpoint was the Clinical Global Impression-Severity (CGI-S) assessment at week 10.

The inclusion criteria for this short term trial included adult inpatients who met DSM-IV-TR criteria for schizophrenia. In addition, all patients entering the trial must have experienced an acute psychotic episode as defined by both PANSS Total Score ≥ 80 and a PANSS score of > 4 on each of four specific psychotic symptoms (conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, unusual thought content) at screening and baseline. Patients had a mean PANSS total score of 103 (range 82 to 144) and a CGIS score of 5.0 (markedly ill) at entry.

In this 12-week study (n=339) comparing Abilify Maintena (n=167) to placebo (n=172), patients were administered 400 mg Abilify Maintena or placebo on days 0, 28, and 56. The dose could be adjusted down and up within the range of 400 to 300 mg on a one time basis. (For the first two weeks of the study, subjects randomized to Abilify Maintena also received concomitant oral Abilify Maintena, 10 to 20 mg/day). Abilify Maintena was superior to placebo in improving the PANSS total score with early onset and sustained efficacy (week 10 scores of -26.8 vs. -11.7 respectively) with a statistical difference at each measured time point, $p < 0.0005$ at week 1 and $p < 0.0001$ for all other time points until study completion. The adjusted mean change in PANSS total score over time (Mixed Model of Repeated Measure MMRM) is demonstrated in Figure 3.

Figure 3: Adjusted Mean Change from Baseline in PANSS Total Score – MMRM



Abilify Maintena also showed improvement in CGI-S score mean changes from baseline that were statistically significant at all post-baseline timepoints (week 10 scores of -1.4 vs. -0.6 at week 10, Abilify Maintena vs. placebo, respectively).

Clinical Efficacy in Maintenance Treatment of Bipolar I Disorder

The safety and efficacy of Abilify Maintena as maintenance treatment in adults with bipolar I disorder aged 18 to 65 years was demonstrated in a 52-week multicenter, randomized, double-blind, placebo-controlled trial (Trial 31-08-250) of patients who met DSM-IV-TR criteria for bipolar I disorder and who were currently experiencing a manic episode at trial entry.

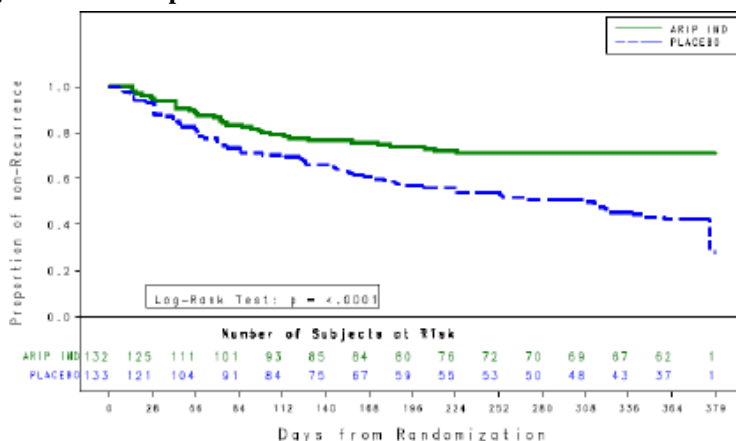
This trial consisted of a screening phase and 4 treatment phases:

- An oral conversion phase (4 to 6 weeks) for all subjects to achieve a monotherapy target starting dose of 15 mg/day oral aripiprazole. A total of 466 patients entered this phase.
- An oral stabilization phase (a minimum of 2 weeks and a maximum of 8 weeks in duration) during which subjects were stabilized on an oral dose of aripiprazole ranging from 15 mg to 30 mg daily. Stabilization was defined as having all of the following stability criteria at one biweekly visit in order to proceed to Abilify Maintena stabilization phase: outpatient status, YMRS total score ≤ 12 , MADRS total score ≤ 12 , 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). A total of 632 patients entered this phase of which 265 patients entered the oral stabilization phase directly.
- Abilify Maintena Stabilization Phase (a minimum of 12 weeks and a maximum of 28 weeks in duration) during which subjects were stabilized on Abilify Maintena 400 mg or 300 mg, as dictated by tolerability. Oral dosing with aripiprazole continued for the first 2 weeks following the injection to maintain therapeutic plasma concentrations. Stabilization was defined as having all of the following for eight consecutive weeks: an outpatient status, YMRS total score ≤ 12 , MADRS total score ≤ 12 , 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). A total of 425 patients entered this phase. The mean baseline YMRS total score was 5.8 (range, 0 to 28). The mean baseline MADRS total score were 3.7 (range, 0 to 28). The mean baseline CGI-BP-S overall score was 2.1 (range, 1 to 5). Patients who demonstrated stability for 8 consecutive weeks were randomized into the double-blind, placebo- controlled treatment phase.
- A randomized, double-blind, placebo-controlled phase (52 weeks). Two hundred sixty six (266) patients eligible for the 52-week double-blind, placebo-controlled phase were randomly assigned in a 1:1 ratio to double-blind treatment with either the last stabilization dose of Abilify Maintena from the previous phase or placebo. During this phase, a single decrease to Abilify Maintena 300 mg was permitted for tolerability, as was a single return to the original 400 mg dose if required. The mean baseline YMRS total score was 2.9, and 2.6 for the Abilify Maintena 400 mg/300 mg and placebo groups, respectively. The mean baseline MADRS total score was 3.0 and 2.4 for the Abilify Maintena 400 mg/300 mg and placebo groups, respectively. The mean baseline CGI-BP-S score was 1.5 and 1.4 for the Abilify Maintena 400 mg/300 mg and placebo groups, respectively.

The primary efficacy endpoint of this trial was the time from randomization to recurrence of any mood episode during the double-blind, placebo-controlled phase.

The time to recurrence of any mood episode was significantly longer in subjects randomized to the Abilify Maintena group compared to placebo-treated subjects. A total of 103 mood events were observed during the double-blind treatment phase: 35 occurred during Abilify Maintena treatment and 68 occurred during placebo treatment (26.5% vs 51.1%, $p < 0.0001$). The hazard ratio from the Cox proportional hazard model for the Abilify Maintena to placebo comparison was 0.451 (95% CI = 0.299, 0.678), subjects in the Abilify Maintena group had less than half the risk of experiencing recurrence of any mood episode compared with subjects in the placebo group. Thus, superiority of Abilify Maintena over placebo was established. The analysis of the primary efficacy endpoint is shown in the Kaplan-Meier curves below (Figure 4).

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



n = number of subjects at risk of recurrence
 ARIP IMD = Aripiprazole IM depot (Abilify Maintena)

Secondary and other efficacy endpoints were generally supportive of the primary efficacy outcome

Abilify Maintena as maintenance treatment in adult with bipolar disorder was assessed in a 52-week multicentre, open-label trial ($n=464$, Trial 31-08-252). Safety and tolerability were supportive of the results observed in the double-blind, placebo-controlled study.

5.2 Pharmacokinetic properties

Absorption

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

The average absorption half-life of Abilify Maintena is 28 days. Absorption of aripiprazole from the IM depot formulation was complete relative to the IM standard (immediate-release) formulation. The dose adjusted C_{max} values for the depot formulation were approximately 5% of C_{max} from IM standard formulation.

Following a single dose administration of Abilify Maintena in the deltoid and gluteal muscle, the extent of absorption (AUC) was similar for both injection sites, but the rate of absorption (C_{max}) was higher following administration to the deltoid muscle.

Following multiple intramuscular doses, the plasma concentrations of aripiprazole gradually rise to a maximum plasma concentration at a median t_{max} of 7 days for the gluteal muscle and 3 days for the deltoid muscle.

Steady state concentrations for the typical subject were attained by the fourth dose for both sites of administration.

Less than dose-proportional increases in aripiprazole and dehydro-aripiprazole concentrations and AUC parameters are observed after monthly Abilify Maintena injections of 300 mg to 400 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 and dehydro-aripiprazole are greater than 99 % bound to serum proteins, binding primarily to albumin.

Biotransformation

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 responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. After multiple dose administration of Abilify Maintena, dehydro-aripiprazole, the active metabolite, represents about 29.1-32.5 % of aripiprazole AUC in plasma.

Elimination

After administration of multiple dose of 400 mg or 300 mg of Abilify Maintena, the mean aripiprazole terminal elimination half-life is respectively 46.5 and 29.9 days presumably due to absorption rate-limited kinetics. Following a single oral dose of [¹⁴C]-labelled aripiprazole, approximately 27 % of the administered radioactivity was recovered in the urine and approximately 60 % in the faeces. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged in the faeces.

Pharmacokinetics 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 and approximately 1.88 L/h (approximately 50 % lower) in poor metabolisers of CYP2D6 (for dose recommendation, see section 4.2 Posology and method of administration).

Elderly

After oral administration of aripiprazole, there are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects. Similarly, there was no detectable effect of age in a population pharmacokinetic analysis of Abilify Maintena in schizophrenia patients.

Gender

After oral administration of aripiprazole, there are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects. Similarly, there was no clinically relevant effect of gender in a population pharmacokinetic analysis of Abilify Maintena in clinical trials in patients with schizophrenia.

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 on 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 that in young healthy subjects.

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, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

5.3 Preclinical safety data

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. With intramuscular injection, however an inflammatory response was seen at the injection site, and consisted of granulomatous inflammation, foci (deposited drug), cellular infiltrates, oedema (swelling) and, in monkeys, fibrosis. These effects gradually resolved with discontinuation of dosing.

Non-clinical safety data for orally administered aripiprazole revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, and carcinogenic potential.

Oral aripiprazole

For oral aripiprazole, toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity in rats after 104 weeks of oral administration at approximately 3 to 10 times the mean steady-state AUC at the maximum recommended human dose and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at approximately 10 times the mean steady-state AUC at the maximum recommended human dose. The highest non-tumorigenic exposure in female rats was approximately 7 times the human exposure at the recommended dose.

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy-metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day or approximately 16 to 81 times the maximum recommended human dose based on mg/m².

However, the concentrations of the sulphate conjugates of hydroxy-aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6 % of the bile concentrations found in the monkeys in the 39-week study and are well below (6 %) their limits of *in vitro* solubility.

In repeat dose studies in juvenile rats and dogs, the toxicity profile of aripiprazole was comparable to that observed in adult animals, and there was no evidence of neurotoxicity or adverse events on development.

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic.

Aripiprazole did not impair fertility in reproductive toxicity studies.

Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in sub-therapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures approximately 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Carmellose sodium

Mannitol

Sodium dihydrogen phosphate monohydrate

Sodium hydroxide

Solvent

Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

After reconstitution

Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C. From a microbiological point of view, unless the method of opening/ reconstitution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of user. Shake the vial vigorously for at least 60 seconds to re-suspend prior to injection. Do not store the reconstituted suspension in the syringe.

6.4 Special precautions for storage

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3 Shelf life.

6.5 Nature and contents of container

Not all pack sizes or kit types may be marketed.

Vial:

Type-I glass vial stoppered with a laminated rubber stopper and sealed with a flip-off aluminium cap.

Solvent:

2 ml Type-1 glass vial stoppered with a laminated rubber stopper and sealed with a flip-off aluminium cap.

Each single pack containing one vial of powder, 2 ml vial of solvent, one 3 ml luer lock syringe with pre-attached 38 mm (1.5 inch) 21 gauge, hypodermic safety needle with needle protection device, one 3 ml disposable syringe with luer lock tip, one vial adapter and three hypodermic safety needles: one 25 mm (1 inch) 23 gauge, one 38 mm (1.5 inch) 22 gauge and one 51 mm (2 inch) 21 gauge.

6.6 Special precautions for disposal and other handling.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Step 1: Preparation prior to reconstitution of the powder.

- a) Lay out and confirm that components listed below are provided:
- Abilify Maintena package leaflet and instructions for healthcare professionals
 - Vial of powder
 - 2 ml vial of solvent
 - **Important:** the solvent vial contains an overfill.
 - One 3 ml luer lock syringe with pre-attached 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device
 - One 3 ml disposable syringe with luer lock tip
 - One vial adapter
 - One 25 mm (1 inch) 23 gauge hypodermic safety needle with needle protection device
 - One 38 mm (1.5 inch) 22 gauge hypodermic safety needle with needle protection device
 - One 51 mm (2 inch) 21 gauge hypodermic safety needle with needle protection device
 - Syringe and needle instructions

Step 2: Reconstitution of the powder

- a) Remove the solvent and powder vial caps and wipe the tops with a sterile alcohol swab.
- b) Using the syringe with pre-attached needle, withdraw the pre-determined solvent volume from the vial of the solvent into the syringe.

400 mg vial:

Add 1.9 ml solvent to reconstitute the powder

A small amount of residual solvent will remain in the vial following withdrawal. Any excess should be discarded.



- c) Slowly inject the solvent into the vial containing the powder.
- d) Withdraw air to equalise the pressure in the vial by pulling back slightly on the plunger.



- e) Subsequently, remove the needle from the vial.
Engage the needle safety device by using the one-handed technique.
Gently press the sheath against a flat surface until the needle is firmly engaged in the needle protection sheath.
Visually confirm that the needle is fully engaged into the needle protection sheath, and discard.



Cover



Discard

- f) Shake the vial vigorously for 30 seconds until the suspension appears uniform.



- g) Visually inspect the reconstituted suspension for particulate matter and discolouration prior to administration. The reconstituted medicine is a white to off-white, fluid suspension. Do not use if reconstituted suspension contains particulate matter or any discolouration.
- h) If the injection is not performed immediately after reconstitution, keep the vial below 25 °C for up to 4 hours and shake it vigorously for at least 60 seconds to re-suspend prior to injection.
- i) Do not store the reconstituted suspension in the syringe.

Step 3: Preparation prior to injection

- a) Remove the cover, but not the adapter from the package.
- b) Using the vial adapter package to handle the vial adapter, attach the pre-packaged luer lock syringe to the vial adapter.



- c) Use the luer lock syringe to remove the vial adapter from the package and discard the vial adapter package. Do not touch the spike tip of the adapter at any time.



- d) Determine the recommended volume for injection.

Abilify Maintena 400 mg Vial	
Dose	Volume to Inject
400 mg	2.0 ml
300 mg	1.5 ml
200 mg	1.0 ml
160 mg	0.8 ml

- e) Wipe the top of the vial of the reconstituted suspension with a sterile alcohol swab.
- f) Place and hold the vial of the reconstituted suspension on a hard surface. Attach the adapter-syringe assembly to the vial by holding the outside of the adapter and pushing the adapter's spike firmly through the rubber stopper, until the adapter snaps in place.

- g) Slowly withdraw the recommended volume from the vial into the luer lock syringe to allow for injection. A small amount of excess product will remain in the vial.

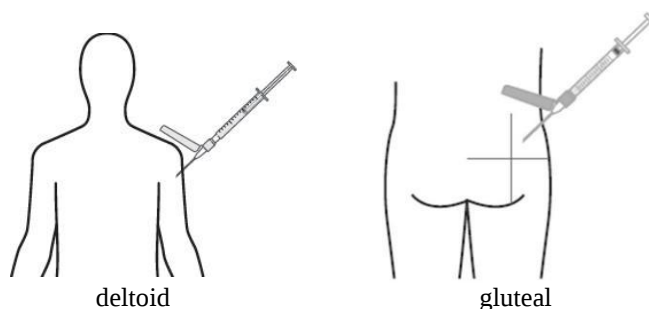


Step 4: Injection procedure

- Detach the luer lock syringe containing the recommended volume of reconstituted Abilify Maintena suspension from the vial.
- Select one of the following hypodermic safety needles depending on the injection site and patient's weight and attach the needle to the luer lock syringe containing the suspension for injection. Ensure the needle is firmly seated on the needle protection device with a push and clockwise twist and then pull the needle cap straight away from the needle.

Body type	Injection site	Needle size
Non-obese	Deltoid Gluteal	25 mm (1 inch) 23 gauge 38 mm (1.5 inch) 22 gauge
Obese	Deltoid Gluteal	38 mm (1.5 inch) 22 gauge 51 mm (2 inch) 21 gauge

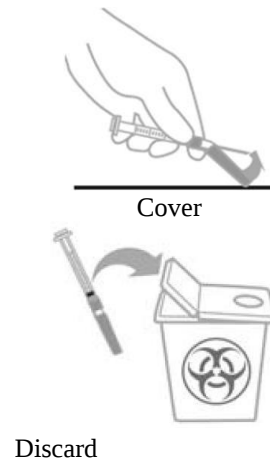
- Slowly inject the recommended volume as a single intramuscular injection into the gluteal or deltoid muscle. Do not massage the injection site. Care must be taken to avoid inadvertent injection into the blood vessel. Do not inject into an area with signs of inflammation, skin damage, lumps and/or bruises. For deep intramuscular gluteal or deltoid injection only.



Remember to rotate sites of injections between the two gluteal or deltoid muscles. If initiating with the two injection start, inject into two different sites in two different muscles. DO NOT inject both injections concomitantly into the same deltoid or gluteal muscle. For known CYP2D6 poor metabolisers administer in either-two separate deltoid muscles or one deltoid and one gluteal muscle. DO NOT inject into two gluteal muscles. Look for signs or symptoms of inadvertent intravenous administration.

Step 5: Procedures after injection

- a) Engage the needle safety device as described in Step 2 e). Dispose of the vials, adapter, needles, and syringe appropriately after injection. The powder and solvent vials are for single-use only.



7 PRODUCT REGISTRATION HOLDER

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8 DATE OF REVISION OF THE TEXT

06/2021