ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection
Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection

Each vial contains 300 mg aripiprazole.

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

Each vial contains 400 mg aripiprazole.

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

Each pre-filled syringe contains 300 mg aripiprazole.

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

Each pre-filled syringe contains 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

Abilify Maintena is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

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 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, one injection of Abilify Maintena 400 mg should be administered and treatment with 10 mg to 20 mg oral aripiprazole per day for 14 consecutive days should be continued to maintain therapeutic aripiprazole concentrations during initiation of therapy.
- Two injection start: On the day of initiation, two separate injections of Abilify Maintena 400 mg should be administered at two different 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 400 mg 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 dose, 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 400 mg/300 mg in the treatment of schizophrenia in patients 65 years of age or older has not been established (see section 4.4).

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

Hepatic impairment
No dose 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).

Known CYP2D6 poor metabolisers
In patients who are known to be CYP2D6 poor metabolisers:

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

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

- One injection start: The starting dose should be reduced to 200 mg (see section 4.5) and treatment should be continued 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 400 mg and 300 mg 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 dose adjustments should be made in patients taking concomitant strong CYP3A4 inhibitors or strong CYP2D6 inhibitors for more than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the dose may need to be increased to the previous dose (see section 4.5). 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 400 mg or 300 mg 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 monthly dose
Patients taking Abilify Maintena 400 mg	
Strong CYP2D6 or strong CYP3A4 inhibitors	300 mg
Strong CYP2D6 and strong CYP3A4 inhibitors	200 mg*
CYP3A4 inducers	Avoid use
Patients taking Abilify Maintena 300 mg	
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 400 mg/300 mg in children and adolescents aged 0 to 17 years have not been established. No data are available.

Method of administration

Abilify Maintena 400 mg and 300 mg is only intended for intramuscular use and must not be administered intravenously or subcutaneously. It should only be administered by a healthcare professional.

The suspension must 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.

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.

Full instructions for use and handling of Abilify Maintena 400 mg and 300 mg are provided in the package leaflet (information intended for healthcare professionals).

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

4.3 Contraindications

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.

Use in patients who are in an acutely agitated or severely psychotic state

Abilify Maintena 400 mg/300 mg should not be used to manage acutely agitated or severely psychotic states when immediate symptom control is warranted.

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

Aripiprazole 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 aripiprazole 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 aripiprazole, dose reduction or discontinuation 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 antipsychotics. 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 antipsychotics, 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 to 99 years), patients treated with aripiprazole were 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 placebo. 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 ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78 to 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).

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

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. Patients treated with aripiprazole should be observed for signs and symptoms of hyperglycaemia (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, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

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).

Dysphagia

Oesophageal dysmotility and aspiration have been associated with the use of aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Gambling disorder and other 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 behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive 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; however, in some cases, urges were reported to have stopped when the dose was reduced or the medicinal product was discontinued. Impulse control disorders may result in harm to the patient and others if not recognised. A dose reduction or stopping of the medicinal product should be considered if a patient develops such urges (see section 4.8).

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).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No 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 central nervous system (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 aripiprazole

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).

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 strong 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 dose of aripiprazole 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 aripiprazole, modest increases in plasma aripiprazole concentrations may be expected.

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 400 mg/300 mg 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 400 mg/300 mg should be avoided because the blood levels of aripiprazole are decreased and may be below the effective levels.

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 Selective Serotonin Reuptake Inhibitors/Serotonin Noradrenaline Reuptake Inhibitors (SSRI/SNRI), or with medicinal products that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

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 aripiprazole..

Prescribers need to be aware of the long-acting properties of Abilify Maintena. Aripiprazole has been detected in plasma in adult patients up to 34 weeks after a single-dose administration of the prolonged-release suspension.

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).

Maternal exposure to Abilify Maintena before and during pregnancy may lead to adverse reactions in the newborn child. Abilify Maintena should not be used during pregnancy unless clearly necessary.

Breast-feeding

Aripiprazole/metabolites are excreted in the breast milk to such an extent that effects on the breast-fed infant are likely if Abilify Maintena is administered to breast-feeding women. Since a single dose of Abilify Maintena is expected to remain for up to 34 weeks in plasma (see section 5.2), breast-fed infants may be at risk even from Abilify Maintena administration long before breast-feeding. Patients currently under treatment or who have been treated in the past 34 weeks with Abilify Maintena should not breast feed.

Fertility

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

4.7 Effects on ability to drive and use machines

Aripiprazole has minor to 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).

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions (ADRs) reported in ≥ 5 % of patients in two double-blind, long-term trials of Abilify Maintena 400 mg/300 mg 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 ADRs associated with aripiprazole therapy are tabulated below. The table is based on adverse reactions reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ class and frequency; very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 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 ADRs listed under the frequency “not known” were reported during post-marketing use.

	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 Panic reaction Depression Affect lability Apathy Dysphoria Sleep disorder Bruxism Libido decreased Mood altered	Completed suicide Suicide attempt Gambling disorder Impulse-control disorder Binge eating Compulsive shopping Poriomania Nervousness Aggression
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 Generalized tonic-clonic seizure Serotonin syndrome Speech disorder
Eye disorders		Oculogyric crisis Vision blurred Eye pain Diplopia Photophobia	

	Common	Uncommon	Not known
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 arrhythmia 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	Gastrooesophageal reflux disease Dyspepsia Vomiting Diarrhoea Nausea Abdominal pain upper Abdominal discomfort Constipation Frequent bowel movements Salivary hypersecretion	Pancreatitis Dysphagia
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)

	Common	Uncommon	Not known
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)
Reproductive system and breast disorders	Erectile dysfunction	Galactorrhoea Gynaecomastia Breast tenderness Vulvovaginal dryness	Priapism
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 long-term 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 %), had 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 400 mg/300 mg 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 400 mg/300 mg was injected in the gluteal muscle, repeated occurrence of injection site pain was more frequent in the deltoid muscle.

Neutropenia
Neutropenia has been reported in the clinical program with Abilify Maintena 400 mg/300 mg and typically started around day 16 after first injection, and lasted a median of 18 days.

Extrapyramidal Symptoms (EPS)
In trials in stable patients with schizophrenia, Abilify Maintena 400 mg/300 mg was associated with a higher frequency of EPS symptoms (18.4 %) than oral aripiprazole treatment (11.7 %). Akathisia was the most frequently observed symptom (8.2 %) and typically started around day 10 after first injection, and lasted a median of 56 days. Subjects with akathisia typically received anti-cholinergic medicines as treatment, primarily benzatropine mesilate and trihexyphenidyl. Less often substances such as propranolol and benzodiazepines (clonazepam and diazepam) were administered to control akathisia. Parkinsonism events followed in frequency of 6.9 % for Abilify Maintena 400 mg/300 mg, 4.15 % for oral aripiprazole 10 mg to 30 mg tablets and 3.0 % for 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 long-term trial (see section 5.1), the incidence of weight gain of ≥ 7 % from baseline to last visit was 9.5 % for Abilify Maintena 400 mg/300 mg and 11.7 % for the oral aripiprazole tablets 10 mg to 30 mg. The incidence of weight loss of ≥ 7 % from baseline to last visit was 10.2 % for Abilify Maintena 400 mg/300 mg and 4.5 % for oral aripiprazole tablets 10 mg to 30 mg. During the double-blind, placebo-controlled phase of the 52-week long-term trial (see section 5.1), the incidence of weight gain of ≥ 7 % from baseline to last visit was 6.4 % for Abilify Maintena 400 mg/300 mg and 5.2 % for placebo. The incidence of weight loss of ≥ 7 % from baseline to last visit was 6.4 % for Abilify Maintena 400 mg/300 mg and 6.7 % for placebo. During double-blind treatment, mean change in body weight from baseline to last visit was −0.2 kg for Abilify Maintena 400 mg/300 mg and −0.4 kg for placebo (p = 0.812).

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

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

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose associated with adverse reactions were reported in clinical studies with aripiprazole. Care must be taken to avoid inadvertent injection of this medicinal product into a blood vessel. Following any confirmed or suspected accidental overdose/inadvertent intravenous administration, 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 4 500 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

It has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors. 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 D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and has moderate

affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic, and histamine H_1 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 mg 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 D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical efficacy and safety

Maintenance treatment of schizophrenia in adults

Abilify Maintena 400 mg/300 mg
The efficacy of Abilify Maintena 400 mg/300 mg in the maintenance treatment of patients with schizophrenia was established in two randomised, double-blind, long-term trials.

The pivotal 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 mg to 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 400 mg/300 mg 2) the stabilisation dose of oral aripiprazole 10 mg to 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 to test assay sensitivity for the non-inferiority design.

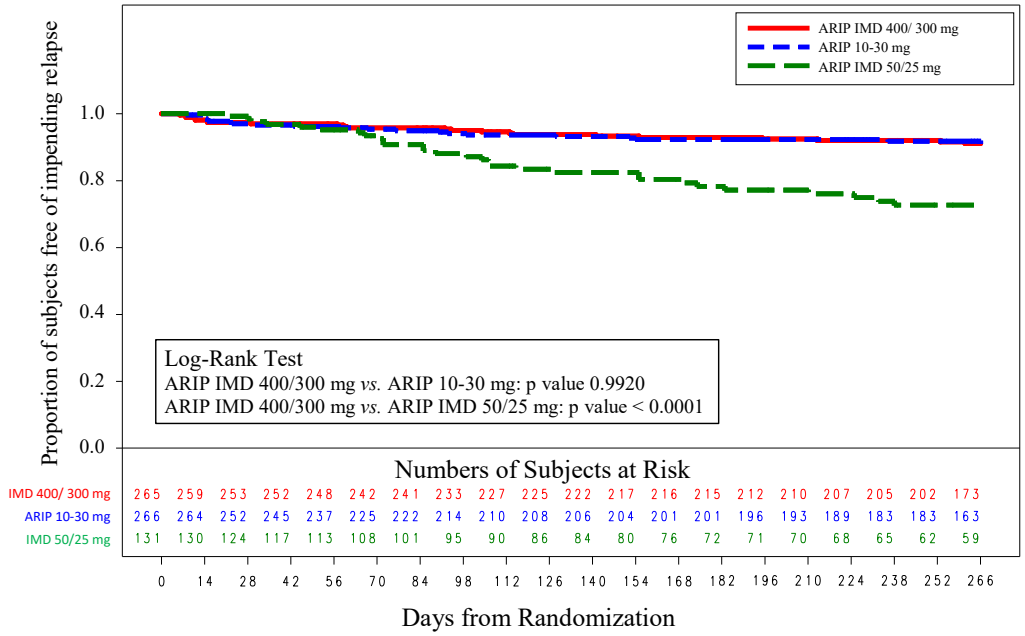
The results of analysis of the primary efficacy endpoint, the estimated proportion of patients experiencing impending relapse by end of week 26 of the double-blind, active-controlled phase, showed that Abilify Maintena 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10 mg to 30 mg.
The estimated relapse rate by end of week 26 was 7.12 % for Abilify Maintena 400 mg/300 mg, and 7.76 % for oral aripiprazole tablets 10 mg to 30 mg, 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 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10 mg to 30 mg.

The estimated proportion of patients experiencing impending relapse by end of week 26 for Abilify Maintena 400 mg/300 mg was 7.12 %, which was statistically significantly lower than in aripiprazole long-acting injectable 50 mg/25 mg (21.80 %; p = 0.0006). Thus, superiority of Abilify Maintena 400 mg/300 mg 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, active-controlled phase for Abilify Maintena 400 mg/300 mg, oral aripiprazole 10 mg to 30 mg, and aripiprazole long-acting injectable 50 mg/25 mg 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 400 mg/300 mg;ARIP 10 mg to 30 mg = oral aripiprazole; ARIP IMD 50/25 mg = Aripiprazole long-acting injectable

Further, the non-inferiority of Abilify Maintena 400 mg/300 mg compared to oral aripiprazole 10 mg to 30 mg is supported by the results of the analysis of the positive and negative syndrome scale score (PANSS).

Table 1 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 US adult patients with a current diagnosis of schizophrenia. This trial consisted of a screening phase and 4 treatment phases: Conversion, oral stabilisation, Abilify Maintena 400 mg/300 mg 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 400 mg/300 mg and began an Abilify Maintena 400 mg/300 mg 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 400 mg/300 mg or placebo, respectively.

The final efficacy analysis included 403 randomised patients and 80 exacerbations of psychotic symptoms/impending relapse events. In the placebo group 39.6 % of the patients had progressed to

impending relapse, whilst in the Abilify Maintena 400 mg/300 mg group impending relapse occurred in 10 % of the patients; thus patients in the placebo group had a 5.03-fold greater risk of experiencing impending relapse.

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 Abilify Maintena 400 mg/300 mg (−0.33 ng/mL) compared with a mean increase in oral aripiprazole tablets 10 mg to 30 mg (0.79 ng/mL; $p < 0.01$). The incidence of Abilify Maintena 400 mg/300 mg 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 mg to 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 Abilify Maintena 400 mg/300 mg (−0.38 ng/mL) compared with a mean increase in placebo (1.67 ng/mL). The incidences of Abilify Maintena 400 mg/300 mg patients with prolactin levels > 1 time the ULN was 1.9 % compared to 7.1 % for placebo patients.

Acute treatment of schizophrenia in adults
The efficacy of Abilify Maintena 400 mg/300 mg in acutely relapsed adult patients with schizophrenia was established in a short-term (12-week), randomised, double-blind, placebo-controlled trial (n = 339).
The primary endpoint (change in PANSS total score from baseline to week 10) showed superiority of Abilify Maintena 400 mg/300 mg (n = 167) over placebo (n = 172).
Similar to the PANSS total score, both the PANSS positive and negative subscale scores also showed an improvement (decrease) from baseline over time.

Table 2 PANSS total score – change from baseline to week 10: randomised efficacy sample

PANSS total score – change from baseline to week 10: randomised efficacy sample [a]		
	Abilify Maintena 400 mg/300 mg	**Placebo**
Mean baseline (SD)	102.4 (11.4) n = 162	103.4 (11.1) n = 167
LS mean change (SE)	−26.8 (1.6) n = 99	−11.7 (1.6) n = 81
P-value	< 0.0001	
Treatment difference[b] (95 % CI)	−15.1 (−19.4, −10.8)	

[a] Data were analysed using a mixed model repeated measures (MMRM) approach. The analysis included only subjects 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 least squares mean change from baseline.

Abilify Maintena 400 mg/300 mg also showed statistically significant improvement in symptoms represented by Clinical Global Impressions Severity, CGI-S (CGI-S) score change from baseline to week 10.

Personal and social functioning were evaluated using the Personal and Social Performance (PSP) scale. The PSP is a validated clinician-rated scale that measures personal and social functioning in four domains: socially useful activities (e.g. work and study), personal and social relationships, self-care, and disturbing and aggressive behaviours. There was a statistically significant treatment difference in favour of Abilify Maintena 400 mg/300 mg compared to placebo at week 10 (+7.1, $p < 0.0001$, 95 % CI: 4.1, 10.1 using an ANCOVA model (LOCF)).

The safety profile was consistent with that known to Abilify Maintena 400 mg/300 mg. Nevertheless, there were differences from what has been observed with maintenance use in the treatment of schizophrenia. In a short-term (12-week), randomised, double-blind, placebo-controlled trial with Abilify Maintena 400 mg/300 mg treated subjects the symptoms which had at least twice the incidence of placebo were increased weight and akathisia. The incidence of weight gain of ≥ 7 % from baseline to last visit (week 12) was 21.5 % for Abilify Maintena 400 mg/300 mg compared with the placebo group 8.5 %. Akathisia was the most frequently observed EPS symptom (Abilify Maintena 400 mg/300 mg 11.4 % and placebo group 3.5 %).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Abilify Maintena in all subsets of the paediatric population in schizophrenia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Aripiprazole absorption into the systemic circulation is slow and prolonged following Abilify Maintena 400 mg/300 mg administration due to low solubility of aripiprazole particles.The average absorption half-life of Abilify Maintena 400 mg/300 mg 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 400 mg/300 mg 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 4 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 400 mg/300 mg, dehydro-aripiprazole, the active metabolite, represents about 29.1 % to 32.5 % of aripiprazole AUC in plasma.

Elimination

After administration of multiple dose of Abilify Maintena 400 mg/300 mg, 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 400 mg/300 mg, the total body clearance of aripiprazole was 3.71 L/h in normal 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 400 mg/300 mg 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 400 mg/300 mg 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 active substance), cellular infiltrates, oedema (swelling) and, in monkeys, fibrosis. These effects gradually resolved with discontinuation of dosing.

Non-clinical safety data for orally administered aripiprazole reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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 mg/kg/day 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 repeated 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 (E421)
Sodium dihydrogen phosphate monohydrate (E339)
Sodium hydroxide (E524)

Solvent

Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

Abilify Maintena 400 mg/300 mg *powder and solvent for prolonged-release suspension for injection*
The suspension should be injected immediately after reconstitution but can be stored below 25 °C for up to 4 hours in the vial.

Abilify Maintena 400 mg/300 mg *powder and solvent for prolonged-release suspension for injection in pre-filled syringe*
The suspension should be injected immediately after reconstitution but can be stored below 25 °C for up to 2 hours in the syringe.

After reconstitution

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection
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. Do not store the reconstituted suspension in the syringe.

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled 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 freeze.

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
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 300 mg powder and solvent for prolonged-release suspension for injection
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection

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

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

Single pack
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.

Multipack
Bundle pack of 3 single packs.

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
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 and other handling

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection

Shake the vial vigorously for at least 30 seconds until the suspension appears uniform.
If the injection is not performed immediately after reconstitution shake it vigorously for at least 60 seconds to re-suspend prior to injection.

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

Vertically shake the syringe vigorously for 20 seconds until medicine is uniformly milky-white and use immediately. 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.

Gluteal muscle administration
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. Gluteal injections should be alternated between the two gluteal muscles.

Deltoid muscle administration
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. Deltoid injections should be alternated between the two deltoid muscles.
The powder and solvent vials and the pre-filled syringe are for single-use only.

Discard vial, adapter, syringe, needles, unused suspension and water for injections appropriately.

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

Full instructions for use and handling of Abilify Maintena 400 mg/300 mg are provided in the package leaflet (information intended for healthcare professionals).

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection

EU/1/13/882/001
EU/1/13/882/003

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

EU/1/13/882/002
EU/1/13/882/004

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

EU/1/13/882/005
EU/1/13/882/007

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

EU/1/13/882/006
EU/1/13/882/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 November 2013
Date of latest renewal: 27 August 2018

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Abilify Maintena 720 mg prolonged-release suspension for injection in pre-filled syringe
Abilify Maintena 960 mg prolonged-release suspension for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each pre-filled syringe contains 720 mg aripiprazole per 2.4 mL (300 mg/mL).

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

Each pre-filled syringe contains 960 mg aripiprazole per 3.2 mL (300 mg/mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release suspension for injection in pre-filled syringe

The suspension is white to off-white. The suspension is pH neutral (approximately 7.0).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abilify Maintena is indicated for maintenance treatment of schizophrenia in adult patients stabilised with aripiprazole.

4.2 Posology and method of administration

Posology

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

Titration of the dose for Abilify Maintena is not required.

Starting regimen

The recommended starting dosing regimen when transitioning from Abilify Maintena 400 mg once monthly is Abilify Maintena 960 mg no sooner than 26 days after previous injection of Abilify Maintena 400 mg. Abilify Maintena 960 mg should then be dosed once every 2 months (every 56 days).

Initiation may also be started by following one of two additional regimens:

- One injection start: On the day of initiation following oral therapy, one injection of Abilify Maintena 960 mg should be administered and treatment with 10 mg to 20 mg oral aripiprazole per day for 14 consecutive days should be continued to maintain therapeutic aripiprazole concentrations during initiation of therapy.
- Two injection start: On the day of initiation following oral therapy, one injection of Abilify Maintena 960 mg and one injection of Abilify Maintena 400 mg should be administered at two

different injection sites (see method of administration), along with one 20 mg dose of oral aripiprazole.

Dosing interval and dosing adjustments

After the injection start, the recommended maintenance dose is one injection of Abilify Maintena 960 mg every second month. Inject Abilify Maintena 960 mg once every two months as a single injection 56 days after the previous injection. Patients may be given the injection up to 2 weeks before or 2 weeks after the scheduled 2-month dose.

If there are adverse reactions with the Abilify Maintena 960 mg dose, reduction to Abilify Maintena 720 mg once every two months should be considered.

Missed doses

If more than 8 weeks and less than 14 weeks have elapsed since the last injection, the next dose of Abilify Maintena 960 mg/720 mg should be administered as soon as possible. The once every two months schedule should then be resumed. If more than 14 weeks have elapsed since the last injection, the next dose of Abilify Maintena 960 mg/720 mg should be administered with concomitant oral aripiprazole for 14 days or with 2 separate injections (one each of Abilify Maintena 960 mg and Abilify Maintena 400 mg or one each Abilify Maintena 720 mg and Abilify Maintena 300 mg) administered together with one 20 mg oral aripiprazole dose. The once every two months schedule should then be resumed.

Special populations

Elderly
The safety and efficacy of Abilify Maintena 960 mg/720 mg in the treatment of schizophrenia in patients 65 years of age or older has not been established (see section 4.4). No recommendations on dosing can be made.

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

Hepatic impairment
No dose 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).

Known CYP2D6 poor metabolisers
In patients who are known to be CYP2D6 poor metabolisers:
- Patients transitioning from Abilify Maintena 300 mg once monthly: The starting dose should be one injection of Abilify Maintena 720 mg g, no sooner than 26 days after previous injection of Abilify Maintena 300 mg.
- One injection start (following transition from oral therapy): The starting dose should be one injection of Abilify Maintena 720 mg and treatment should be continued with the prescribed dose of oral aripiprazole per day for 14 consecutive days.
- Two injection start (following transition from oral therapy): The starting dose should be 2 separate injections; one Abilify Maintena 720 mg and one Abilify Maintena 300 mg injection, together with a single dose of 20 mg oral aripiprazole (see method of administration).

Thereafter, a maintenance dose of Abilify Maintena 720 mg should be administered once every two months as a single injection.

Maintenance dose adjustments due to interactions with CYP2D6 and/or CYP3A4 inhibitors and/or CYP3A4 inducers
Maintenance dose adjustments should be made in patients taking concomitant strong CYP3A4 inhibitors or strong CYP2D6 inhibitors for more than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the dose may need to be increased to the previous dose (see section 4.5). In case of adverse reactions despite dose adjustments of Abilify Maintena 960 mg, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

Concomitant use of CYP3A4 inducers with Abilify Maintena 960 mg/720 mg for more than 14 days should be avoided because the blood levels of aripiprazole are decreased and may be below the effective levels (see section 4.5).

Abilify Maintena 960 mg/720 mg should not be used in patients who are known to be CYP2D6 poor metabolisers and concomitantly use a strong CYP2D6 and/or CYP3A4 inhibitor.

Table 1: 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 2-monthly dose
Patients taking Abilify Maintena 960 mg*	
Strong CYP2D6 or strong CYP3A4 inhibitors	720 mg
Strong CYP2D6 and strong CYP3A4 inhibitors	Avoid use
CYP3A4 inducers	Avoid use

*Avoid use in patients who already take 720 mg, e.g. due to adverse rections to the higher dose.

Paediatric population
The safety and efficacy of Abilify Maintena 960 mg/720 mg in children and adolescents aged 0 to 17 years have not been established. No data are available.

Method of administration

Abilify Maintena 960 mg and 720 mg is only intended for gluteal intramuscular injection and must not be administered intravenously or subcutaneously. It must only be administered by a healthcare professional.

The suspension must be injected slowly as a single injection (doses must not be divided) into the gluteal muscle, alternating the injections between the right and left side. Care must be taken to avoid inadvertent injection into a blood vessel.

If initiating with any of the options that require two injections (one Abilify Maintena 960 mg or 720 mg and one Abilify Maintena 400 mg or 300 mg), inject into two different sites. DO NOT inject both injections concomitantly into the same gluteal muscle.

Full instructions for use and handling of Abilify Maintena 960 mg/720 mg are provided in the package leaflet (information intended for healthcare professionals).

4.3 Contraindications

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.

Use in patients who are in an acutely agitated or severely psychotic state

Abilify Maintena should not be used to manage acutely agitated or severely psychotic states when immediate symptom control is warranted.

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

Aripiprazole 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 aripiprazole 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 aripiprazole, dose reduction or discontinuation 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 antipsychotics. 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 antipsychotics, 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 to 99 years), patients treated with aripiprazole were 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 placebo. 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 ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78 to 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).

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

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with aripiprazole. No specific studies have been conducted with Abilify Maintena in patients with hyperglycaemia or diabetes mellitus. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. Patients treated with aripiprazole should be observed for signs and symptoms of hyperglycaemia (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, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

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 the use of aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Gambling disorder and other 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 behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive 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; however, in some cases, urges were reported to have stopped when the dose was reduced or the medicinal product was discontinued. Impulse control disorders may

result in harm to the patient and others if not recognised. A dose reduction or stopping of the medicinal product should be considered if a patient develops such urges (see section 4.8).

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).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Abilify Maintena. The information below is obtained from studies with oral aripiprazole. The 2-month dosing interval and long half-life of aripiprazole after dosing with Abilify Maintena 960 mg or 720 mg should also be considered when assessing the drug-drug interaction potential.

Due to its α1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive medicinal products.

Given the primary central nervous system (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 aripiprazole

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).

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 strong 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 dose of aripiprazole 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 aripiprazole, modest increases in plasma aripiprazole concentrations may be expected.

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 960 mg/720 mg 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 960 mg/720 mg should be avoided because the blood levels of aripiprazole are decreased and may be below the effective levels.

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 Selective Serotonin Reuptake Inhibitor/Serotonin Noradrenaline Reuptake Inhibitor (SSRI/SNRI), or with medicinal products that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

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 aripiprazole.

Prescribers need to be aware of the long-acting properties of Abilify Maintena. Aripiprazole has been detected in plasma in adult patients up to 34 weeks after a single-dose administration of the prolonged-release suspension.

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).

Maternal exposure to Abilify Maintena before and during pregnancy may lead to adverse reactions in the newborn child. Abilify Maintena should not be used during pregnancy unless clearly necessary.

Breast-feeding

Aripiprazole/metabolites are excreted in the breast milk to such an extent that effects on the breast-fed infant are likely if Abilify Maintena is administered to breast-feeding women. *S*ince a single dose of Abilify Maintena is expected to remain for up to 34 weeks in plasma (see section 5.2), breast-fed infants may be at risk even from Abilify Maintena administration long before breast-feeding. Patients currently under treatment or who have been treated in the past 34 weeks with Abilify Maintena should not breast feed.

Fertility

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

4.7 Effects on ability to drive and use machines

Aripiprazole has minor to 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).

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Abilify Maintena 960 mg and Abilify Maintena 720 mg for the treatment of schizophrenia in adults is based on adequate and well-controlled studies of Abilify Maintena 400 mg and Abilify Maintena 300 mg. In general, the observed adverse drug reactions (ADRs) in Abilify Maintena 960 mg/720 mg clinical trials were similar to the ADRs observed in the Abilify Maintena 400 mg/300 mg clinical trials.

The most frequently observed ADRs reported in ≥ 5 % of patients in two double-blind, long-term trial of Abilify Maintena 400 mg/300 mg were weight increased (9.0%), akathisia (7.9%) and insomnia (5.8%). In the Abilify Maintena 960 mg/720 mg clinical trials, weight increased (22.7%), injection site pain (18.2%) akathisia (9.8 %), anxiety (8.3 %), headache (7.6 %), insomnia (7.6 %), and constipation (6.1 %) were the most frequently observed ADRs.

Tabulated list of adverse reactions

The incidences of the ADRs associated with Abilify Maintena 400 mg/300 mg and 960 mg/720 mg are tabulated below. The table is based on adverse reactions reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ class and frequency; very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 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 ADRs listed under the frequency “not known” were reported during post-marketing use.

System organ class	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

System organ class	Common	Uncommon	Not known
Metabolism and nutrition disorders	Weight increased[a] Diabetes mellitus Weight decreased	Hyperglycaemia Hypercholesterolaemia Hyperinsulinaemia Hyperlipidaemia Hypertriglyceridaemia Appetite disorder	Anorexia Decreased appetite[b] Hyponatraemia
Psychiatric disorders	Agitation Anxiety Restlessness Insomnia	Suicidal ideation Psychotic disorder Hallucination Delusion Hypersexuality Panic reaction Depression Affect lability Apathy Dysphoria Sleep disorder Bruxism Libido decreased Mood altered	Completed suicide Suicide attempt Gambling disorder Impulse-control disorder Binge eating Compulsive shopping Poriomania Nervousness Aggression
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 Generalised tonic-clonic seizure 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 death Cardiac arrest Torsades de pointes Ventricular arrhythmia QT prolonged
Vascular disorders		Hypertension Orthostatic hypotension Blood pressure increased	Syncope Venous embolism (including pulmonary embolism and deep vein thrombosis)

System organ class	Common	Uncommon	Not known
Respiratory, thoracic and mediastinal disorders		Cough Hiccups	Oropharyngeal spasm Laryngospasm Aspiration pneumonia
Gastrointestinal disorders	Dry mouth	Gastrooesophageal reflux disease Dyspepsia Vomiting Diarrhoea Nausea Abdominal pain upper Abdominal discomfort Constipation Frequent bowel movements Salivary hypersecretion	Pancreatitis Dysphagia
Hepatobiliary disorders		Liver function test abnormal Hepatic enzyme increased Alanine aminotransferase increased Gamma-glutamyltransferase 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

System organ class	Common	Uncommon	Not known
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	Erectile dysfunction	Galactorrhoea Gynaecomastia Breast tenderness Vulvovaginal dryness	Priapism
General disorders and administration site conditions	Injection site pain[a] 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

a: Reported as very common in Abilify Maintena 960 mg/720 mg clinical trials.
b: Reported only in Abilify Maintena 960 mg/720 mg clinical trial program

Description of selected adverse reactions

Injection site reactions
The percentage of patients in an open-label study reporting any injection site-related adverse reaction (all reported as injection site pain) was 18.2 % for patients treated with Abilify Maintena 960 mg and 9.0 % for patients treated with Abilify Maintena 400 mg. In both treatment groups, the majority of the reported injection site pain occurred with the first injection of Abilify Maintena 960 mg patients (21 of 24 patients) or Abilify Maintena 400 mg (7 of 12 patients), resolved within 5 days, and were reported with decreasing frequency and severity upon subsequent injections. The overall mean site visual analog scale scores (0 = no pain to 100 = unbearably painful) for patient reported rating of pain were similar in both treatment groups at the last injection: 0.8 pre-dose and 1.4 post-dose for the Abilify Maintena 960 mg group compared to 1.3 post-dose for the Abilify Maintena 400 mg group.

Neutropenia
Neutropenia has been reported in the clinical program with Abilify Maintena 400 mg/300 mg and typically started around day 16 after first injection, and lasted a median of 18 days.

Extrapyramidal Symptoms (EPS)
In trials in stable patients with schizophrenia, Abilify Maintena 400 mg/300 mg was associated with a higher frequency of EPS symptoms (18.4 %) than oral aripiprazole treatment (11.7 %). Akathisia was

the most frequently observed symptom (8.2 %) and typically started around Day 10 after first injection, and lasted a median of 56 days. Subjects with akathisia typically received anti-cholinergic medicines as treatment, primarily benzatropine mesilate and trihexyphenidyl. Less often substances such as propranolol and benzodiazepines (clonazepam and diazepam) were administered to control akathisia. Parkinsonism events followed in frequency of 6.9 % for Abilify Maintena 400 mg/300 mg, 4.2 % for oral aripiprazole 10 mg to 30 mg tablets and 3.0 % for placebo, respectively.

Data from an open-label study of patients treated with Abilify Maintena 960 mg, showed minimal change from baseline in EPS scores, as assessed by the Simpson-Angus Rating scale (SAS), the Abnormal Involuntary Movement Scale (AIMS) and the Barnes Akathisia Rating Scale (BARS). The incidence of reported EPS-related events for patients treated with Abilify Maintena 960 mg was 18.2 % compared to the incidence of patients treated with Abilify Maintena 400 mg, which was 13.4 %.

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 long-term trial (see section 5.1), the incidence of weight gain of ≥ 7 % from baseline to last visit was 9.5 % for Abilify Maintena 400 mg/300 mg and 11.7 % for the oral aripiprazole tablets 10 mg to 30 mg. The incidence of weight loss of ≥ 7 % from baseline to last visit was 10.2 % for Abilify Maintena 400 mg/300 mg and 4.5 % for oral aripiprazole tablets 10 mg to 30 mg. During the double-blind, placebo-controlled phase of the 52-week long-term trial (see section 5.1), the incidence of weight gain of ≥ 7 % from baseline to last visit was 6.4 % for Abilify Maintena 400 mg/300 mg and 5.2 % for placebo. The incidence of weight loss of ≥ 7 % from baseline to last visit was 6.4 % for Abilify Maintena 400 mg/300 mg and 6.7 % for placebo. During double-blind treatment, mean change in body weight from baseline to last visit was −0.2 kg for Abilify Maintena 400 mg/300 mg and −0.4 kg for placebo (p = 0.812).

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

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

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

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose associated with adverse reactions were reported in clinical studies with aripiprazole. While experience with aripiprazole overdose is limited, among the few cases of overdose (accidental or intentional) reported in clinical trials and post marketing experience with oral aripiprazole, the highest estimated ingestion was a total of 1260 mg with no fatalities.

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

Signs and symptoms

Care must be taken to avoid inadvertent injection of this medicinal product into a blood vessel. Following any confirmed or suspected accidental overdose/inadvertent intravenous administration with aripiprazole, close observation of the patient is needed. The potentially medically significant signs and symptoms observed in overdose included lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting and diarrhoea.

Management of overdose

There is no specific antidote to aripiprazole. Management of overdose should concentrate on supportive care, including close medical supervision and monitoring. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures. Treatment should consist of general measures employed in the management of overdose with any medicinal product. Consider the possibility of multiple medicinal product overdose. Consider the long-acting nature of the medicinal product and the long elimination half-life of aripiprazole when assessing treatment needs and recovery.

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 D_2 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 D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and has moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic, and histamine H_1 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 mg 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 D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical efficacy and safety

Maintenance treatment of schizophrenia in adults
The efficacy of Abilify Maintena 960 mg, administered once every two months, was established in part, on the basis of pharmacokinetic bridging through an open-label, multiple-dose, randomized, parallel-arm multi-centre study. The study demonstrated that Abilify Maintena 960 mg provides similar aripiprazole concentrations, and thus similar effectiveness, to Abilify Maintena 400 mg over the dosing interval (see section 5.2).

The similarity of aripiprazole plasma concentrations of Abilify Maintena 960 mg to Abilify Maintena 400 mg is presented in table 1.

Table 2: Geometric mean ratio and confidence interval (CI) following the fourth administration of Abilify Maintena 960 mg or the seventh and eighth Abilify Maintena 400 mg in the open-label study

Parameter	Ratio (Abilify Maintena 960 mg/Abilify Maintena 400 mg)	90 % CI
AUC_{0-56}[a]	1.006[c]	0.851 - 1.190
C_{56}/C_{28}[b]	1.011[d]	0.893 - 1.145
C_{max}[b]	1.071[c]	0.903 - 1.270

[a] AUC_{0-56} following the fourth administration of Abilify Maintena 960 mg or the sum of AUC_{0-28} following the seventh and eighth administration of Abilify Maintena 400 mg.
[b] Aripiprazole plasma concentrations following the fourth administration of Abilify Maintena 960 mg (C_{56}) or the eighth administration of Abilify Maintena 400 mg (C_{28}).
[c] Abilify Maintena 960 mg (n = 34), Abilify Maintena 400 mg (n = 32)
[d] Abilify Maintena 960 mg (n = 96), Abilify Maintena 400 mg (n = 82).

The effectiveness of Abilify Maintena 960 mg/720 mg in the treatment of schizophrenia is further supported by the established effectiveness of Abilify Maintena 400 mg/300 mg, as summarised below:

Efficacy of Abilify Maintena 400 mg/300 mg
The efficacy of Abilify Maintena 400 mg/300 mg in the maintenance treatment of patients with schizophrenia was established in two randomised, double-blind, long-term trials.

The pivotal 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 mg to 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 mg to 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 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 mg to 30 mg.

The estimated relapse rate by end of week 26 was 7.12 % for Abilify Maintena 400 mg/300 mg, and 7.76 % for oral aripiprazole tablets 10 mg to 30 mg, a difference of −0.64 %.

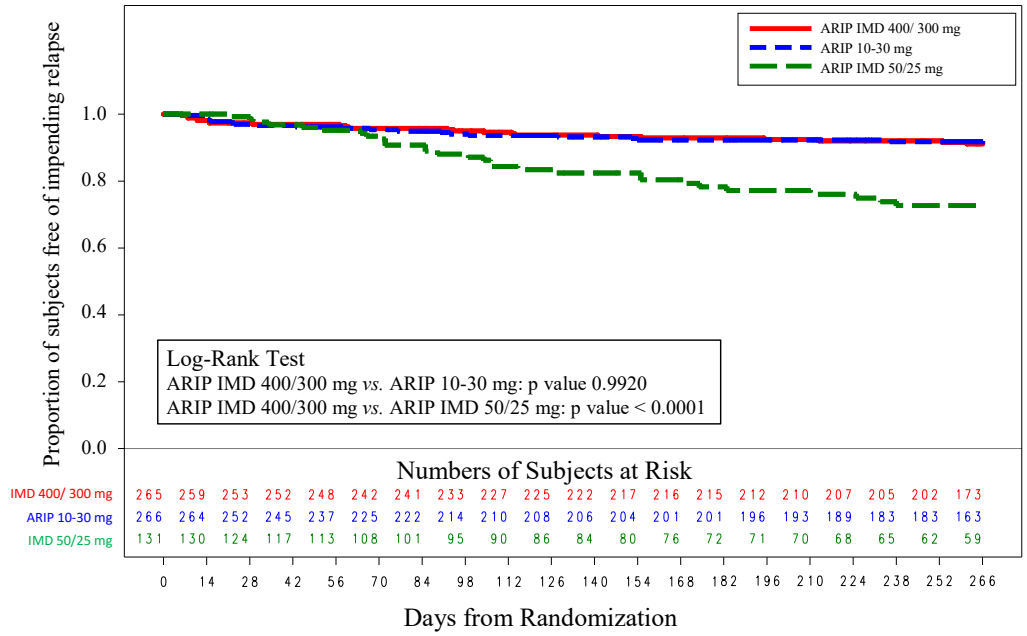
The 95 % CI (−5.26, 3.99) for the difference in the estimated proportion of patients experiencing impending relapse by end of week 26 excluded the predefined non-inferiority margin, 11.5 %.

Therefore, Abilify Maintena 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10 mg to 30 mg.

The estimated proportion of patients experiencing impending relapse by end of week 26 for Abilify Maintena 400 mg/300 mg was 7.12 %, which was statistically significantly lower than in aripiprazole long-acting injectable 50 mg/25 mg (21.80 %; p = 0.0006). Thus, superiority of Abilify Maintena 400 mg/300 mg 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, active-controlled phase for Abilify Maintena 400 mg/300 mg, oral aripiprazole 10 mg to 30 mg, and aripiprazole long-acting injectable 50 mg/25 mg 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 mg to 30 mg = oral aripiprazole; ARIP IMD 50/25 mg = Aripiprazole long-acting injectable

Further, the non-inferiority of Abilify Maintena compared to oral aripiprazole 10 mg to 30 mg is supported by the results of the analysis of the positive and negative syndrome scale score (PANSS).

Table 3: PANSS total score – change from baseline to week 38-Last Observation Carried Forward (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 US adult patients with a current diagnosis of schizophrenia. This trial consisted of a screening phase and 4 treatment phases: Conversion, oral stabilisation, IM 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 400 mg/300 mg and began an IM 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 400 mg/300 mg or placebo, respectively.

The final efficacy analysis included 403 randomised patients and 80 exacerbations of psychotic symptoms/impending relapse events. In the placebo group 39.6 % of the patients had progressed to impending relapse, whilst in the Abilify Maintena 400 mg/300 mg group impending relapse occurred in 10 % of the patients; thus, patients in the placebo group had a 5.03-fold greater risk of experiencing impending relapse.

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 Abilify Maintena 400 mg/300 mg (−0.33 ng/mL) compared with a mean increase in oral aripiprazole tablets 10 mg to 30 mg (0.79 ng/mL; $p < 0.01$). The incidence of Abilify Maintena 400 mg/300 mg 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 mg to 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 Abilify Mainten 400 mg/300 mg a (−0.38 ng/mL) compared with a mean increase in placebo (1.67 ng/mL). The incidences of Abilify Maintena 400 mg/300 mg patients with prolactin levels > 1 time the ULN was 1.9 % compared to 7.1 % for placebo patients.

Acute treatment of schizophrenia in adults
The efficacy of Abilify Maintena 400 mg/300 mg in acutely relapsed adult patients with schizophrenia was established in a short-term (12-week), randomised, double-blind, placebo-controlled trial (n = 339). The primary endpoint (change in PANSS total score from baseline to week 10) showed superiority of Abilify Maintena 400 mg/300 mg (n = 167) over placebo (n = 172). Similar to the PANSS total score, both the PANSS positive and negative subscale scores also showed an improvement (decrease) from baseline over time.

Table 4: PANSS total score – change from baseline to week 10: randomised efficacy sample [a]

	Abilify Maintena 400 mg/300 mg	**Placebo**
Mean baseline (SD)	102.4 (11.4) n = 162	103.4 (11.1) n = 167
LS mean change (SE)	−26.8 (1.6) n = 99	−11.7 (1.6) n = 81
P-value	< 0.0001	
Treatment difference[b] (95 % CI)	−15.1 (−19.4, −10.8)	

[a] Data were analysed using a mixed model repeated measures (MMRM) approach. The analysis included only subjects 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 least squares mean change from baseline.

Abilify Maintena 400 mg/300 mg also showed statistically significant improvement in symptoms represented by Clinical Global Impressions Severity, CGI-S (CGI-S) score change from baseline to week 10.

Personal and social functioning were evaluated using the Personal and Social Performance (PSP) scale. The PSP is a validated clinician-rated scale that measures personal and social functioning in four domains: socially useful activities (e.g., work and study), personal and social relationships, self-care, and disturbing and aggressive behaviours. There was a statistically significant treatment difference in favour of Abilify Maintena 400 mg/300 mg compared to placebo at week 10 (+7.1, $p < 0.0001$, 95 % CI: 4.1, 10.1 using an ANCOVA model (LOCF)).

The safety profile was consistent with that known to Abilify Maintena 400 mg/300 mg. Nevertheless, there were differences from what has been observed with maintenance use in the treatment of schizophrenia. In a short-term (12-week), randomised, double-blind, placebo-controlled trial with Abilify Maintena 400 mg/300 mg treated subjects the symptoms which had at least twice the incidence of placebo were increased weight and akathisia. The incidence of weight gain of ≥ 7 % from baseline to last visit (Week 12) was 21.5 % for Abilify Maintena 400 mg/300 mg compared with the placebo group 8.5 %. Akathisia was the most frequently observed EPS symptom (Abilify Maintena 400 mg/300 mg 11.4 % and placebo group 3.5 %).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Abilify Maintena in all subsets of the paediatric population in schizophrenia (see section 4.2 for information on paediatric use).

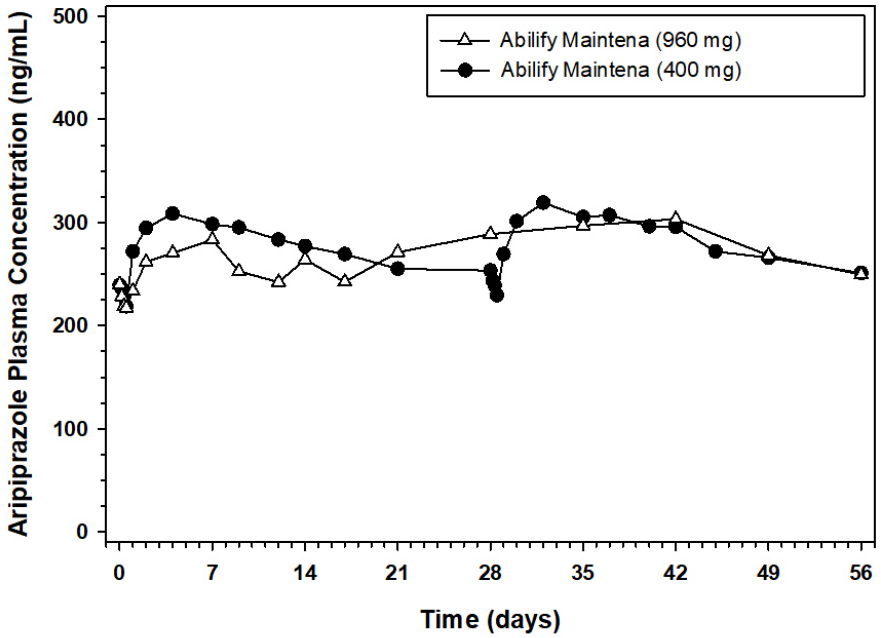
5.2 Pharmacokinetic properties

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

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

The mean aripiprazole plasma concentration compared to the time profiles following the fourth administration of Abilify Maintena 960 mg (n = 102) or the seventh and eighth administration of Abilify Maintena 400 mg (n = 93) in the gluteal muscle of patients with schizophrenia (and bipolar I disorder) are shown in figure 2.

Figure 2: Mean Aripiprazole plasma concentration vs. time profile following the fourth administration of Abilify Maintena 960 mg or the seventh and eighth administration of Abilify Maintena 400 mg



Absorption/Distribution

Aripiprazole absorption into the systemic circulation is slow and prolonged following gluteal injection due to low solubility of aripiprazole particles. The release profile of aripiprazole from Abilify Maintena 960 mg/720 mg results in sustained plasma concentrations over 2 months following gluteal injection(s). The release of the active substance after a single 780 mg dose of 2-monthly aripiprazole ready-to-use long-acting-injectable starts Day 1 and lasts for as long as 34 weeks.

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. Following administration of multiple doses of Abilify Maintena 960 mg/720 mg, dehydro-aripiprazole, the active metabolite, represents approximately 30 % of aripiprazole AUC in plasma.

Elimination

Following a single oral dose of [^{14}C]-labelled aripiprazole, approximately 25 % and 55 % of the administered radioactivity was recovered in the urine faeces, respectively. 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

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

CYP2D6 poor metabolisers
Based on population pharmacokinetic analysis, the plasma concentrations of aripiprazole is around 2-fold higher in poor metabolisers of CYP2D6 compared with normal CYP2D6 metabolisers. (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 aripiprazole 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 aripiprazole 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 active substance), cellular infiltrates, oedema (swelling) and, in monkeys, fibrosis. These effects gradually resolved with discontinuation of dosing.

Non-clinical safety data for orally administered aripiprazole reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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 mg/kg/day 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 repeated 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 in humans. 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

Carmellose sodium
Macrogol
Povidone (E1201)
Sodium chloride
Sodium dihydrogen phosphate monohydrate (E339)
Sodium hydroxide (for pH adjustment) (E524)

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

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

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

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

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

6.6 Special precautions for disposal and other handling

Tap the syringe on your hand at least 10 times. After tapping, shake the syringe vigorously for at least 10 seconds.

Gluteal muscle administration
The recommended needle for gluteal administration is a 38 mm (1.5 inch), 22 gauge sterile safety needle; for obese patients (Body mass index > 28 kg/m^2), a 51 mm (2 inch), 21 gauge sterile safety needle should be used.

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

Full instructions for use and handling of Abilify Maintena 960 mg/720 mg are provided in the package leaflet (information intended for healthcare professionals).

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

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

EU/1/13/882/009

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

EU/1/13/882/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 March 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Abilify Maintena 300 mg / 400 mg powder and solvent for prolonged-release suspension for injection

H. Lundbeck A/S
Ottiliavej 9
DK 2500 Valby
Denmark

Abilify Maintena 300 mg / 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

H. Lundbeck A/S
Ottiliavej 9
DK 2500 Valby
Denmark

Elaiapharm
2881 Route des Crêtes Z.I Les Bouillides Sophia Antipolis
06550 Valbonne
France

Abilify Maintena 720 mg / 960 mg prolonged-release suspension for injection in pre-filled syringe

Elaiapharm
2881 Route des Crêtes Z.I Les Bouillides Sophia Antipolis
06550 Valbonne
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing

authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton - Single pack 300 mg

1. NAME OF THE MEDICINAL PRODUCT

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 300 mg aripiprazole. After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

One vial of powder
One vial of 2 mL solvent
Two sterile syringes, one with needle for reconstitution
Three hypodermic safety needles
One vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Shake the vial vigorously for at least 30 seconds until the suspension appears uniform.
If the injection is not performed immediately after reconstitution shake it vigorously for at least 60 seconds to re-suspend prior to injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 4 hours below 25 °C
Do not store the reconstituted suspension in the syringe.

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard vial, adapter, syringe, needles, unused suspension and water for injections appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer label (with blue box) - Multipack 300 mg

1. NAME OF THE MEDICINAL PRODUCT

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 300 mg aripiprazole. After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

Multipack: Three single packages, each containing:

One vial of powder
One vial of 2 mL solvent
Two sterile syringes, one with needle for reconstitution
Three hypodermic safety needles
One vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Shake the vial vigorously for at least 30 seconds until the suspension appears uniform.
If the injection is not performed immediately after reconstitution shake it vigorously for at least 60 seconds to re-suspend prior to injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 4 hours below 25 °C
Do not store the reconstituted suspension in the syringe.

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard vial, adapter, syringe, needles, unused suspension and water for injections appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (without blue box) – component of multipack 300 mg

1. NAME OF THE MEDICINAL PRODUCT

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 300 mg aripiprazole.
After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

Single package containing:

One vial of powder
One vial of 2 mL solvent
Two sterile syringes, one with needle for reconstitution
Three hypodermic safety needles
One vial adapter

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Shake the vial vigorously for at least 30 seconds until the suspension appears uniform.
If the injection is not performed immediately after reconstitution shake it vigorously for at least 60 seconds to re-suspend prior to injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 4 hours below 25 °C
Do not store the reconstituted suspension in the syringe.

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard vial, adapter, syringe, needles, unused suspension and water for injections appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial powder 300 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abilify Maintena 300 mg powder for prolonged-release injection
aripiprazole
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton - Single pack 400 mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 400 mg aripiprazole.
After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

One vial of powder
One vial of 2 mL solvent
Two sterile syringes, one with needle for reconstitution
Three hypodermic safety needles
One vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Shake the vial vigorously for at least 30 seconds until the suspension appears uniform.
If the injection is not performed immediately after reconstitution shake it vigorously for at least 60 seconds to re-suspend prior to injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 4 hours below 25 °C
Do not store the reconstituted suspension in the syringe.

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard vial, adapter, syringe, needles, unused suspension and water for injections appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer label (with blue box) - Multipack 400 mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 400 mg aripiprazole.
After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

Multipack: Three single packages, each containing:

One vial of powder
One vial of 2 mL solvent
Two sterile syringes, one with needle for reconstitution
Three hypodermic safety needles
One vial adapter

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Shake the vial vigorously for at least 30 seconds until the suspension appears uniform.
If the injection is not performed immediately after reconstitution shake it vigorously for at least 60 seconds to re-suspend prior to injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 4 hours below 25 °C
Do not store the reconstituted suspension in the syringe.

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard vial, adapter, syringe, needles, unused suspension and water for injections appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (without blue box) – component of multipack 400 mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 400 mg aripiprazole.
After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

Single package containing:

One vial of powder
One vial of 2 mL solvent
Two sterile syringes, one with needle for reconstitution
Three hypodermic safety needles
One vial adapter

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Shake the vial vigorously for at least 30 seconds until the suspension appears uniform.
If the injection is not performed immediately after reconstitution shake it vigorously for at least 60 seconds to re-suspend prior to injection.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 4 hours below 25 °C
Do not store the reconstituted suspension in the syringe.

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard vial, adapter, syringe, needles, unused suspension and water for injections appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial Powder 400 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abilify Maintena 400 mg powder for prolonged-release injection
aripiprazole
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial solvent

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Abilify Maintena
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton - Single pack 300 mg

1. NAME OF THE MEDICINAL PRODUCT

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 300 mg aripiprazole.
After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

One pre-filled syringe containing powder in the front chamber and solvent in the rear chamber.
Three hypodermic safety needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Vertically shake the syringe vigorously for 20 seconds until medicine is uniformly milky-white and use immediately.
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.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 2 hours below 25 °C

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard pre-filled syringe and needles appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer label (with blue box) - Multipack 300 mg

1. NAME OF THE MEDICINAL PRODUCT

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 300 mg aripiprazole.
After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

Multipack: Three single packages, each containing:

One pre-filled syringe containing powder in the front chamber and solvent in the rear chamber.
Three hypodermic safety needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Vertically shake the syringe vigorously for 20 seconds until medicine is uniformly milky-white and use immediately.
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.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 2 hours below 25 °C

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard pre-filled syringe and needles appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (without blue box) – component of multipack 300 mg

1. NAME OF THE MEDICINAL PRODUCT

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 300 mg aripiprazole.
After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

Single package containing:

One pre-filled syringe containing powder in the front chamber and solvent in the rear chamber.
Three hypodermic safety needles

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Vertically shake the syringe vigorously for 20 seconds until medicine is uniformly milky-white and use immediately.
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.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 2 hours below 25 °C

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard pre-filled syringe and needles appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe - 300 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abilify Maintena 300 mg injection, prolonged-release
aripiprazole
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton - Single pack 400 mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 400 mg aripiprazole.
After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

One pre-filled syringe containing powder in the front chamber and solvent in the rear chamber.
Three hypodermic safety needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Vertically shake the syringe vigorously for 20 seconds until medicine is uniformly milky-white and use immediately.
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.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 2 hours below 25 °C

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard pre-filled syringe and needles appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer label (with blue box) - Multipack 400 mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 400 mg aripiprazole.
After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

Multipack: Three single packages, each containing:

One pre-filled syringe containing powder in the front chamber and solvent in the rear chamber.
Three hypodermic safety needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Vertically shake the syringe vigorously for 20 seconds until medicine is uniformly milky-white and use immediately.
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.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 2 hours below 25 °C

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard pre-filled syringe and needles appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (without blue box) – component of multipack 400 mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 400 mg aripiprazole.
After reconstitution each mL of suspension contains 200 mg aripiprazole.

3. LIST OF EXCIPIENTS

Powder
Carmellose sodium, mannitol, sodium dihydrogen phosphate monohydrate, sodium hydroxide

Solvent
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection

Single package containing:

One pre-filled syringe containing powder in the front chamber and solvent in the rear chamber.
Three hypodermic safety needles

Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use only

Administer once monthly

Vertically shake the syringe vigorously for 20 seconds until medicine is uniformly milky-white and use immediately.
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.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf-life after reconstitution: 2 hours below 25 °C

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard pre-filled syringe and needles appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe - 400 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abilify Maintena 400 mg injection, prolonged-release
aripiprazole
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton 720 mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 720 mg aripiprazole per 2.4 mL (300 mg/mL).

3. LIST OF EXCIPIENTS

Carmellose sodium, macrogol 400, povidone K17, sodium chloride, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release suspension for injection in pre-filled syringe

1 pre-filled syringe
2 sterile safety needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use.

Administer once every 2 months.
Tap the syringe on your hand at least 10 times. After tapping, shake the syringe vigorously for at least 10 seconds.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

A justification for not including Braille is included in module 1.3.6.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe 720 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abilify Maintena 720 mg injection, prolonged-release
aripiprazole
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

720 mg/2.4 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton 960 mg

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 960 mg aripiprazole per 3.2 mL (300 mg/mL).

3. LIST OF EXCIPIENTS

Carmellose sodium, macrogol 400, povidone K17, sodium chloride, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release suspension for injection in pre-filled syringe

1 pre-filled syringe
2 sterile safety needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular use.

Administer once every 2 months.
Tap the syringe on your hand at least 10 times. After tapping, shake the syringe vigorously for at least 10 seconds.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

A justification for not including Braille is included in module 1.3.6.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe 960 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abilify Maintena 960 mg injection, prolonged-release
aripiprazole
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

960 mg/3.2 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection
aripiprazole

Read all of this leaflet carefully before you receive this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Abilify Maintena is and what it is used for

Abilify Maintena contains the active substance aripiprazole in a vial. Aripiprazole belongs to a group of medicines called antipsychotics. Abilify Maintena is used to treat schizophrenia - a disease with symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.

Abilify Maintena is intended for adult patients with schizophrenia who are sufficiently stabilised during treatment with aripiprazole taken by mouth.

2. What you need to know before you are given Abilify Maintena

Do not use Abilify Maintena
- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or nurse before you are given Abilify Maintena.

Suicidal thoughts and behaviours have been reported during treatment with this medicine. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself before or after receiving Abilify Maintena.

Before treatment with Abilify Maintena, tell your doctor if you suffer from

- an acutely agitated state or a severely psychotic state
- heart problems or have a history of stroke, especially if you know that you have other risks factors for stroke
- high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite and feeling weak) or family history of diabetes
- fits (seizures) since your doctor may want to monitor you more closely
- involuntary, irregular muscle movements, especially in the face

- experience a combination of fever, sweating, faster breathing, muscle stiffness and drowsiness or sleepiness (may be signs of neuroleptic malignant syndrome)
- dementia (loss of memory and other mental abilities) especially if you are elderly
- cardiovascular diseases (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure
- irregular heart beat or if someone else in your family has a history of irregular heart beat (including so called QT prolongation seen with ECG monitoring).
- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots
- have any difficulty in swallowing
- past experience with excessive gambling
- severe liver problems.

If you notice you are gaining weight, develop unusual movements, experience sleepiness that interferes with normal daily activities, any difficulty in swallowing or have allergic symptoms, please talk to your doctor immediately.

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings.
Your doctor may need to adjust or stop your dose.

This medicine may cause sleepiness, fall in blood pressure when standing up, dizziness and changes in your ability to move and balance, which may lead to falls. Caution should be taken, particularly if you are an elderly patient or have some debility.

Children and adolescents
Do not use this medicine in children and adolescents under 18 years of age. It is not known if it is safe and effective in these patients.

Other medicines and Abilify Maintena
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Blood pressure-lowering medicines: Abilify Maintena may increase the effect of medicines used to lower the blood pressure. Be sure to tell your doctor if you take a medicine to keep your blood pressure under control.

Receiving Abilify Maintena with some medicines may mean the doctor will need to change your dose of Abilify Maintena or the other medicines. It is especially important to mention the following to your doctor:

- medicines to correct heart rhythm (such as quinidine, amiodarone, flecainide)
- antidepressants or herbal remedy used to treat depression and anxiety (such as fluoxetine, paroxetine, St. John's Wort)
- antifungal medicines (such as itraconazole)
- ketoconazole (used to treat Cushing’s syndrome when the body produces an excess of cortisol)
- certain medicines to treat HIV infection (such as efavirenz, nevirapine, and protease inhibitors e.g. indinavir, ritonavir)
- anticonvulsants used to treat epilepsy (such as carbamazepine, phenytoin, phenobarbital)
- certain antibiotics used to treat tuberculosis (rifabutin, rifampicin)
- medicines that are known to prolong QT prolongation.

These medicines may increase the risk of side effects or reduce the effect of Abilify Maintena; if you get any unusual symptom taking any of these medicines together with Abilify Maintena, you should see your doctor.

Medicines that increase the level of serotonin are typically used in conditions including depression, generalised anxiety disorder, obsessive-compulsive disorder (OCD) and social phobia as well as migraine and pain:

- triptans, tramadol and tryptophan used for conditions including depression, generalised anxiety disorder, obsessive compulsive disorder (OCD) and social phobia as well as migraine and pain
- SSRI s (such as paroxetine and fluoxetine) used for depression, OCD, panic and anxiety
- other anti-depressants (such as venlafaxine and tryptophan) used in major depression
- tricyclic's (such as clomipramine and amitriptyline) used for depressive illness
- St John's Wort (*Hypericum perforatum*) used as a herbal remedy for mild depression
- painkillers (such as tramadol and pethidine) used for pain relief
- triptans (such as sumatriptan and zolmitripitan) used for treating migraine.

These medicines may increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with Abilify Maintena, you should see your doctor.

Abilify Maintena with alcohol
Alcohol should be avoided.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this medicine.

You should not be given Abilify Maintena if you are pregnant unless you have discussed this with your doctor. Be sure to tell your doctor immediately if you are pregnant, think you may be pregnant, or if you are planning to become pregnant.

The following symptoms may occur in new-born babies, of mothers that have received Abilify Maintena in the last three months of their pregnancy (last trimester):
shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding.

If your baby develops any of these symptoms you need to contact your doctor.

If you are receiving Abilify Maintena, your doctor will discuss with you whether you should breast-feed considering the benefit to you of your therapy and the benefit to your baby of breast-feeding. You should not do both. Talk to your doctor about the best way to feed your baby if you are receiving Abilify Maintena.

Driving and using machines
Dizziness and vision problems may occur during treatment with this medicine (see section 4). This should be considered in cases where full alertness is required, e.g., when driving a car or handling machines.

Abilify Maintena contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Abilify Maintena is given

Abilify Maintena comes as a powder which your doctor or nurse will make into a suspension.

Your doctor will decide on the dose of Abilify Maintena that is right for you. The recommended starting dose is 400 mg unless your doctor decided to give you a lower starting or follow up dose.

There are two ways to start Abilify Maintena, your doctor will decide which way is right for you.
- If you are given one injection of Abilify Maintena on your first day the treatment with aripiprazole by mouth is continued for 14 days after the first injection.
- If you are given two injections of Abilify Maintena on your first day, you will also take one tablet of aripiprazole by mouth at this visit.

After that, treatment is given with injections of Abilify Maintena unless your doctor tells you otherwise.

Your doctor will give it to you as a single injection into the gluteal or deltoid muscle (buttock or shoulder) every month. You may feel a little pain during the injection. Your doctor will alternate the injections between your right and left side. The injections will not be given intravenously.

If you are given more Abilify Maintena than you should
This medicine will be given to you under medical supervision; it is therefore unlikely that you will be given too much. If you see more than one doctor, be sure to tell them that you are receiving Abilify Maintena.

Patients who have been given too much of this medicine have experienced the following symptoms:

- rapid heartbeat, agitation/aggressiveness, problems with speech.
- unusual movements (especially of the face or tongue) and reduced level of consciousness.

Other symptoms may include:

- acute confusion, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating,
- muscle stiffness, and drowsiness or sleepiness, slower breathing, choking, high or low blood pressure, abnormal rhythms of the heart.

Contact your doctor or hospital immediately if you experience any of the above.

If you miss an injection of Abilify Maintena
It is important not to miss your scheduled dose. You should be given an injection every month but not before the 26 days has passed from the last injection. If you miss an injection, you should contact your doctor to arrange your next injection as soon as you can.

If you stop receiving Abilify Maintena
Do not stop your treatment just because you feel better. It is important that you carry on receiving Abilify Maintena for as long as your doctor has told you to.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor immediately if you have any of the following serious side effects:

- a combination of any of these symptoms: excessive sleepiness, dizziness, confusion, disorientation, difficulty talking, difficulty walking, muscle stiffness or shaking, fever, weakness, irritability, aggression, anxiety, increase in blood pressure, or seizures that can lead to unconsciousness.
- unusual movement mainly of the face or tongue, since your doctor may want to lower your dose.

- if you have symptoms such as swelling, pain, and redness in the leg, because this may mean you have a blood clot, which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.
- a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness since this may be a sign of a condition called neuroleptic malignant syndrome (NMS).
- thirstiness more than usual, need to urinate more than usual, feel very hungry, feel weak or tired, feel sick, feel confused or your breath smells fruity, since this may be a sign of diabetes.
- suicidal thoughts, behaviours or thoughts and feelings about hurting yourself.

The side effects listed below may also occur after receiving Abilify Maintena.
Talk to your doctor or nurse if you are affected by any of these side effects:

Common side effects (may affect up to 1 in 10 people):

- weight gain
- diabetes mellitus
- weight loss
- feeling restless
- feeling anxious
- unable to keep still, difficulty sitting still
- difficulty sleeping (insomnia)
- jerky resistance to passive movement as muscles tense and relax, abnormally increased muscle tone, slow body movement
- akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly)
- shaking or trembling
- uncontrollable twitching, jerking or writhing movements
- changes in your level of alertness, drowsiness
- sleepiness
- dizziness
- headache
- dry mouth
- muscle stiffness
- inability to have or maintain an erection during sexual intercourse
- pain at the injection site, hardening of the skin at the injection site
- weakness, loss of strength or extreme tiredness
- during blood tests your doctor may find higher amounts of creatine phosphokinase in your blood (enzyme important for muscle function)

Uncommon side effects (may affect up to 1 in 100 people):

- low level of a specific type of white blood cells (neutropenia), low haemoglobin or red blood cell count, low level of blood platelets
- allergic reactions (hypersensitivity)
- decreased or increased blood levels of the hormone prolactin
- high blood sugar
- increased blood fats such as high cholesterol, high triglycerides and also low level of cholesterol and low level of triglycerides
- increased levels of insulin, a hormone regulating blood sugar levels
- decreased or increased appetite
- thoughts about suicide
- mental disorder characterised by defective or lost contact with reality
- hallucination
- delusion
- increased sexual interest
- panic reaction
- depression

- affect lability
- state of indifference with lack of emotion, feelings of emotional and mental discomfort
- sleep disorder
- grinding of teeth or clenching of the jaw
- reduced sexual interest (libido is decreased)
- altered mood
- muscle problems
- muscle movements that you cannot control such as grimacing, lip-smacking and tongue movements. They usually affect the face and mouth first but can affect other parts of the body. These could be signs of a condition called “tardive dyskinesia”.
- parkinsonism - medical condition with many various symptoms which include decreased or slow movements, slowness of thought, jerks when bending the limbs (cogwheel rigidity), shuffling, hurried steps, shaking, little or no facial expression, muscle stiffness, drooling
- movement problems
- extreme restlessness and restless legs
- distortion of the senses of taste and smell
- fixation of the eyeballs in one position
- blurred vision
- eye pain
- double vision
- eye sensitivity to light,
- abnormal heartbeat, slow or fast heart rate, abnormal electrical conduction of the heart, abnormal reading (ECG) of the heart
- high blood pressure
- dizziness when getting up from a lying or sitting position due to a drop in blood pressure
- cough
- hiccups
- gastroesophageal reflux disease. Excess amount of gastric juice flowing back (refluxes) into the esophagus (gullet or the tube that goes from mouth to stomach through which food passes), causing heartburn and possibly damaging the esophagus
- heartburn
- vomiting
- diarrhoea
- feeling sick
- stomach ache
- stomach discomfort
- constipation
- frequent bowel movement
- drooling, more saliva in mouth than normal
- abnormal hair loss
- acne, skin condition of the face where the nose and cheeks are unusually red, eczema, skin hardening
- muscle rigidity, muscle spasms, muscle twitching, muscle tightness, mucle pain (myalgia), pain in extremity
- joint pain (arthralgia), back pain, decreased range of motion of joints, stiff neck, limited opening of mouth
- kidney stones, sugar (glucose) in urine
- spontaneous flow of milk from the breasts (galactorrhoea)
- enlargement of breast in men, breast tenderness, vaginal dryness
- fever
- loss of strength
- gait disturbance
- chest discomfort
- injection site reactions such as redness, swelling discomfort and injection site itching
- thirst
- sluggishness
- liver function tests may show abnormal results

- during tests your doctor may find
  - higher amounts of liver enzymes
  - higher amounts of alanine aminotransferase
  - higher amounts of gamma-glutamyl transferase
  - higher amounts of bilirubin in your blood
  - higher amounts of aspartate aminotransferase
  - higher or lower amounts of blood glucose
  - higher amounts of glycosylated haemoglobin
  - lower amounts of cholesterol in your blood
  - lower amounts of triglycerides in your blood
  - a higher waist circumference

The following side effects have been reported since the marketing of medicines containing the same active substance that are taken by mouth but the frequency for them to occur is not known (frequency cannot be estimated from the available data):

- low levels of white blood cells
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives), rash
- unusual heartbeat, sudden unexplained death, heart attack
- diabetic ketoacidosis (ketones in the blood and urine) or coma
- loss of appetite (anorexia), difficulty in swallowing
- low sodium level in the blood
- suicide attempt and suicide
- inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences
  - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive
  - uncontrollable excessive shopping
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)
  - a tendency to wander away

  Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms.
- nervousness
- aggression
- neuroleptic malignant syndrome (a syndrome with symptoms such as fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate)
- seizure (fits)
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles)
- speech disorders
- heart problems including torsades de pointes, stopping of the heart, irregularities in heart rhythm that may be due to abnormal nerve impulses in the heart, abnormal readings during heart examination (ECG) QT prolongation
- fainting
- symptoms related to blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing
- spasm of the muscles around the voice box
- accidental inhalation of food with risk of pneumonia (lung infection)
- inflammation of the pancreas
- difficulty swallowing
- liver failure
- jaundice (yellowing of the skin and white part of eyes)
- inflammation of the liver

- rash
- skin sensitivity to light
- excessive sweating
- serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia).
- muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell, have a high temperature or have dark urine. They may be caused by an abnormal muscle breakdown which can be life threatening and lead to kidney problems (a condition called rhabdomyolysis)
- difficulty in passing urine
- involuntary loss of urine (incontinence)
- drug withdrawal symptoms in new-born infant
- prolonged and/or painful erection
- difficulty controlling core body temperature or overheating
- chest pain
- swelling of hands, ankles or feet
- during tests your doctor may find
  - higher amounts alkaline phosphatase
  - fluctuating results during tests to measure glucose in your blood

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Abilify Maintena

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial. The expiry date refers to the last day of that month.

Do not freeze.

The reconstituted suspension should be used immediately but may be stored below 25 °C for up to 4 hours in the vial. Do not store the reconstituted suspension in the syringe.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Abilify Maintena contains
- The active substance is aripiprazole.
  Each vial contains 300 mg aripiprazole.
  After reconstitution each mL of suspension contains 200 mg aripiprazole.
  Each vial contains 400 mg aripiprazole.
  After reconstitution each mL of suspension contains 200 mg aripiprazole.

- The other ingredients are
  Powder

Carmellose sodium, mannitol (E421), sodium dihydrogen phosphate monohydrate (E339), sodium hydroxide (E524)
Solvent
Water for injections

What Abilify Maintena looks like and contents of the pack
Abilify Maintena is a powder and solvent for prolonged-release suspension for injection.

Abilify Maintena comes as a white to off-white powder in a clear glass vial. Your doctor or nurse will make it into a suspension that will be given as an injection using the vial of solvent for Abilify Maintena that comes as a clear solution in a clear glass vial.

Single pack
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.

Multipack
Bundle pack of 3 single packs.

Not all pack sizes may be marketed.

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Manufacturer
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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

INSTRUCTIONS FOR HEALTH CARE PROFESSIONALS

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

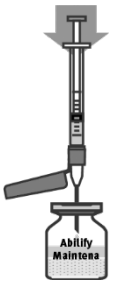
Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection
aripiprazole

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.
- 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.

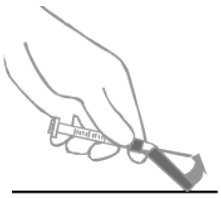
Step 2: Reconstitution of the powder
a) Remove the solvent and powder vial caps and wipe the tops with a sterile alcohol swab.
b) Using the syringe with pre-attached needle, withdraw the pre-determined solvent volume from the vial of the solvent into the syringe.
   300 mg vial:
   Add 1.5 mL solvent to reconstitute the powder.
   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

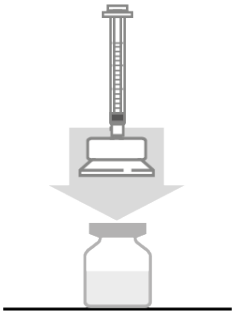
Discard

f) <u>Shake the vial vigorously for at least 30 seconds until the suspension appears uniform.</u>

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.

<u>Step 3: Preparation prior to injection</u>
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.



Abilify Maintena

d) Determine the recommended volume for injection.

Abilify Maintena 300 mg vial	
Dose	Volume to Inject
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300 mg	1.5 mL
200 mg	1.0 mL
160 mg	0.8 mL

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.

Abilify Maintena

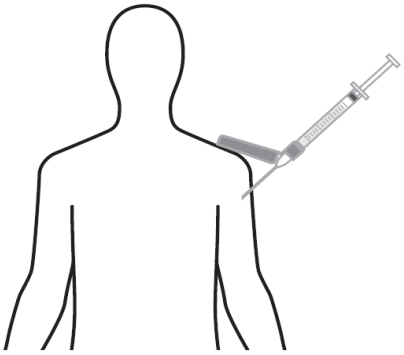
Step 4: Injection procedure

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

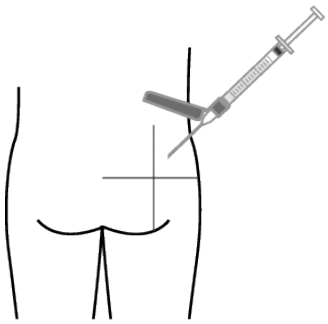
b) Select one of the following hypodermic safety needles depending on the injection site and patient's weight and attach the needle to the luer lock syringe containing the suspension for injection. Ensure the needle is firmly seated on the needle protection device with a push and clockwise twist and 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.



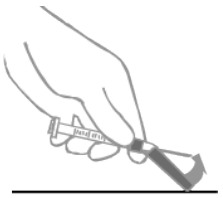
deltoid



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
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.



Cover

Discard

Package leaflet: Information for the user

Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
aripiprazole

Read all of this leaflet carefully before you receive this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Abilify Maintena is and what it is used for

Abilify Maintena contains the active substance aripiprazole in a pre-filled syringe. Aripiprazole belongs to a group of medicines called antipsychotics. Abilify Maintena is used to treat schizophrenia - a disease with symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.

Abilify Maintena is intended for adult patients with schizophrenia who are sufficiently stabilised during treatment with aripiprazole taken by mouth.

2. What you need to know before you are given Abilify Maintena

Do not use Abilify Maintena
- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or nurse before you are given Abilify Maintena.

Suicidal thoughts and behaviours have been reported during treatment with this medicine. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself before or after receiving Abilify Maintena.

Before treatment with Abilify Maintena, tell your doctor if you suffer from

- an acutely agitated state or a severely psychotic state
- heart problems or have a history of stroke, especially if you know that you have other risks factors for stroke
- high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite and feeling weak) or family history of diabetes

- fits (seizures) since your doctor may want to monitor you more closely
- involuntary, irregular muscle movements, especially in the face
- experience a combination of fever, sweating, faster breathing, muscle stiffness and drowsiness or sleepiness (may be signs of neuroleptic malignant syndrome)
- dementia (loss of memory and other mental abilities) especially if you are elderly
- cardiovascular diseases (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure
- irregular heart beat or if someone else in your family has a history of irregular heart beat (including so called QT prolongation seen with ECG monitoring).
- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots
- have any difficulty in swallowing
- past experience with excessive gambling
- severe liver problems.

If you notice you are gaining weight, develop unusual movements, experience sleepiness that interferes with normal daily activities, any difficulty in swallowing or have allergic symptoms, please talk to your doctor immediately.

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings.
Your doctor may need to adjust or stop your dose.

This medicine may cause sleepiness, fall in blood pressure when standing up, dizziness and changes in your ability to move and balance, which may lead to falls. Caution should be taken, particularly if you are an elderly patient or have some debility.

Children and adolescents
Do not use this medicine in children and adolescents under 18 years of age. It is not known if it is safe and effective in these patients.

Other medicines and Abilify Maintena
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Blood pressure-lowering medicines: Abilify Maintena may increase the effect of medicines used to lower the blood pressure. Be sure to tell your doctor if you take a medicine to keep your blood pressure under control.

Receiving Abilify Maintena with some medicines may mean the doctor will need to change your dose of Abilify Maintena or the other medicines. It is especially important to mention the following to your doctor:

- medicines to correct heart rhythm (such as quinidine, amiodarone, flecainide)
- antidepressants or herbal remedy used to treat depression and anxiety (such as fluoxetine, paroxetine, St. John's Wort)
- antifungal medicines (such as itraconazole)
- ketoconazole (used to treat Cushing’s syndrome when the body produces an excess of cortisol)
- certain medicines to treat HIV infection (such as efavirenz, nevirapine, and protease inhibitors e.g. indinavir, ritonavir)
- anticonvulsants used to treat epilepsy (such as carbamazepine, phenytoin, phenobarbital)
- certain antibiotics used to treat tuberculosis (rifabutin, rifampicin)
- medicines that are known to prolong QT prolongation.

These medicines may increase the risk of side effects or reduce the effect of Abilify Maintena; if you get any unusual symptom taking any of these medicines together with Abilify Maintena, you should see your doctor.

Medicines that increase the level of serotonin are typically used in conditions including depression, generalised anxiety disorder, obsessive-compulsive disorder (OCD) and social phobia as well as migraine and pain:

- triptans, tramadol and tryptophan used for conditions including depression, generalised anxiety disorder, obsessive compulsive disorder (OCD) and social phobia as well as migraine and pain
- SSRI s (such as paroxetine and fluoxetine) used for depression, OCD, panic and anxiety
- other anti-depressants (such as venlafaxine and tryptophan) used in major depression
- tricyclic's (such as clomipramine and amitriptyline) used for depressive illness
- St John's Wort (*Hypericum perforatum*) used as a herbal remedy for mild depression
- painkillers (such as tramadol and pethidine) used for pain relief
- triptans (such as sumatriptan and zolmitripitan) used for treating migraine.

These medicines may increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with Abilify Maintena, you should see your doctor.

Abilify Maintena with alcohol
Alcohol should be avoided.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this medicine.

You should not be given Abilify Maintena if you are pregnant unless you have discussed this with your doctor. Be sure to tell your doctor immediately if you are pregnant, think you may be pregnant, or if you are planning to become pregnant.

The following symptoms may occur in new-born babies, of mothers that have received Abilify Maintena in the last three months of their pregnancy(last trimester):
shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding.

If your baby develops any of these symptoms you need to contact your doctor.

If you are receiving Abilify Maintena, your doctor will discuss with you whether you should breast-feed considering the benefit to you of your therapy and the benefit to your baby of breast-feeding. You should not do both. Talk to your doctor about the best way to feed your baby if you are receiving Abilify Maintena.

Driving and using machines
Dizziness and vision problems may occur during treatment with this medicine (see section 4). This should be considered in cases where full alertness is required, e.g., when driving a car or handling machines.

Abilify Maintena contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Abilify Maintena is given

Abilify Maintena comes as a pre-filled syringe.

Your doctor will decide on the dose of Abilify Maintena that is right for you. The recommended starting dose is 400 mg unless your doctor decided to give you a lower starting or follow up dose.

There are two ways to start Abilify Maintena, your doctor will decide which way is right for you.
- If you are given one injection of Abilify Maintena on your first day the treatment with aripiprazole by mouth is continued for 14 days after the first injection.
- If you are given two injections of Abilify Maintena on your first day, you will also take one tablet of aripiprazole by mouth at this visit.

After that, treatment is given with injections of Abilify Maintena unless your doctor tells you otherwise.

Your doctor will give it to you as a single injection into the gluteal or deltoid muscle (buttock or shoulder) every month. You may feel a little pain during the injection. Your doctor will alternate the injections between your right and left side. The injections will not be given intravenously.

If you are given more Abilify Maintena than you should
This medicine will be given to you under medical supervision; it is therefore unlikely that you will be given too much. If you see more than one doctor, be sure to tell them that you are receiving Abilify Maintena.

Patients who have been given too much of this medicine have experienced the following symptoms:

- rapid heartbeat, agitation/aggressiveness, problems with speech.
- unusual movements (especially of the face or tongue) and reduced level of consciousness.

Other symptoms may include:

- acute confusion, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating,
- muscle stiffness, and drowsiness or sleepiness, slower breathing, choking, high or low blood pressure, abnormal rhythms of the heart.

Contact your doctor or hospital immediately if you experience any of the above.

If you miss an injection of Abilify Maintena
It is important not to miss your scheduled dose. You should be given an injection every month but not before the 26 days has passed from the last injection. If you miss an injection, you should contact your doctor to arrange your next injection as soon as you can.

If you stop receiving Abilify Maintena
Do not stop your treatment just because you feel better. It is important that you carry on receiving Abilify Maintena for as long as your doctor has told you to.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor immediately if you have any of the following serious side effects:

- a combination of any of these symptoms: excessive sleepiness, dizziness, confusion, disorientation, difficulty talking, difficulty walking, muscle stiffness or shaking, fever, weakness, irritability, aggression, anxiety, increase in blood pressure, or seizures that can lead to unconsciousness.

- unusual movement mainly of the face or tongue, since your doctor may want to lower your dose.
- if you have symptoms such as swelling, pain, and redness in the leg, because this may mean you have a blood clot, which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.
- a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness since this may be a sign of a condition called neuroleptic malignant syndrome (NMS).
- thirstiness more than usual, need to urinate more than usual, feel very hungry, feel weak or tired, feel sick, feel confused or your breath smells fruity, since this may be a sign of diabetes.
- suicidal thoughts, behaviours or thoughts and feelings about hurting yourself.

The side effects listed below may also occur after receiving Abilify Maintena.
Talk to your doctor or nurse if you are affected by any of these side effects:
Common side effects (may affect up to 1 in 10 people):

- weight gain
- diabetes mellitus
- weight loss
- feeling restless
- feeling anxious
- unable to keep still, difficulty sitting still
- difficulty sleeping (insomnia)
- jerky resistance to passive movement as muscles tense and relax, abnormally increased muscle tone, slow body movement
- akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly)
- shaking or trembling
- uncontrollable twitching, jerking or writhing movements
- changes in your level of alertness, drowsiness
- sleepiness
- dizziness
- headache
- dry mouth
- muscle stiffness
- inability to have or maintain an erection during sexual intercourse
- pain at the injection site, hardening of the skin at the injection site
- weakness, loss of strength or extreme tiredness
- during blood tests your doctor may find higher amounts of creatine phosphokinase in your blood (enzyme important for muscle function)

Uncommon side effects (may affect up to 1 in 100 people):

- low level of a specific type of white blood cells (neutropenia), low haemoglobin or red blood cell count, low level of blood platelets
- allergic reactions (hypersensitivity)
- decreased or increased blood levels of the hormone prolactin
- high blood sugar
- increased blood fats such as high cholesterol, high triglycerides and also low level of cholesterol and low level of triglycerides
- increased levels of insulin, a hormone regulating blood sugar levels
- decreased or increased appetite
- thoughts about suicide
- mental disorder characterised by defective or lost contact with reality
- hallucination
- delusion
- increased sexual interest
- panic reaction

- depression
- affect lability
- state of indifference with lack of emotion, feelings of emotional and mental discomfort
- sleep disorder
- grinding of teeth or clenching of the jaw
- reduced sexual interest (libido is decreased)
- altered mood
- muscle problems
- muscle movements that you cannot control such as grimacing, lip-smacking and tongue movements. They usually affect the face and mouth first but can affect other parts of the body. These could be signs of a condition called “tardive dyskinesia”.
- parkinsonism - medical condition with many various symptoms which include decreased or slow movements, slowness of thought, jerks when bending the limbs (cogwheel rigidity), shuffling, hurried steps, shaking, little or no facial expression, muscle stiffness, drooling
- movement problems
- extreme restlessness and restless legs
- distortion of the senses of taste and smell
- fixation of the eyeballs in one position
- blurred vision
- eye pain
- double vision
- eye sensitivity to light,
- abnormal heartbeat, slow or fast heart rate, abnormal electrical conduction of the heart, abnormal reading (ECG) of the heart
- high blood pressure
- dizziness when getting up from a lying or sitting position due to a drop in blood pressure
- cough
- hiccups
- gastroesophageal reflux disease. Excess amount of gastric juice flowing back (refluxes) into the esophagus (gullet or the tube that goes from mouth to stomach through which food passes), causing heartburn and possibly damaging the esophagus
- heartburn
- vomiting
- diarrhoea
- feeling sick
- stomach ache
- stomach discomfort
- constipation
- frequent bowel movement
- drooling, more saliva in mouth than normal
- abnormal hair loss
- acne, skin condition of the face where the nose and cheeks are unusually red, eczema, skin hardening
- muscle rigidity, muscle spasms, muscle twitching, muscle tightness, mucle pain (myalgia), pain in extremity
- joint pain (arthralgia), back pain, decreased range of motion of joints, stiff neck, limited opening of mouth
- kidney stones, sugar (glucose) in urine
- spontaneous flow of milk from the breasts (galactorrhoea)
- enlargement of breast in men, breast tenderness, vaginal dryness
- fever
- loss of strength
- gait disturbance
- chest discomfort
- injection site reactions such as redness, swelling discomfort and injection site itching
- thirst
- sluggishness

- liver function tests may show abnormal results
- during tests your doctor may find
  - higher amounts of liver enzymes
  - higher amounts of alanine aminotransferase
  - higher amounts of gamma-glutamyl transferase
  - higher amounts of bilirubin in your blood
  - higher amounts of aspartate aminotransferase
  - higher or lower amounts of blood glucose
  - higher amounts of glycosylated haemoglobin
  - lower amounts of cholesterol in your blood
  - lower amounts of triglycerides in your blood
  - a higher waist circumference

The following side effects have been reported since the marketing of medicines containing the same active substance that are taken by mouth but the frequency for them to occur is not known (frequency cannot be estimated from the available data):

- low levels of white blood cells
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives), rash
- unusual heartbeat, sudden unexplained death, heart attack
- diabetic ketoacidosis (ketones in the blood and urine) or coma
- loss of appetite (anorexia), difficulty in swallowing
- low sodium level in the blood
- suicide attempt and suicide
- inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences
  - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive
  - uncontrollable excessive shopping
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)
  - a tendency to wander away

  Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms.
- nervousness
- aggression
- neuroleptic malignant syndrome (a syndrome with symptoms such as fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate)
- seizure (fits)
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles)
- speech disorders
- heart problems including torsades de pointes, stopping of the heart, irregularities in heart rhythm that may be due to abnormal nerve impulses in the heart, abnormal readings during heart examination (ECG) QT prolongation
- fainting
- symptoms related to blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing
- spasm of the muscles around the voice box
- accidental inhalation of food with risk of pneumonia (lung infection)
- inflammation of the pancreas
- difficulty swallowing
- liver failure
- jaundice (yellowing of the skin and white part of eyes)

- inflammation of the liver
- rash
- skin sensitivity to light
- excessive sweating
- serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia).
- muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell, have a high temperature or have dark urine. They may be caused by an abnormal muscle breakdown which can be life threatening and lead to kidney problems (a condition called rhabdomyolysis)
- difficulty in passing urine
- involuntary loss of urine (incontinence)
- drug withdrawal symptoms in new-born infant
- prolonged and/or painful erection
- difficulty controlling core body temperature or overheating
- chest pain
- swelling of hands, ankles or feet
- during tests your doctor may find
  - higher amounts alkaline phosphatase
  - fluctuating results during tests to measure glucose in your blood

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Abilify Maintena

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the pre-filled syringe. The expiry date refers to the last day of that month.

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

If the injection is not performed immediately after reconstitution, the syringe can be kept below 25 °C for up to 2 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Abilify Maintena contains
- The active substance is aripiprazole.
  Each pre-filled syringe contains 300 mg aripiprazole.
  After reconstitution each mL of suspension contains 200 mg aripiprazole.
  Each pre-filled syringe contains 400 mg aripiprazole.
  After reconstitution each mL of suspension contains 200 mg aripiprazole.

- The other ingredients are

Powder
Carmellose sodium, mannitol (E421), sodium dihydrogen phosphate monohydrate (E339), sodium hydroxide (E524)
Solvent
Water for injections

What Abilify Maintena looks like and contents of the pack
Abilify Maintena comes in a pre-filled syringe containing a white to off-white powder in the front chamber and a clear solvent in the rear chamber. Your doctor will make it into a suspension that will be given as an injection.

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.

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Elaiapharm
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

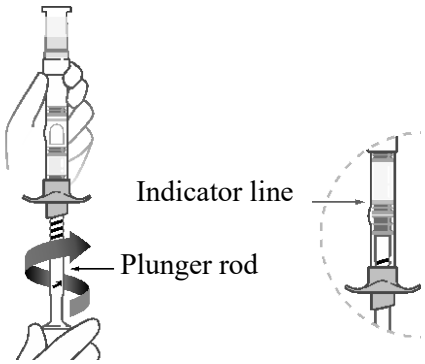
INSTRUCTIONS FOR HEALTH CARE PROFESSIONALS

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

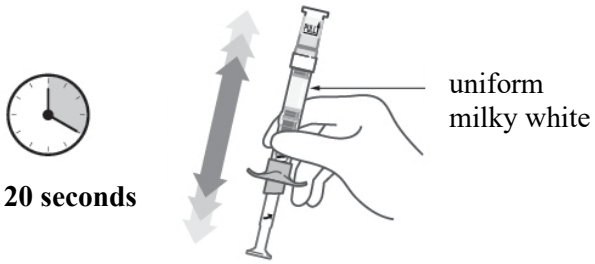
Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
aripiprazole

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.

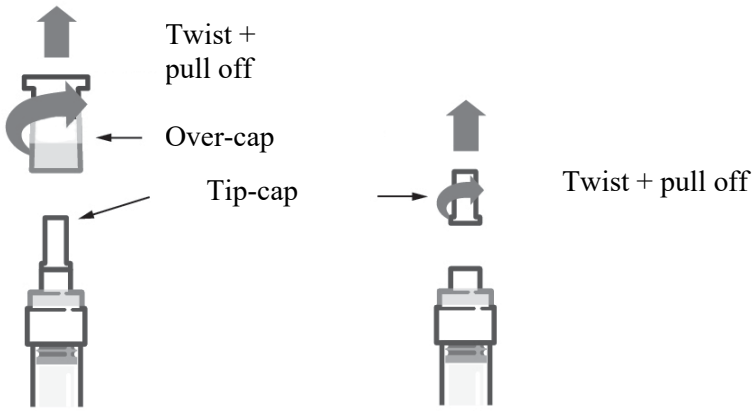


c) Visually inspect the syringe for particulate matter and discoloration prior to administration. The reconstituted product suspension should appear to be a uniform, homogeneous suspension that is opaque and milky-white in colour.

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

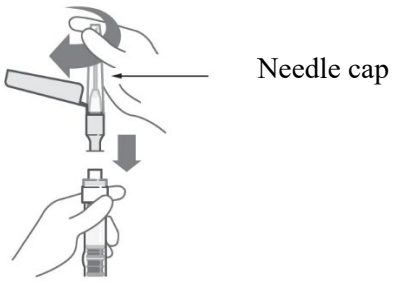
a) Twist and pull off over-cap and tip-cap.



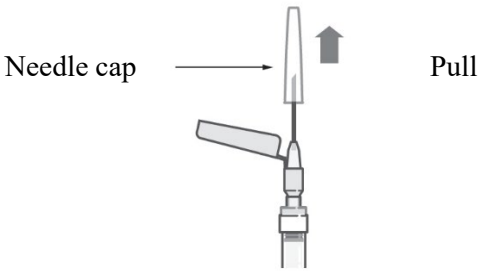
b) Select one of the following hypodermic safety needles depending on the injection site and patient's weight.

Body type	Injection site	Needle size
Non-obese	**Deltoid** **Gluteal**	**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**

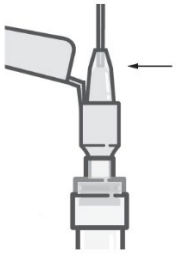
c) While holding the needle cap, ensure the needle is firmly seated on the safety device with a push and twist clockwise until snugly fitted.



d) Then **pull** needle-cap straight up.



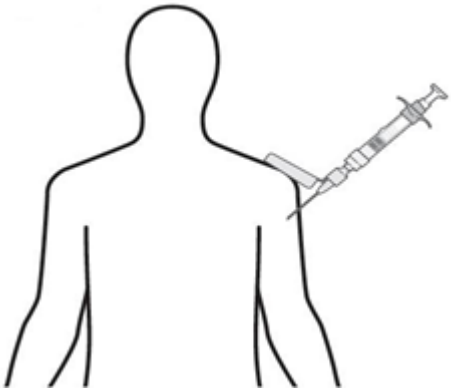
e) Hold syringe **upright and advance plunger rod slowly to expel the air**. If it's not possible to advance plunger rod to expel the air, check that plunger rod is rotated to a complete stop. It is not possible to re-suspend after the air in the syringe is expelled.



Expel air until suspension fills needle base*

***If there's resistance or difficulty expelling air,** check that plunger rod is rotated to a complete stop.

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.



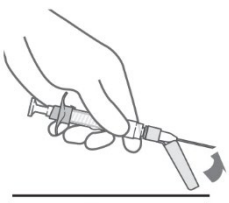
deltoid

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 4: Procedures after injection

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



Cover

Discard

Package leaflet: Information for the user

Abilify Maintena 720 mg prolonged-release suspension for injection in pre-filled syringe
Abilify Maintena 960 mg prolonged-release suspension for injection in pre-filled syringe
aripiprazole

Read all of this leaflet carefully before you receive this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Abilify Maintena is and what it is used for

Abilify Maintena contains the active substance aripiprazole in a pre-filled syringe.
Aripiprazole belongs to a group of medicines called antipsychotics. Abilify Maintena is used to treat schizophrenia - a disease with symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.

Abilify Maintena is intended for adult patients with schizophrenia who are sufficiently stabilised during treatment with aripiprazole.

If you have responded well to treatment with aripiprazole taken by mouth or the medicine Abilify Maintena, your doctor may start treatment with Abilify Maintena. It can help alleviate the symptoms of your disease and reduce the risk of your symptoms coming back.

2. What you need to know before you are given Abilify Maintena

Do not use Abilify Maintena
- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or nurse before you are given Abilify Maintena.

Suicidal thoughts and behaviours have been reported during treatment with this medicine. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself before or after reveiving Abilify Maintena.

Before treatment with this medicine, tell your doctor if you suffer from:

- an acutely agitated state or a severely psychotic state
- cardiovascular diseases (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure

- heart problems or have a history of stroke, especially if you know that you have other risks factors for stroke
- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots
- irregular heartbeat or if someone else in your family has a history of irregular heartbeat (including so called QT prolongation seen with ECG monitoring)
- involuntary, irregular muscle movements, especially in the face (tardive dykinesia)
- experience a combination of fever, sweating, faster breathing, muscle stiffness and drowsiness or sleepiness (may be signs of neuroleptic malignant syndrome)
- fits (seizures) since your doctor may want to monitor you more closely
- dementia (loss of memory and other mental abilities) especially if you are elderly
- high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite and feeling weak) or family history of diabetes
- have any difficulty in swallowing
- past experience with excessive gambling.

If you notice you are gaining weight, develop unusual movements, experience sleepiness that interferes with normal daily activities, any difficulty in swallowing or have allergic symptoms, please talk to your doctor immediately.

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings.
Your doctor may need to adjust or stop your dose.

This medicine may cause sleepiness, fall in blood pressure when standing up, dizziness and changes in your ability to move and balance, which may lead to falls. Caution should be taken, particularly if you are an elderly patient or have some debility.

Children and adolescents
Do not use this medicine in children and adolescents under 18 years of age. It is not known if it is safe and effective in these patients.

Other medicines and Abilify Maintena
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Blood pressure-lowering medicines: Abilify Maintena may increase the effect of medicines used to lower the blood pressure. Be sure to tell your doctor if you take a medicine to keep your blood pressure under control.

Receiving Abilify Maintena with some medicines may mean the doctor will need to change your dose of Abilify Maintena or the other medicines. It is especially important to mention the following to your doctor:

- medicines to correct heart rhythm (such as quinidine, amiodarone, flecainide, diltiazem)
- antidepressants or herbal remedy used to treat depression and anxiety (such as fluoxetine, paroxetine, escitalopram, St. John's Wort)
- antifungal medicines (such as itraconazole)
- ketoconazole (used to treat Cushing’s syndrome when the body produces an excess of cortisol)
- certain medicines to treat HIV infection (such as efavirenz, nevirapine, and protease inhibitors e.g., indinavir, ritonavir)
- anticonvulsants used to treat epilepsy (such as carbamazepine, phenytoin, phenobarbital primidone)
- certain antibiotics used to treat tuberculosis (rifabutin, rifampicin)
- medicines that are known to prolong QT prolongation.

These medicines may increase the risk of side effects or reduce the effect of Abilify Maintena; if you get any unusual symptom taking any of these medicines together with Abilify Maintena, you should see your doctor.

Medicines that increase the level of serotonin are typically used in conditions including depression, generalised anxiety disorder, obsessive-compulsive disorder (OCD) and social phobia as well as migraine and pain:

- triptans, tramadol and tryptophan used for conditions including depression, generalised anxiety disorder, OCD and social phobia as well as migraine and pain
- selective serotonin reuptake inhibitor/serotonin noradrenaline reuptake inhibitor (SSRI/SNRI s) such as paroxetine and fluoxetine used for depression, OCD, panic, and anxiety
- other anti-depressants (such as venlafaxine and tryptophan) used in major depression
- tricyclic's (such as clomipramine and amitriptyline) used for depressive illness
- St John's Wort (*Hypericum perforatum*) used as an herbal remedy for mild depression
- painkillers (such as tramadol and pethidine) used for pain relief
- triptans (such as sumatriptan and zolmitripitan) used for treating migraine.

These medicines may increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with Abilify Maintena, you should see your doctor.

Abilify Maintena with alcohol
Alcohol should be avoided.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this medicine.

You should not be given Abilify Maintena if you are pregnant unless you have discussed this with your doctor. Be sure to tell your doctor immediately if you are pregnant, think you may be pregnant, or if you are planning to become pregnant.

The following symptoms may occur in new-born babies, of mothers that receive this medicine in the last three months of their pregnancy (last trimester):
Shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding.

If your baby develops any of these symptoms you need to contact your doctor.

If you are receiving Abilify Maintena, your doctor will discuss with you whether you should breast-feed considering the benefit to you of your therapy and the benefit to your baby of breast-feeding. You should not do both. Talk to your doctor about the best way to feed your baby if you are receiving this medicine.

Driving and using machines
Dizziness and vision problems may occur during treatment with this medicine (see section 4). This should be considered in cases where full alertness is required, e.g., when driving or handling machines.

Abilify Maintena contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How Abilify Maintena is given

Abilify Maintena comes as a suspension in a pre-filled syringe which your doctor or nurse will administer.

Your doctor will decide on the dose that is right for you. The recommended starting dose is 960 mg injected once every 2 months (56 days after the previous injection) unless your doctor decided to give you a lower starting or follow up dose (720 mg) injected once every 2 months (56 days after the previous injection).

There are three ways to start Abilify Maintena 960 mg, your doctor will decide which way is right for you.

- If you received Abilify Maintena 400 mg 1 or more months before your doctor started treatment with Abilify Maintena 960 mg, your next dose may be replaced with one injection of Abilify Maintena 960 mg.
- If you are given one injection of Abilify Maintena 960 mg on your first day without administration of Abilify Maintena 400 mg 1 month before, the treatment with aripiprazole by mouth is continued for 14 days after the first injection.
- If you are given two injections (one of Abilify Maintena 960 mg and one of Abilify Maintena 400 mg) on your first day, you will also take one tablet of aripiprazole by mouth at this visit. Your doctor will give the injections in two different sites.
-

After that, treatment is given with injections of Abilify Maintena 960 mg or 720 mg unless your doctor tells you otherwise.

Your doctor will give it to you as a single injection into the gluteal muscle (buttock) once every two months. You may feel a little pain during the injection. Your doctor will alternate the injections between your right and left side. The injections will not be given intravenously.

If you are given more Abilify Maintena than you should
This medicine will be given to you under medical supervision; it is therefore unlikely that you will be given too much. If you see more than one doctor, be sure to tell them that you are receiving this medicine.

Patients who have been given too much of this medicine have experienced the following symptoms:

- rapid heartbeat, agitation/aggressiveness, problems with speech.
- unusual movements (especially of the face or tongue) and reduced level of consciousness.

Other symptoms may include:

- acute confusion, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating,
- muscle stiffness, and drowsiness or sleepiness, slower breathing, choking, high or low blood pressure, abnormal rhythms of the heart.

Contact your doctor or hospital immediately if you experience any of the above.

If you miss an injection of Abilify Maintena
It is important not to miss your scheduled dose. You should be given an injection once every 2 months. If you miss an injection, you should contact your doctor to arrange your next injection as soon as you can.

If you stop receiving Abilify Maintena
Do not stop your treatment just because you feel better. It is important that you carry on receiving this medicine for as long as your doctor has told you to.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Tell your doctor immediately if you have any of the following serious side effects:

- a combination of any of these symptoms: excessive sleepiness, dizziness, confusion, disorientation, difficulty talking, difficulty walking, muscle stiffness or shaking, fever, weakness, irritability, aggression, anxiety, increase in blood pressure, or seizures that can lead to unconsciousness.
- unusual movement mainly of the face or tongue, since your doctor may want to lower your dose.
- if you have symptoms such as swelling, pain, and redness in the leg, because this may mean you have a blood clot, which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.
- a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness since this may be a sign of a condition called neuroleptic malignant syndrome (NMS).
- thirstiness more than usual, need to urinate more than usual, feel very hungry, feel weak or tired, feel sick, feel confused or your breath smells fruity, since this may be a sign of diabetes.
- suicidal thoughts, behaviours or thoughts and feelings about hurting yourself.

The side effects listed below may also occur after receiving Abilify Maintena
Talk to your doctor or nurse if you are affected by any of these side effects:

Common side effects (may affect up to 1 in 10 people):

- diabetes mellitus
- feeling restless
- feeling anxious
- unable to keep still, difficulty sitting still
- difficulty sleeping (insomnia)
- jerky resistance to passive movement as muscles tense and relax, abnormally increased muscle tone, slow body movement
- akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly)
- shaking or trembling
- uncontrollable twitching, jerking or writhing movements
- changes in your level of alertness, drowsiness
- sleepiness
- dizziness
- headache
- dry mouth
- muscle stiffness
- inability to have or maintain an erection during sexual intercourse
- pain at the injection site, hardening of the skin at the injection site
- weakness, loss of strength or extreme tiredness
- during blood tests your doctor may find higher amounts of creatine phosphokinase in your blood (enzyme important for muscle function)
- weight gain
- weight loss

Uncommon side effects (may affect up to 1 in 100 people):

- low level of a specific type of white blood cells (neutropenia), low haemoglobin or red blood cell count, low level of blood platelets
- allergic reactions (e.g., swelling in the mouth, tongue, face and throat, itching, hives)
- increased blood levels of the hormone prolactin
- high blood sugar
- increased blood fats such as high cholesterol and high triglycerides
- increased levels of insulin, a hormone regulating blood sugar levels
- decreased or increased appetite
- thoughts about suicide
- mental disorder characterised by defective or lost contact with reality
- hallucination (e.g. seeing and hearing things that are not real)
- delusion (e.g. believing things that are not true)
- increased sexual interest (may lead to behaviour of significant concern to you or to others)
- panic reaction
- depression
- affect lability
- state of indifference with lack of emotion, feelings of emotional and mental discomfort
- sleep disorder
- grinding of teeth or clenching of the jaw
- reduced sexual interest (libido is decreased)
- altered mood
- muscle problems
- muscle movements that you cannot control such as grimacing, lip-smacking and tongue movements. They usually affect the face and mouth first but can affect other parts of the body. These could be signs of a condition called “tardive dyskinesia”.
- parkinsonism - medical condition with many various symptoms which include decreased or slow movements, slowness of thought, jerks when bending the limbs (cogwheel rigidity), shuffling, hurried steps, shaking, little or no facial expression, muscle stiffness, drooling
- movement problems
- extreme restlessness and restless legs
- fixation of the eyeballs in one position
- blurred vision
- eye pain
- double vision
- eye sensitivity to light
- distortion of the senses of taste and smell
- abnormal heartbeat, slow or fast heart rate
- high blood pressure
- dizziness when getting up from a lying or sitting position due to a drop in blood pressure
- cough
- hiccups
- gastrooesophageal reflux disease. Excess amount of gastric juice flowing back (refluxes) into the oesophagus (gullet or the tube that goes from mouth to stomach through which food passes), causing heartburn and possibly damaging the oesophagus
- heartburn
- vomiting
- diarrhoea
- feeling sick
- stomach ache
- stomach discomfort
- constipation
- frequent bowel movement
- drooling, more saliva in mouth than normal
- abnormal hair loss
- acne, skin condition of the face where the nose and cheeks are unusually red, eczema, skin hardening

- muscle rigidity, muscle spasms, muscle twitching, muscle tightness, muscle pain (myalgia), pain in extremity
- joint pain (arthralgia), back pain, decreased range of motion of joints, stiff neck, limited opening of mouth
- kidney stones, sugar (glucose) in urine
- spontaneous flow of milk from the breasts (galactorrhoea)
- enlargement of breast in men, breast tenderness, vaginal dryness
- fever
- loss of strength
- gait disturbance
- chest discomfort
- injection site reactions such as redness, swelling, discomfort and injection site itching
- thirst
- sluggishness
- during tests your doctor may find
  - higher or lower amounts of blood glucose
  - higher amounts of glycosylated haemoglobin
  - a higher waist circumference
  - lower amounts of cholesterol in your blood
  - lower amounts of triglycerides in your blood
  - lower amounts of white blood cells and neutrophils in your blood
  - higher amounts of liver enzymes
  - lower amounts of the hormone prolactin in your blood
  - abnormal reading (ECG) of the heart (e.g. T wave amplitude decreased or inverted)
  - higher amounts of alanine aminotransferase
  - higher amounts of gamma-glutamyl transferase
  - higher amounts of bilirubin in your blood
  - higher amounts of aspartate aminotransferase
- liver function tests may show abnormal results

The following side effects have been reported since the marketing of medicines containing the same active substance that are taken by mouth but the frequency for them to occur is not known (frequency cannot be estimated from the available data):

- low levels of white blood cells
- decreased appetite
- low sodium level in the blood
- suicide and suicide attempt
- inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences
  - uncontrollable excessive shopping
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)
  - a tendency to wander away

  Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms.
- nervousness
- aggression
- neuroleptic malignant syndrome (a syndrome with symptoms such as fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate)
- seizure (fits)
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles)
- speech disorders
- diabetic ketoacidosis (ketones in the blood and urine) or coma

- fainting
- heart problems including stopping of the heart, torsades de pointes, irregularities in heart rhythm that may be due to abnormal nerve impulses in the heart
- symptoms related to blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing
- spasm in your throat that can lead to a feeling as though a large object is stuck in your throat
- spasm of the muscles around the voice box
- accidental inhalation of food with risk of pneumonia (lung infection)
- inflammation of the pancreas
- difficulty in swallowing
- liver failure
- jaundice (yellowing of the skin and white part of eyes)
- inflammation of the liver
- rash
- skin sensitivity to light
- excessive sweating
- serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia).
- muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell, have a high temperature or have dark urine. They may be caused by an abnormal muscle breakdown which can be life threatening and lead to kidney problems (a condition called rhabdomyolysis)
- difficulty in passing urine
- involuntary loss of urine (incontinence)
- withdrawal symptoms in new-born infant
- prolonged and/or painful erection
- sudden unexplained death
- difficulty controlling core body temperature or overheating
- chest pain
- swelling of hands, ankles or feet
- during tests your doctor may find
  - fluctuating results during tests to measure glucose in your blood
  - QT prolongation (an abnormal readings during heart examination (ECG))
  - higher amounts of alkaline phosphatase in your blood

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Abilify Maintena

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the pre-filled syringe. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Abilify Maintena contains

- The active substance is aripiprazole.

  Abilify Maintena 720 mg prolonged-release suspension for injection in pre-filled syringe
  Each pre-filled syringe contains 720 mg aripiprazole.

  Abilify Maintena 960 mg prolonged-release suspension for injection in pre-filled syringe
  Each pre-filled syringe contains 960 mg aripiprazole.

- The other ingredients are:
  Carmellose sodium, macrogol, povidone (E1201), sodium chloride, sodium dihydrogen phosphate monohydrate (E339), sodium hydroxide (E524), water for injections.(see section 2, Abilify Maintena contains sodium)

What Abilify Maintena looks like and contents of the pack
Abilify Maintena is a prolonged-release suspension for injection in a pre-filled syringe.

Abilify Maintena is a white to off-white prolonged-release suspension for injection in a pre-filled syringe.

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

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

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Manufacturer
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for medical or healthcare professionals only:

INSTRUCTIONS FOR HEALTH CARE PROFESSIONALS

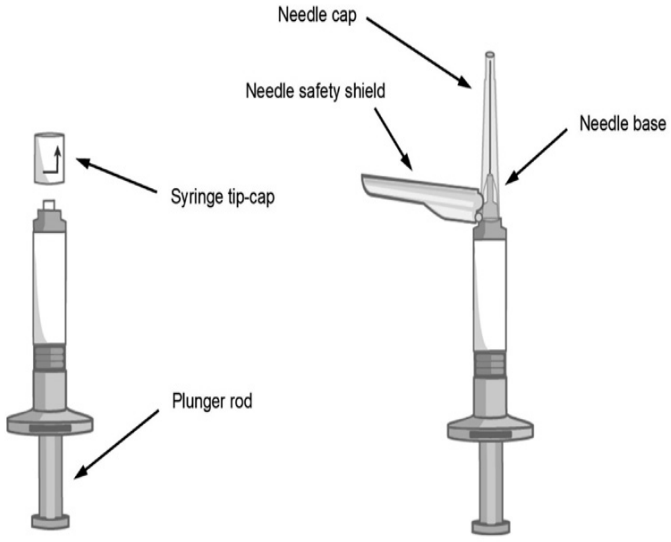
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Abilify Maintena 720 mg prolonged-release suspension for injection in pre-filled syringe
Abilify Maintena 960 mg prolonged-release suspension for injection in pre-filled syringe
aripiprazole

- To be administered by a healthcare professional once every 2 months. Read complete instructions prior to use.
- The suspension for injection is for single use only.
- **For intramuscular use. Gluteal injection only**. **Do not** administer by any other route.
- Prior to administration, visually inspect the syringe for particulate matter and discolouration.
- The suspension should appear to be a uniform, homogeneous suspension that is opaque and milky-white in colour. Do not use Abilify Maintena if it is discoloured, or particulate matter is present.

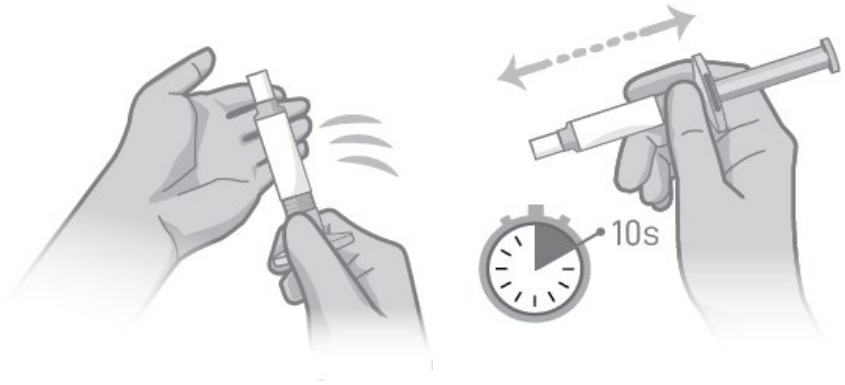
Contents of kit

Confirm that components listed below are provided:
- One pre-filled syringe containing either Abilify Maintena 960 mg or 720 mg prolonged-release injectable suspension and two safety needles.
- One sterile 38 mm (1.5 inch) 22 gauge needle with black needle hub.
- One sterile 51 mm (2 inch) 21 gauge needle with green needle hub.



Prepare for injection

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



Select the appropriate needle

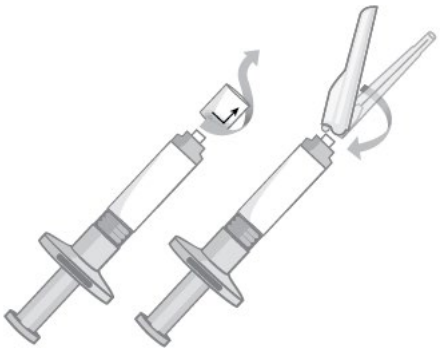
For gluteal intramuscular administration only.

Needle selection is determined by patient body type.

Body type	Needle size	Needle shield colour
Non-obese (BMI < 28 kg/m^2)	38 mm, 22 gauge	Black
Obese (BMI > 28 kg/m^2)	51 mm, 21 gauge	Green

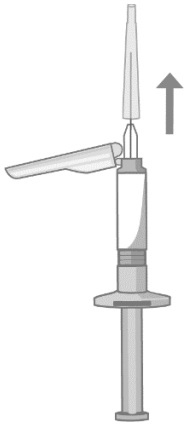
Attach the needle

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



Expel air

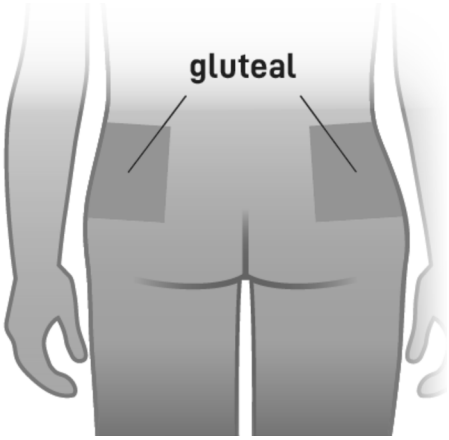
- When you are ready to administer the injection, hold the syringe upright and remove the needle cap by pulling straight up. **Do not** twist the needle cap as this may loosen the needle from the syringe.



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

Inject the dose

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

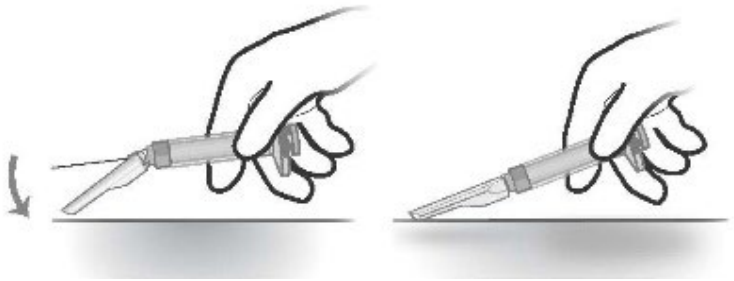


- Remember to rotate sites of injections between the two gluteal muscles.
- If initiating with the two injection start, inject into two different gluteal muscle. DO NOT inject both injections concomitantly into the same gluteal muscle.

- Look for signs or symptoms of inadvertent intravenous administration.

Disposal procedure

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



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