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

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
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
Powder and solvent for prolonged-release suspension for injection in pre-filled syringe

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.

The recommended starting and maintenance dose of Abilify Maintena is 400 mg.

Titration of the dose of this medicinal product is not required. It should be administered once monthly as a single injection (no sooner than 26 days after the previous injection).

After the first injection, treatment with 10 mg to 20 mg oral aripiprazole should be continued for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy.

If there are adverse reactions with the 400 mg dosage, reduction of the dose to 300 mg once monthly should be considered.

Missed doses

Missed doses	
If 2nd or 3rd dose is missed and time since last injection is:	**Action**
> 4 weeks and < 5 weeks	The injection should be administered as soon as possible and then resume monthly injection schedule.
> 5 weeks	Concomitant oral aripiprazole should be restarted for 14 days with next administered injection and then resume monthly injection schedule.
If 4th or subsequent doses are missed (i.e., after attainment of steady state) and time since last injection is:	**Action**
> 4 weeks and < 6 weeks	The injection should be administered as soon as possible and then resume monthly injection schedule.
> 6 weeks	Concomitant oral aripiprazole should be restarted for 14 days with next administered injection and then resume monthly injection schedule.

Special populations

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

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

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

Known CYP2D6 poor metabolisers
In patients who are known to be CYP2D6 poor metabolisers, the starting and maintenance dose should be 300 mg. When used concomitantly with strong CYP3A4 inhibitors the dose should be reduced to 200 mg (see section 4.5).

Dose adjustments due to interactions
Dosage adjustments should be made in patients taking concomitant strong CYP3A4 inhibitors or strong CYP2D6 inhibitors for more than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the dosage may need to be increased to the previous dose (see section 4.5). In case of

adverse reactions despite dose adjustments of Abilify Maintena, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

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

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

	Adjusted dose
Patients taking 400 mg of Abilify Maintena	
Strong CYP2D6 or strong CYP3A4 inhibitors	300 mg
Strong CYP2D6 and strong CYP3A4 inhibitors	200 mg*
CYP3A4 inducers	Avoid use
Patients taking 300 mg of Abilify Maintena	
Strong CYP2D6 or strong CYP3A4 inhibitors	200 mg*
Strong CYP2D6 and strong CYP3A4 inhibitors	160 mg*
CYP3A4 inducers	Avoid use

* 200 mg and 160 mg can be achieved via adjustment of the injection volume only by using Abilify Maintena powder and solvent for prolonged-release suspension for injection.

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

Method of administration

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

Abilify Maintena 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 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.

The suspension should be injected slowly as a single injection (doses must not be divided) into the gluteal or deltoid muscle. Care should be taken to avoid inadvertent injection into a blood vessel.

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 50 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.

Full instructions for use and handling of Abilify Maintena 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 that 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 antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient

develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including aripiprazole, must be discontinued (see section 4.8).

Seizure

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

Elderly patients with dementia-related psychosis

Increased mortality
In three placebo-controlled trials of oral aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n = 938; mean age: 82.4 years; range: 56-99 years), patients treated with aripiprazole 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: 78-88 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 atypical antipsychotic medicines, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotic medicines are not available to allow direct comparisons. Patients treated with any antipsychotic medicinal products, including aripiprazole, should be observed for signs and symptoms of 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.

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 antipsychotic medicinal product use, including aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling

Post-marketing reports of pathological gambling have been reported among patients prescribed oral aripiprazole, regardless of whether these patients had a prior history of gambling. Patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully (see section 4.8).

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 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

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

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

Ketoconazole and other strong CYP3A4 inhibitors
In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63 % and 37 %, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolisers (see section 4.2). When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should, therefore, be applied (see section 4.2). Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of 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 this medicinal product, 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 and other inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects. The concomitant use of CYP3A4 inducers with Abilify Maintena should be avoided because the blood levels of aripiprazole are decreased and may be below the effective levels.

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

Potential for aripiprazole to affect other medicinal products

In clinical studies, oral doses of 10-30 mg/day of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, Abilify Maintena is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.
When aripiprazole was administered concomitantly with lamotrigine, dextromethorphan, warfarin, omeprazole, escitalopram, or venlafaxine there was no clinically important change in concentrations of these medicinal products. Thus, no dosage adjustment of these medicinal products is required when co-administered with Abilify Maintena.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The most frequently observed adverse drug reactions (ADRs) reported in ≥ 5 % of patients in two double-blind, long-term trials of Abilify Maintena were weight increased (9.0 %), akathisia (7.9 %), insomnia (5.8 %), and injection site pain (5.1 %).

Tabulated list of adverse reactions
The incidences of the ADRs associated with aripiprazole therapy are tabulated below. The table is based on adverse events reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ class and frequency; very common (≥ 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 frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known".

	Common	**Uncommon**	**Not known**
Blood and lymphatic system disorders		Neutropenia Anaemia Thrombocytopenia Neutrophil count decreased White blood cell count decreased	Leukopenia
Immune system disorders		Hypersensitivity	Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders		Blood prolactin decreased Hyperprolactinaemia	Diabetic hyperosmolar coma Diabetic ketoacidosis
Metabolism and nutrition disorders	Weight increased Diabetes mellitus Weight decreased	Hyperglycaemia Hypercholesterolaemia Hyperinsulinaemia Hyperlipidaemia Hypertriglyceridaemia Appetite disorder	Anorexia Hyponatraemia

	Common	Uncommon	Not known
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 Pathological gambling 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 Grand mal convulsion Serotonin syndrome Speech disorder
Eye disorders		Oculogyric crisis Vision blurred Eye pain Diplopia	
Cardiac disorders		Ventricular extrasystoles Bradycardia Tachycardia Electrocardiogram T wave amplitude decreased Electrocardiogram abnormal Electrocardiogram T wave inversion	Sudden unexplained death Cardiac arrest Torsades de pointes Ventricular arrhythmias QT prolongation
Vascular disorders		Hypertension Orthostatic hypotension Blood pressure increased	Syncope Venous thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders		Cough Hiccups	Oropharyngeal spasm Laryngospasm Aspiration pneumonia
Gastrointestinal disorders	Dry mouth	Gastrooesophageal reflux disease Dyspepsia Vomiting Diarrhoea Nausea Abdominal pain upper	Pancreatitis Dysphagia

	Common	Uncommon	Not known
		Abdominal discomfort Constipation Frequent bowel movement Salivary hypersecretion	
Hepatobiliary disorders		Liver function test abnormal Hepatic enzyme increased Alanine aminotransferase increased Gamma-glutamyl transferase increased Blood bilirubin increased Aspartate aminotransferase increased	Hepatic failure Jaundice Hepatitis Alkaline phosphatase increased
Skin and subcutaneous tissue disorders		Alopecia Acne Rosacea Eczema Skin induration	Rash Photosensitivity reaction Hyperhidrosis
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

	Common	Uncommon	Not known
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 administered in the deltoid or gluteal muscle, injection site related reactions were slightly more frequent in the deltoid muscle. The majority were mild and improved on subsequent injections. When compared to studies where Abilify Maintena was injected in the gluteal muscle, repeated occurrence of injection site pain was more frequent in the deltoid muscle.

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

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

During double-blind treatment, mean change in body weight from baseline to last visit was -0.2 kg for Abilify Maintena and -0.4 kg for placebo (p = 0.812).

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).

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 Abilify Maintena. Care must be taken to avoid inadvertent injection of this medicinal product into a blood vessel. Following any confirmed or suspected accidental overdose/inadvertent intravenous administration, close observation of the patient is needed and if any potentially medically serious sign or symptom develops, monitoring, which should include continuous electrocardiographic monitoring, is required. The medical supervision and monitoring should continue until the patient recovers.

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

Signs and symptoms

In clinical trials and post-marketing experience, accidental or intentional acute overdose of aripiprazole alone was identified in adult patients with reported estimated doses up to 1,260 mg (41 times highest recommended daily aripiprazole dose) with no fatalities. The potentially medically important signs and symptoms observed included lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting and diarrhoea. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence, transient loss of consciousness and extrapyramidal symptoms.

Management of overdose

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple medicinal product involvement should be considered. Therefore, cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

Haemodialysis

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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 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 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 10-30 mg as maintenance treatment in adult patients with schizophrenia. This trial consisted of a screening phase and 3 treatment phases: Conversion Phase, Oral Stabilisation Phase, and Double-blind, Active-controlled Phase.

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

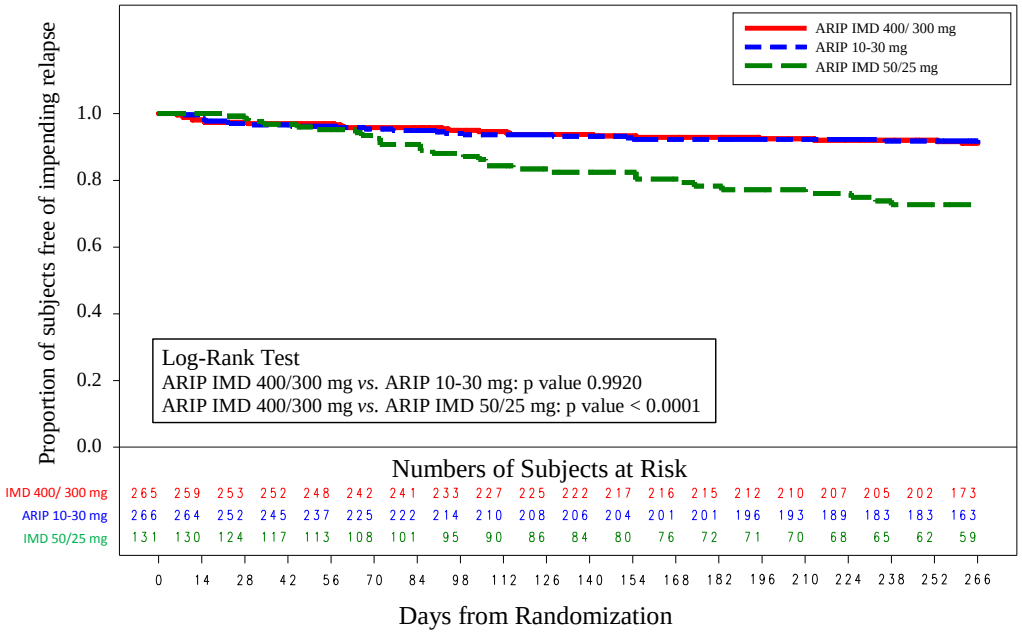
The results of analysis of the primary efficacy endpoint, the estimated proportion of patients experiencing impending relapse by end of Week 26 of the Double-blind, Active-controlled Phase, showed that Abilify Maintena 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10-30 mg. The estimated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

The estimated proportion of patients experiencing impending relapse by end of Week 26 for Abilify Maintena 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 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, oral aripiprazole 10-30 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 10-30 mg = oral aripiprazole; ARIP IMD 50/25 mg = Long-acting Injectable

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

Table 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 Stabilisation, and Double-blind Placebo-controlled. Patients fulfilling the oral stabilisation requirement in the Oral Stabilisation Phase were assigned to receive, in a single-blind fashion, Abilify Maintena and began an Abilify Maintena Stabilisation Phase for a minimum of 12 weeks and a maximum of 36 weeks. Patients eligible for the Double-blind, Placebo-controlled Phase were randomly assigned in a 2:1 ratio to double-blind treatment with Abilify Maintena or placebo, respectively.

The final efficacy analysis included 403 randomised patients and 80 exacerbations of psychotic symptoms/impending relapse events. In the placebo group 39.6 % of the patients had progressed to impending relapse, whilst in the Abilify Maintena 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 (−0.33 ng/ml) compared with a mean increase in oral aripiprazole tablets 10-30 mg (0.79 ng/ml; $p < 0.01$). The incidence of Abilify Maintena patients with prolactin levels > 1 time the upper limit of normal range (ULN) at any assessment was 5.4 % compared with 3.5 % of the patients on oral aripiprazole tablets 10-30 mg.
Male patients generally had a higher incidence than female patients in each treatment group.

In the Double-blind Placebo-controlled Phase of the 52-week trial, from baseline to last visit there was a mean decrease in prolactin levels in Abilify Maintena (−0.38 ng/ml) compared with a mean increase in placebo (1.67 ng/ml). The incidences of Abilify Maintena patients with prolactin levels > 1 time the upper limit of normal range (ULN) was 1.9 % compared to 7.1 % for placebo patients.

Acute treatment of schizophrenia in adults
The efficacy of Abilify Maintena 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 (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 also showed statistically significant improvement in symptoms represented by CGIS 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. 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 compared with the placebo group 8.5 %. Akathisia was the most frequently observed EPS symptom (Abilify Maintena 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).

5.2 Pharmacokinetic properties

Absorption

Aripiprazole absorption into the systemic circulation is slow and prolonged following Abilify Maintena administration due to low solubility of aripiprazole particles.The average absorption half-life of Abilify Maintena is 28 days. Absorption of aripiprazole from the IM depot formulation was complete relative to the IM standard (immediate-release) formulation. The dose adjusted C_{max} values for the depot formulation were approximately 5 % of C_{max} from IM standard formulation.Following a single dose administration of Abilify Maintena in the deltoid and gluteal muscle, the extent of absorption (AUC) was similar for both injection sites, but the rate of absorption (C_{max}) was higher following administration to the deltoid muscle.Following multiple intramuscular doses, the plasma concentrations of aripiprazole gradually rise to a maximum plasma concentration at a median t_{max} of 7 days for the gluteal muscle and 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, dehydro-aripiprazole, the active metabolite, represents about 29.1-32.5 % of aripiprazole AUC in plasma.

Elimination

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

Pharmacokinetics in special patient groups

CYP2D6 poor metabolisers
Based on population pharmacokinetic evaluation of Abilify Maintena, the total body clearance of aripiprazole was 3.71 L/h in extensive metabolisers of CYP2D6 and approximately 1.88 L/h

(approximately 50 % lower) in poor metabolisers of CYP2D6 (for dose recommendation, see section 4.2).

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

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

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

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

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

Hepatic impairment
A single-dose study with oral administration of aripiprazole to subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

5.3 Preclinical safety data

The toxicological profile for aripiprazole administered to experimental animals by intramuscular injection is generally similar to that seen following oral administration at comparable plasma levels. With intramuscular injection, however an inflammatory response was seen at the injection site, and consisted of granulomatous inflammation, foci (deposited drug), cellular infiltrates, oedema (swelling) and, in monkeys, fibrosis. These effects gradually resolved with discontinuation of dosing.

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

<u>Oral aripiprazole</u>

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

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy-metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day or approximately16 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
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide

Solvent
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

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. Shake the vial vigorously for at least 60 seconds to re-suspend prior to injection. Do not store the reconstituted suspension in the syringe.

Abilify Maintena 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. 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.

6.4 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

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

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

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 50 mm (2 inch) 21 gauge.

Multipack
Bundle pack of 3 single packs.

Pre-filled syringe
Type-I glass pre-filled syringe containing powder in the front chamber and solvent in the rear chamber.

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 50 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

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 are provided in the package leaflet (information intended for healthcare professionals).

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

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

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.

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

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

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

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**

The requirements for submission of periodic safety update reports 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 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

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

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

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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

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

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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

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

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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

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

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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

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

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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

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

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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

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

Vertically shake the syringe vigorously for 20 seconds until drug 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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

Vertically shake the syringe vigorously for 20 seconds until drug 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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

Vertically shake the syringe vigorously for 20 seconds until drug 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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

Vertically shake the syringe vigorously for 20 seconds until drug 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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

Vertically shake the syringe vigorously for 20 seconds until drug 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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

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

Vertically shake the syringe vigorously for 20 seconds until drug 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 Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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
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

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
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

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 and belongs to a group of medicines called antipsychotics. It 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 oral aripiprazole.

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 aripiprazole treatment. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself.

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

- 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
- cardiovascular diseases (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure
- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots
- 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.

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 plan to take any other medicines, including medicines obtained without a prescription.

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, venlafaxine, St. John's Wort)
- antifungal medicines (such as ketoconazole, itraconazole)
- certain medicines to treat HIV infection (such as efavirenz, nevirapine, an protease inhibitors e.g. indinavir, ritonavir)
- anticonvulsants used to treat epilepsy (such as carbamazepine, phenytoin, phenobarbital)
- certain antibiotics used to treat tuberculosis (rifabutin, rifampicin)

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 trimester (last three months of their pregnancy):
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
Do not drive or use any tools or machines, until you know how Abilify Maintena affects you since dizziness, sedation, double vision and sleepiness have been reported as potential side effects of this medicine.

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 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.

Your doctor will decide on the dose of Abilify Maintena that is right for you. The recommended and starting dose is 400 mg unless your doctor decided to give you a lower starting or follow up dose (300 mg, 200 mg or 160 mg). Treatment with aripiprazole by mouth is continued for 14 days after the first injection. After that, treatment is given with injections of Abilify Maintena unless your doctor tells you otherwise.

If you are given more Abilify Maintena than you need
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 aripiprazole have experienced the following symptoms:

- rapid heart beat, 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 have any further questions on the use of this medicine, ask your doctor or nurse.

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.

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.

The side effects listed below may also occur after receiving Abilify Maintena.

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

- weight gain, weight loss
- feeling anxious, difficulty sleeping (insomnia)
- feeling restless and unable to keep still, difficulty sitting still, trembling, uncontrollable twitching, jerking or writhing movements, restless legs
- changes in your level of alertness, drowsiness
- 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; this is a medical term that includes several symptoms such as muscle stiffness, jerks when bending the limbs, slow or impaired body movements, no expression on the face, muscle tightness, shuffling, hurried steps and lack of normal arm movements when walking
- jerky resistance to passive movement as muscles tense and relax, abnormally increased muscle tone, muscle stiffness, slow body movement
- dizziness, headache
- dry mouth
- pain at the injection site, hardening of the skin at the injection site
- weakness, loss of strength or extreme tiredness
- high blood levels of the enzyme creatine phosphokinase

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

- decreased or increased appetite, distortion of the senses of taste and smell
- 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, decreased 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
- thoughts about suicide
- mental disorder characterized by defective or lost contact with reality, hallucination, delusion
- altered or increased sexual interest
- panic reaction, depression, affect lability, state of indifference with lack of emotion, feelings of emotional and mental discomfort, altered mood
- sleep disorder
- grinding of teeth or clenching of the jaw
- hiccups
- fixation of the eyeballs in one position, blurred vision, eye pain, double vision
- abnormal heart beat, slow or fast heart rate, abnormal electrical conduction of the heart, abnormal reading (ECG) of the heart
- dizziness when getting up from a lying or sitting position due to a drop in blood pressure, high blood pressure
- cough
- upset stomach, indigestion, drooling, more saliva in mouth than normal, vomiting, nausea, diarrhoea, constipation, stomach ache or discomfort, frequent bowel movement
- abnormal liver blood values
- 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, gait disturbance,joint pain (arthralgia), back pain, decreased range of motion of joints, stiff neck, limited opening of mouth
- kidney stones, sugar (glucose) in urine
- enlargement of breast in men, breast tenderness, vaginal dryness
- loss of strength
- chest discomfort
- injection site reactions such as redness, swelling discomfort and injection site itching
- increased waist circumference

The following side effects have been reported since the marketing of oral aripiprazole but the frequency for them to occur is not known:

- low levels of white blood cells
- unusual heartbeat, sudden unexplained death, heart attack
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives), rash
- ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood
- loss of appetite (anorexia), difficulty in swallowing
- aggression
- nervousness, excessive gambling, suicide attempt and suicide; speech disorder, seizure, serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate (neuroleptic malignant syndrome)

- fainting, spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia (lung infection), inflammation of the pancreas
- liver failure, inflammation of the liver, yellowing of the skin and white part of eyes, sensitivity to light, excessive sweating, stiffness or cramps, muscle pain, weakness
- involuntary loss of urine (incontinence), difficulty in passing urine
- prolonged and/or painful erection
- difficulty controlling core body temperature or overheating, chest pain, and swelling of hands, ankles or feet

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. 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. 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, sodium dihydrogen phosphate monohydrate, sodium hydroxide
  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 50 mm (2 inch) 21 gauge.

Multipack
Bundle pack of 3 single packs.

Not all pack sizes may be marketed.

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Otsuka Pharmaceutical Europe Ltd.
Gallions, Wexham Springs, Framewood Road,
Wexham, SL3 6PJ - United Kingdom

Manufacturer
H. Lundbeck A/S
Ottiliavej 9, 2500 Valby
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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:

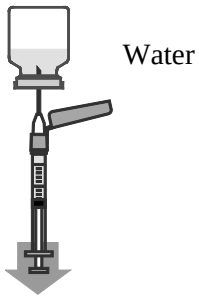
INSTRUCTIONS FOR HEALTH CARE PROFESSIONALS

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

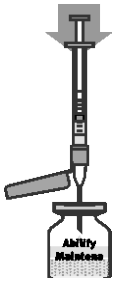
Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection
aripiprazole

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 50 mm (2 inch) 21 gauge hypodermic safety needle with needle protection device.
- Syringe and needle instructions.

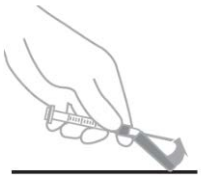
Step 2: Reconstitution of the powder
a) Remove the solvent and powder vial caps and wipe the tops with a sterile alcohol swab.
b) Using the syringe with pre-attached needle, withdraw the pre-determined solvent volume from the vial of the solvent into the syringe.
   300 mg vial:
   Add 1.5 ml solvent 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 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. <u>Do not touch the spike tip of the adapter at any time.</u>

d) Determine the recommended volume for injection.

Abilify Maintena 300 mg Vial	
Dose	Volume to Inject
---	---
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

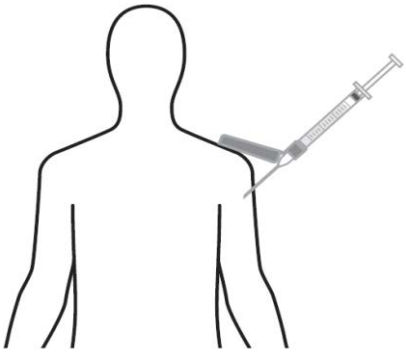
e) Wipe the top of the vial of the reconstituted suspension with a sterile alcohol swab.
f) Place and hold the vial of the reconstituted suspension on a hard surface. Attach the adapter-syringe assembly to the vial by holding the outside of the adapter and pushing the adapter's spike firmly through the 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.
<u>A small amount of excess product will remain in the vial.</u>

<u>Step 4: Injection procedure</u>
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.

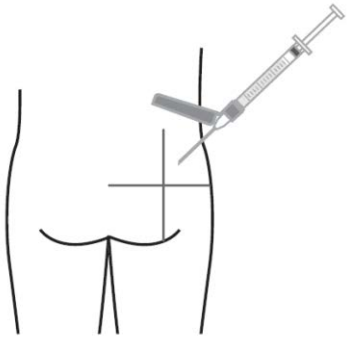
Body type	**Injection site**	**Needle size**
Non-obese	**Deltoid** **Gluteal**	**25 mm (1 inch) 23 gauge** **38 mm (1.5 inch) 22 gauge**

Obese	**Deltoid** **Gluteal**	**38 mm (1.5 inch) 22 gauge** **50 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.



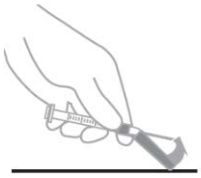
deltoid



gluteal

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



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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 and belongs to a group of medicines called antipsychotics. It 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 oral aripiprazole.

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 aripiprazole treatment. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself.

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

- 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
- cardiovascular diseases (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure

- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots
- 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.

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 plan to take any other medicines, including medicines obtained without a prescription.

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, venlafaxine, St. John's Wort)
- antifungal medicines (such as ketoconazole, itraconazole)
- certain medicines to treat HIV infection (such as efavirenz, nevirapine, an protease inhibitors e.g. indinavir, ritonavir)
- anticonvulsants used to treat epilepsy (such as carbamazepine, phenytoin, phenobarbital)
- certain antibiotics used to treat tuberculosis (rifabutin, rifampicin)

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 trimester (last three months of their pregnancy):
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
Do not drive or use any tools or machines, until you know how Abilify Maintena affects you since dizziness, sedation, double vision and sleepiness have been reported as potential side effects of this medicine.

3. How Abilify Maintena is given

Abilify Maintena comes as a pre-filled syringe. 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.

Your doctor will decide on the dose of Abilify Maintena that is right for you. The recommended and starting dose is 400 mg unless your doctor decided to give you a lower starting or follow up dose (300 mg, 200 mg or 160 mg). Treatment with aripiprazole by mouth is continued for 14 days after the first injection. After that, treatment is given with injections of Abilify Maintena unless your doctor tells you otherwise.

If you are given more Abilify Maintena than you need
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 aripiprazole have experienced the following symptoms:

- rapid heart beat, 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 have any further questions on the use of this medicine, ask your doctor or nurse.

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.

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.

The side effects listed below may also occur after receiving Abilify Maintena.

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

- weight gain, weight loss
- feeling anxious, difficulty sleeping (insomnia)
- feeling restless and unable to keep still, difficulty sitting still, trembling, uncontrollable twitching, jerking or writhing movements, restless legs
- changes in your level of alertness, drowsiness
- 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; this is a medical term that includes several symptoms such as muscle stiffness, jerks when bending the limbs, slow or impaired body movements, no expression on the face, muscle tightness, shuffling, hurried steps and lack of normal arm movements when walking
- jerky resistance to passive movement as muscles tense and relax, abnormally increased muscle tone, muscle stiffness, slow body movement
- dizziness, headache
- dry mouth
- pain at the injection site, hardening of the skin at the injection site
- weakness, loss of strength or extreme tiredness
- high blood levels of the enzyme creatine phosphokinase

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

- decreased or increased appetite, distortion of the senses of taste and smell
- 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, decreased 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
- thoughts about suicide
- mental disorder characterized by defective or lost contact with reality, hallucination, delusion
- altered or increased sexual interest
- panic reaction, depression, affect lability, state of indifference with lack of emotion, feelings of emotional and mental discomfort, altered mood
- sleep disorder
- grinding of teeth or clenching of the jaw
- hiccups
- fixation of the eyeballs in one position, blurred vision, eye pain, double vision
- abnormal heart beat, slow or fast heart rate, abnormal electrical conduction of the heart, abnormal reading (ECG) of the heart
- dizziness when getting up from a lying or sitting position due to a drop in blood pressure, high blood pressure
- cough
- upset stomach, indigestion, drooling, more saliva in mouth than normal, vomiting, nausea, diarrhoea, constipation, stomach ache or discomfort, frequent bowel movement
- abnormal liver blood values
- 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, gait disturbance,joint pain (arthralgia), back pain, decreased range of motion of joints, stiff neck, limited opening of mouth
- kidney stones, sugar (glucose) in urine
- enlargement of breast in men, breast tenderness, vaginal dryness
- loss of strength
- chest discomfort
- injection site reactions such as redness, swelling discomfort and injection site itching
- increased waist circumference

The following side effects have been reported since the marketing of oral aripiprazole but the frequency for them to occur is not known:

- low levels of white blood cells
- unusual heartbeat, sudden unexplained death, heart attack
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives), rash
- ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood
- loss of appetite (anorexia), difficulty in swallowing
- aggression
- nervousness, excessive gambling, suicide attempt and suicide; speech disorder, seizure, serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), combination

of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate (neuroleptic malignant syndrome)
- fainting, spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia (lung infection), inflammation of the pancreas
- liver failure, inflammation of the liver, yellowing of the skin and white part of eyes, sensitivity to light, excessive sweating, stiffness or cramps, muscle pain, weakness
- involuntary loss of urine (incontinence), difficulty in passing urine
- prolonged and/or painful erection
- difficulty controlling core body temperature or overheating, chest pain, and swelling of hands, ankles or feet

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. 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. 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, sodium dihydrogen phosphate monohydrate, sodium hydroxide
  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 50 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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Denmark

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:

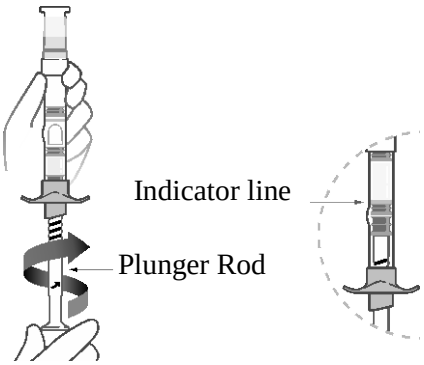
INSTRUCTIONS FOR HEALTH CARE PROFESSIONALS

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

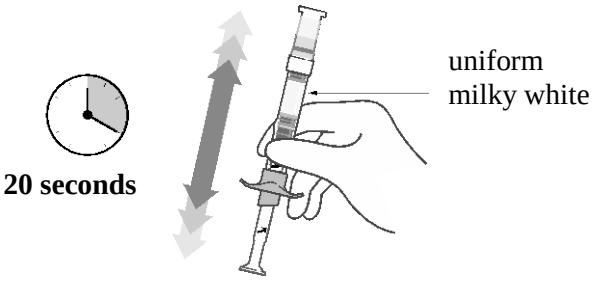
Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe
aripiprazole

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 50 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.

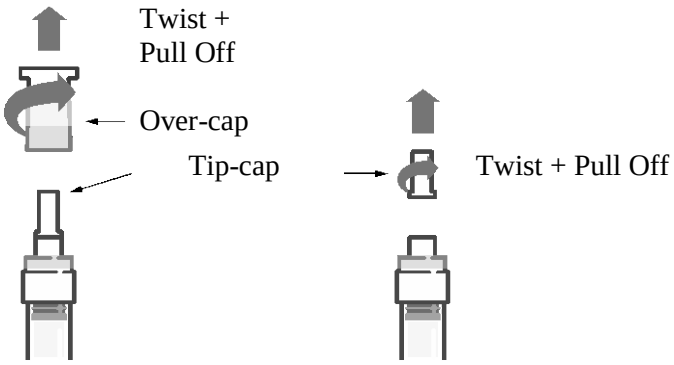


c) Visually inspect the syringe for particulate matter and discoloration prior to administration.The reconstituted product suspension should appear to be a uniform, homogeneous suspension that is opaque and milky-white in color.

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

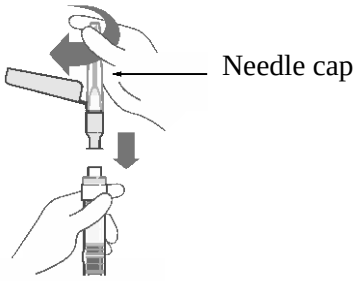
a) Twist and pull off Over-cap and Tip-cap.



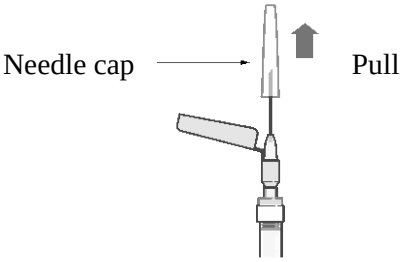
b) Select one of the following hypodermic safety needles depending on the injection site and patient's weight.

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** **50 mm (2 inch) 21 gauge**

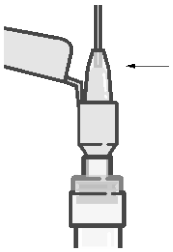
c) While holding the needle cap, ensure the needle is firmly seated on the safety device with a push. Twist clockwise until snugly fitted.



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

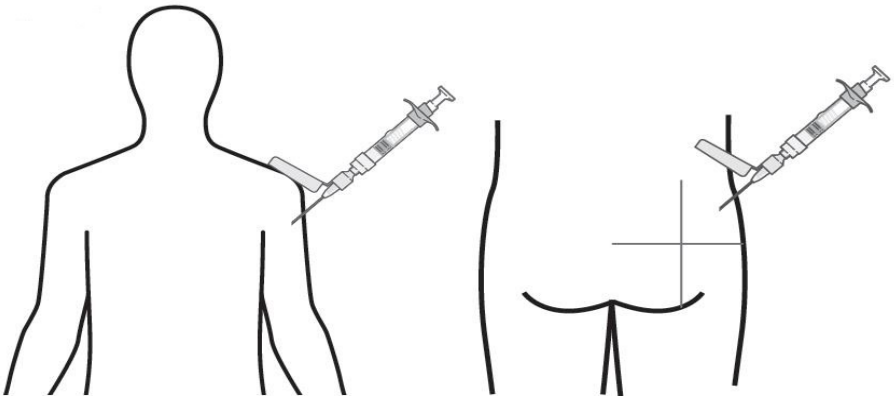


e) Hold syringe **upright and advance plunger rod slowly to expel the air**. If it's not possible to advance plunger rod to expel the air, check that plunger rod is rotated to a complete stop. It is not possible to re-suspend after the air in the syringe is expelled.



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

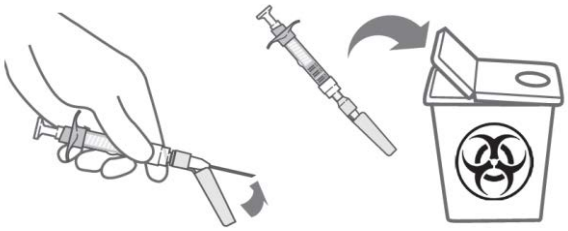
f) Slowly inject into the gluteal or deltoid muscle. Do not massage the injection site. Care must be taken to avoid inadvertent injection into the blood vessel. Do not inject into an area with signs of inflammation, skin damage, lumps and/or bruises. For deep intramuscular gluteal or deltoid injection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



deltoid gluteal

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

<u>Step 4: Procedures after injection</u>
Engage the needle safety device. Dispose of the needle and pre-filled syringe appropriately after injection.



Cover Discard

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSURs for aripiprazole, the scientific conclusions of the CHMP are as follows:

From the review of safety databases, clinical database and literature, most of the reports of hiccups were non-serious and resolved spontaneously without any intervention. Considering the number of case reports of hiccups with aripiprazole (primarily oral formulation), the time to onset of hiccups from the start of the aripiprazole therapy, several reports of positive dechallenge and of positive rechallenge, there appears to be some degree of causal association between aripiprazole exposure and hiccups. In addition, the disproportionality analyses scores in Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and VigiBase databases suggests a potential association between aripiprazole and hiccups. The PRAC considered that the product information of aripiprazole should be updated to include the adverse event 'Hiccups" in section 4.8 of the SmPC, since a contributory role of aripiprazole in the reported cases could not be ruled out. The package leaflet should be updated accordingly.
Therefore, in view of the data presented in the reviewed PSURs, the PRAC considered that changes to the product information of medicinal products containing aripiprazole were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for aripiprazole the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing aripiprazole is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisations should be varied.