1. NAME OF THE MEDICINAL PRODUCT

Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection
Each vial contains 416 mg aripiprazole monohydrate equivalent to 400mg aripiprazole.

Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
Each pre-filled syringe contains 416 mg aripiprazole monohydrate equivalent to 400 mg aripiprazole.
After reconstitution, each ml of suspension contains 200 mg aripiprazole.

For the full list of excipients, see section 6.1.

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

- For the acute and 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 Posology and method of administration

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

Titration of the dose for Abilify Maintena 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 resume monthly injection schedule.
> 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 resume monthly injection schedule.
> 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 patients

The effectiveness and safety of Abilify Maintena in the treatment of schizophrenia in patients > 61 years and in the treatment of bipolar I disorder in patients ≥ 66 years have not been evaluated.

Renal impairment

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

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 requiring cautious dosing, oral formulation should be preferred (see section 5.2).

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 method of administration) along with one single dose of the previous prescribed dose of oral aripiprazole.

After the injection start, the maintenance dose of Abilify Maintena in known CYP2D6 poor metabolisers is 300mg.

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) 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 done 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). 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).

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
Patients taking 300 mg of Abilify Maintena	
Strong CYP2D6 or strong CYP3A4 inhibitors	200 mg*
Strong CYP2D6 and strong CYP3A4 inhibitors	160 mg*
CYP3A4 inducers	Avoid use

*200 mg and 160 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/m^2), 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).

The powder and solvent vials and the pre-filled syringe are for single-use only.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contra-indications

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

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). 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 ischemic 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).

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).

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). 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).

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).

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).

Cerebrovascular adverse reactions

In the same trials with oral aripiprazole, cerebrovascular adverse reactions (e.g. stroke, transient ischemic 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).

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 antipsychotic medicines, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycemia-related adverse reactions (including diabetes) or in abnormal glycemia laboratory values compared to placebo. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotic medicines are not available to allow direct comparisons. Patients treated with any antipsychotic medicinal products, including aripiprazole, should be observed for signs and symptoms of hyperglycemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control (see section 4.8).

Hypersensitivity
Hypersensitivity reactions, characterized 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 lifestyle 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).

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 Other Compulsive Behaviors
Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other compulsive urges reported less frequently include: sexual urges, shopping, eating or binge eating, and other impulsive and compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or intense gambling urges, compulsive sexual urges, compulsive shopping, 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. In some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued.

Compulsive behaviors 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.

Falls
Aripiprazole may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls. Caution should be taken when treating patients at higher risk, and a lower starting dose should be considered (e.g. elderly or debilitated patients; see section 4.2).

Sleep Apnoea
Sleep apnoea and related disorders have been reported in patients treated with atypical antipsychotic drugs, including aripiprazole, with or without concomitant weight gain or prior history of sleep apnoea.
Aripiprazole should be used with caution in patients who have sleep apnoea or risk factors for developing sleep apnoea, which include: overweight/obesity, males, and concomitant use of central nervous system depressants

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 α1-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).

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).

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).

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).
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 coadministration 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).

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). 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.

New-born infants exposed to antipsychotics (including aripiprazole) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, new-born infants should be monitored carefully (see section 4.8).

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 (see section 4.8). 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

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 Abilify Maintena 400 mg/300 mg injections (i.e., have been treated for at least 12 months).

Abilify has been evaluated for safety in 13543 patients who participated in multiple-dose clinical trials across all approved indications including schizophrenia and bipolar I disorder, and who had approximately 7619 patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole short acting injection. A total of 3390 patients were treated with oral aripiprazole for at least 180 days and 1933 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 below.

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)
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)
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				

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)**
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)

The most frequently observed treatment emergent adverse event (TEAE) reported in ≥5% of patients treated with Abilify Maintena in the 12-week clinical trial in acutely relapsed patients were weight increased (16.8%), headache (14.4%), akathisia (11.4%), constipation (9.6%), cough (6.0%), dyspepsia (6.0%), agitation (5.4%), injection site pain (5.4%), sedation (5.4%) and toothache (5.4%). The TEAEs that occurred in at least 2% of patients and greater than placebo during the active treatment phase of the 12-week clinical trial in patients in the acute phase of schizophrenia are listed in table below.

Incidence of Treatment–emergent Adverse Events Occurring in ≥ 2% of Aripiprazole IM Depot Patients with Schizophrenia and Greater than Placebo in the Acute Treatment Phase of the Acute Phase Placebo-controlled Trial

System organ class MedDRA preferred term	Aripiprazole IM Depot 400/300mg (N=167)	Placebo (N=172)
	n (%)	n (%)
Gastrointestinal Disorders		
Abdominal discomfort	4 (2.4)	2 (1.2)
Constipation	16 (9.6)	12 (7.0)
Diarrhea	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)

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%).

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)
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)

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 benzatropine 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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.

Pathological gambling and other impulsive control disorders
Pathological gambling, hypersexuality, compulsive shopping and binge or compulsive eating can occur in patients treated with aripiprazole (see section 4.4).

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-glutamyl transferase increased, glucose urine present, glycosylated hemoglobin 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, hypercholesterolemia, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertriglyceridemia, hyperuricemia, hypoglycemia, increased appetite, overweight, type 2 diabetes mellitus.

Musculoskeletal and connective tissue disorders

Arthritis, joint swelling, muscle rigidity, muscle hemorrhage, 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 legs syndrome, sedation, sinus headache, syncope, tardive dyskinesia, tension headache, dizziness, transient ischemic 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, galactorrhea, 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.

Endocrine disorders

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

Metabolism and nutrition disorders

Anorexia, hyponatremia.

Psychiatric disorders

Agitation, hypersexuality, pathological gambling, impulse-control disorders, obsessive-compulsive disorder, eating disorder, Sleep-related eating disorder (SRED), Somnambulism (sleep walking)

Nervous system disorders

Speech disorder, grand mal convulsion, restless legs syndrome.

Eye disorders

Diplopia.

Vascular disorders

Syncope, hypertension.

Respiratory, thoracic and mediastinal disorders

Aspiration pneumonia, hiccups.

Gastrointestinal disorders

Pancreatitis, dysphagia, diarrhea.

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 hemoglobin increased, weight increased, weight decreased, Alanine Aminotransferase increased, Aspartate Aminotransferase increased, Gamma-glutamyl transferase increased. Blood prolactin decreased.

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.

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.

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 diarrhea. 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
It has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D2 and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2A 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-HT1A and 5-HT2A receptors and has moderate affinity for dopamine D4, serotonin 5-HT2C 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:

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).

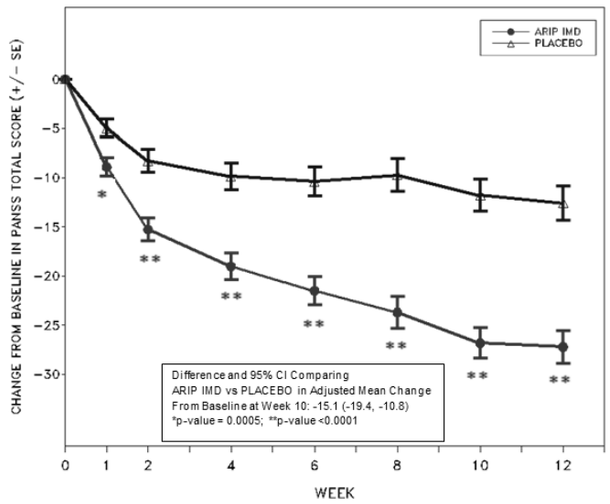
The primary endpoint was the change from baseline to Week 10 in PANSS Total Score. Abilify Maintena was superior to placebo in improving the PANSS total score, with Week 10 scores of -26.8 and -11.7, respectively (see Table 1). A statistically significant difference (p≤0.0001) was seen at each measured 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.

Table 1: 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

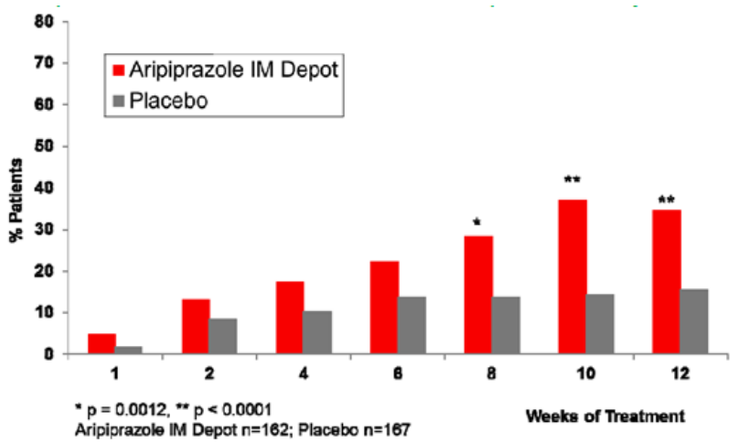
Figure 1: Adjusted Mean Change from Baseline in PANSS Total Score (MMRM)



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



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.

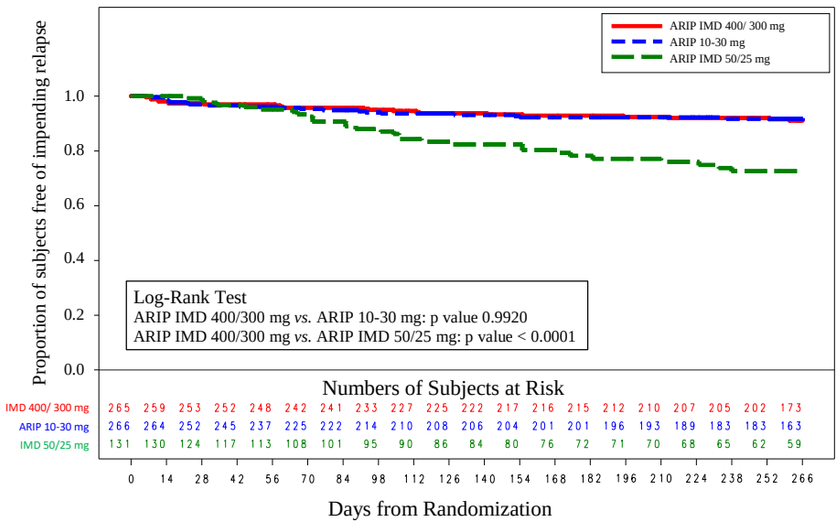
The results of analysis of the primary efficacy endpoint, the estimated proportion of patients experiencing impending relapse by end of Week 26 of the Double-blind, Active-controlled Phase, showed that Abilify Maintena 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10-30 mg. The estimated 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 50mg/ 25 mg groups are shown in Figure 3.

Figure 3: 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 the Positive and Negative Syndrome Scale score (PANSS).

Table 2: PANNS Total Score – Change from Baseline to Week 38-LOCF

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.

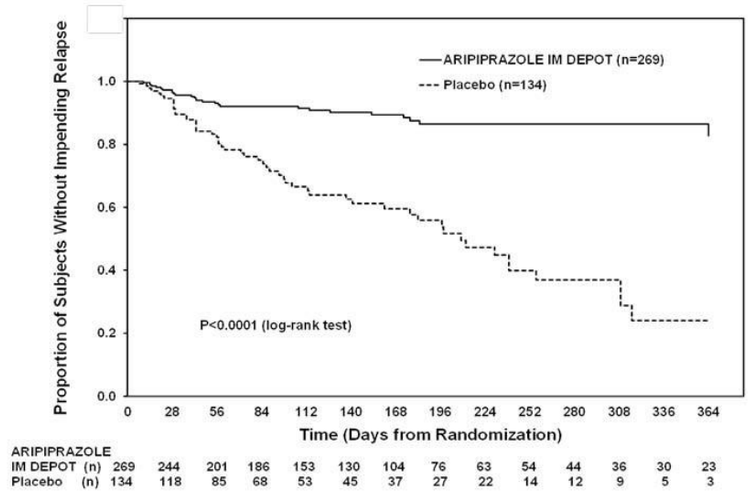
The second trial was a 52-week, randomised, withdrawal, double-blind, trial conducted in adult patients with a current diagnosis of schizophrenia. This trial consisted of a screening phase and 4 treatment phases: Conversion, Oral Stabilisation, Abilify Maintena Stabilisation, and Double-blind Placebo-controlled. 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. These 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 4.

Figure 4: 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 3: 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
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

Bipolar I Disorder

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

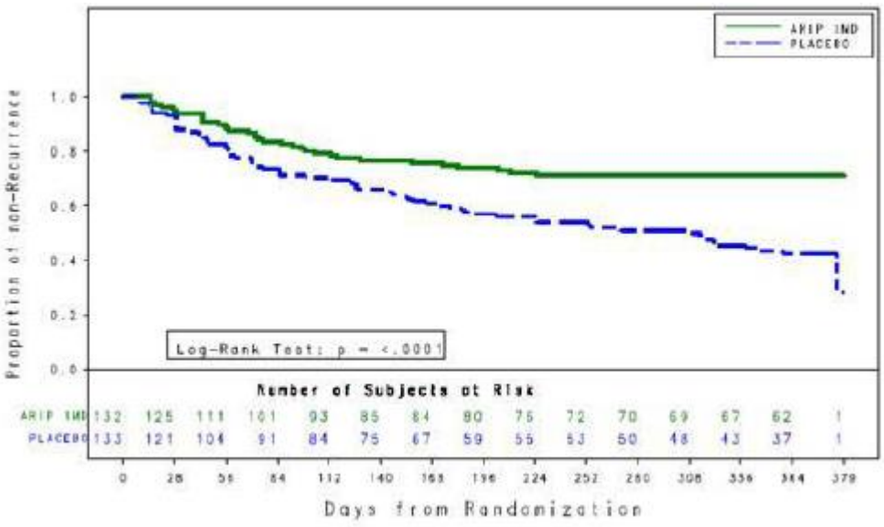
The efficacy and safety of Abilify Maintena as treatment in adults aged 18 to 65 years was demonstrated in a 52-week, double-blind, placebo-controlled randomized withdrawal trial in patients who met DSM-IV-TR criteria for bipolar I disorder and who were experiencing a manic episode at trial entry. This trial consisted of a screening phase and 4 treatment phases: oral conversion, oral stabilization, Abilify Maintena stabilization, and a randomized, 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 randomized 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 5). 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.

Figure 5: Kaplan-Meier Curves of Time to Recurrence for Any Mood Episode



ARID IMD = Aripiprazole IM Depot

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 4).

Table 4: 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 endpoint.

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 [^{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 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).
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 hydroxymetabolites 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/m^2.
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

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

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

Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
If the injection is not performed immediately after reconstitution, the syringe can be kept below 25 °C for up to 2 hours.

6.4 Special precautions for storage
Do not store above 30 ºC.
Do not freeze.

Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
Keep the syringe in the outer carton in order to protect from light.

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

6.5 Nature and contents of container
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection

400 mg powder: 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.

Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

Clear glass pre-filled syringe (type-I glass) with grey chlorobutyl stoppers (front-, middle- and end stopper), polypropylene front assembly, polypropylene finger grip, plunger rod, and silicone over-cap. The front chamber between front stopper and middle stopper contains the powder and the rear chamber between middle stopper and end stopper the solvent.

Single pack
Each single pack containing one pre-filled syringe, 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.

Multipack
Bundle pack of 3 single packs.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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

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

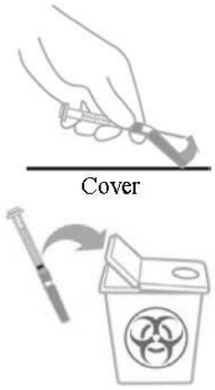
Step 2: Reconstitution of the powder
a) Remove the solvent and powder vial caps and wipe the tops with a sterile alcohol swab.

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.



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.

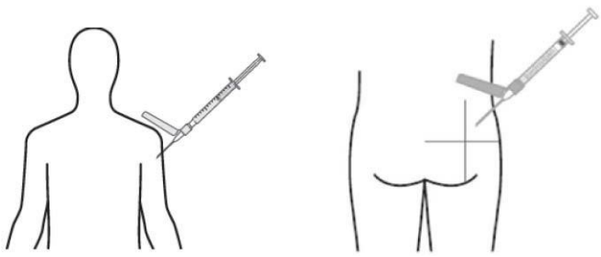
Step 4: Injection procedure

a) Detach the luer lock syringe containing the recommended volume of reconstituted Abilify Maintena suspension from the vial.

b) 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

c) 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.

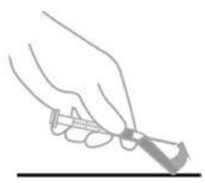


deltoid gluteal

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 2e. Dispose of the vials, adapter, needles, and syringe appropriately after injection. The powder and solvent vials are for single-use only.



Cover

Discard

Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

Step 1: Preparation prior to reconstitution of the powder

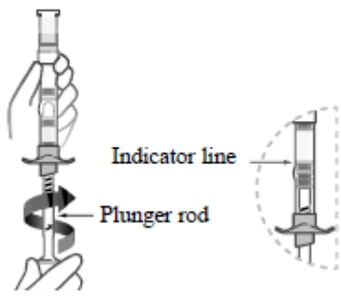
Lay out and confirm that components listed below are provided:

Abilify Maintena package leaflet and instructions for healthcare professionals.

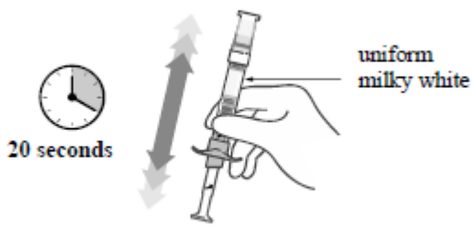
- One Abilify Maintena pre-filled syringe.
- One 25 mm (1 inch) 23 gauge hypodermic safety needle with needle protection device.
- One 38 mm (1.5 inch) 22 gauge hypodermic safety needle with needle protection device.
- One 51 mm (2 inch) 21 gauge hypodermic safety needle with needle protection device.
- Syringe and needle instructions.

Step 2: Reconstitution of the powder

a) Push plunger rod slightly to engage threads. And then, rotate plunger rod until the rod stops rotating to release diluent. After plunger rod is at complete stop, middle stopper will be at the indicator line.



b) Vertically shake the syringe vigorously for 20 seconds until the reconstituted suspension appears uniform. The suspension should be injected immediately after reconstitution.

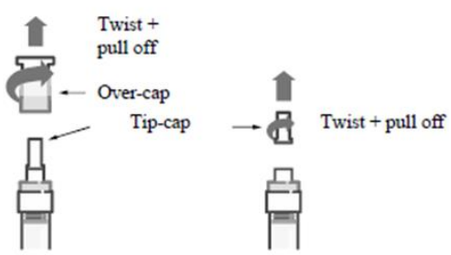


c) Visually inspect the syringe for particulate matter and discoloration prior to administration. The reconstituted product suspension should appear to be a uniform, homogeneous suspension that is opaque and milky-white in colour.

d) If the injection is not performed immediately after reconstitution, the syringe can be kept below 25 °C for up to 2 hours. Shake the syringe vigorously for at least 20 seconds to re-suspend prior to injection if the syringe has been left for more than 15 minutes.

Step 3: Injection procedure

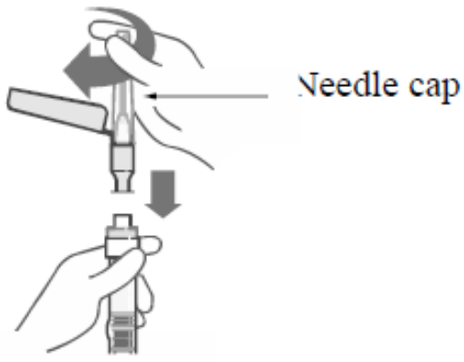
a) Twist and pull off over-cap and tip-cap.



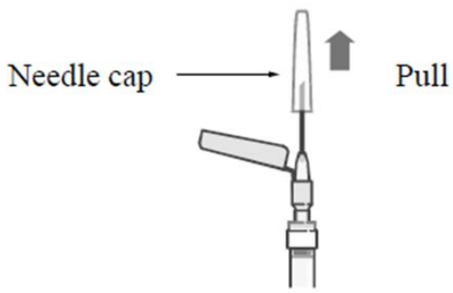
b) Select one of the following hypodermic safety needles depending on the injection site and patient's weight.

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

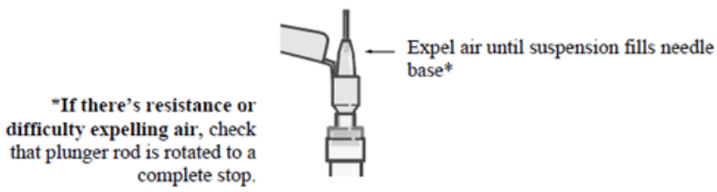
c) While holding the needle cap, ensure the needle is firmly seated on the safety device with a push. Twist clockwise until snugly fitted.



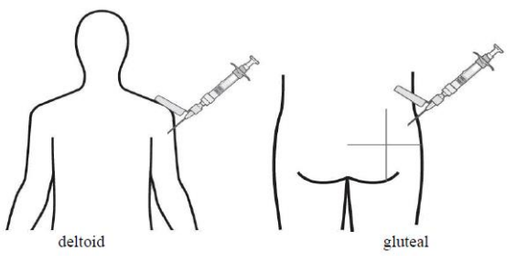
d) Then pull needle-cap straight up.



e) Hold syringe upright and advance plunger rod slowly to expel the air. If it's not possible to advance plunger rod to expel the air, check that plunger rod is rotated to a complete stop. It is not possible to re-suspend after the air in the syringe is expelled.



f) Slowly inject 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.

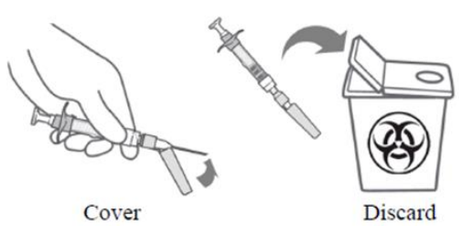


Remember to rotate sites of injections between the two gluteal or deltoid muscles.

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 4: Procedures after injection
Engage the needle safety device.
Dispose of the needle and pre-filled syringe appropriately after injection.



7 MANUFACTURER

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8 DATE OF REVISION OF THE TEXT

August 2023