**Attachment 1: Product information for AusPAR Abilify Maintena Aripiprazole Lundbeck Australia Pty Ltd PM-2013-01100-1-1 Final 25 November 2014. This Product Information was approved at the time this AusPAR was published.**

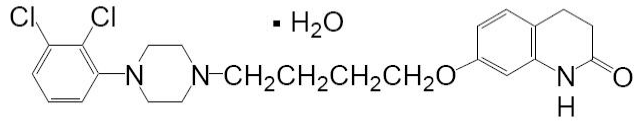
# PRODUCT INFORMATION

# Abilify Maintena®

## NAME OF THE MEDICINE

Abilify Maintena (aripiprazole).

Aripiprazole is present in Abilify Maintena as aripiprazole monohydrate. The chemical name of aripiprazole monohydrate is 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-carbostyril, as monohydrate (1:1). The molecular formula is $C_{23}H_{27}Cl_2N_3O_2.H_2O$ and its molecular weight is 466.40. The CAS registry number for aripiprazole monohydrate is 851220-85-4. Aripiprazole monohydrate has the structural formula:




## DESCRIPTION

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

Abilify Maintena is presented as a sterile, single-dose, lyophilised powder for reconstitution with water for injections to give a prolonged-release suspension for injection to deliver 400 mg of aripiprazole in 400-mg/vial strength or 300 mg of aripiprazole in 300-mg/vial strength. Abilify Maintena is intended for intramuscular injection only. The excipients are sodium carmellose, mannitol, monobasic monohydrate sodium phosphate and sodium hydroxide.

Abilify Maintena powder and solvent for prolonged-release suspension for injection is available as a one-month convenience kit. Each convenience kit contains one vial of lyophilised powder, one vial of water for injections, one 3 mL sterile syringe with a 21 gauge needle for reconstitution, one sterile syringe without a needle, one 1.5-inch (38 mm) and one 2-inch (50 mm) 21 gauge sterile safety needle for injection and one vial adapter.

## PHARMACOLOGY

### Pharmacodynamics

The mechanism of action of aripiprazole, as well as other drugs having efficacy in schizophrenia, is unknown. 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.

Abilify Maintena activity is primarily due to the parent drug, aripiprazole. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine $D_2$ and $D_3$, serotonin 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors ($K_i$ values of 0.3, 0.8, 1.7, and 3.4 nM, respectively), and moderate affinity for dopamine $D_4$, serotonin 5-$HT_{2C}$ and 5-$HT_7$, α1-adrenergic, and histamine $H_1$ receptors ($K_i$ values of 44, 15, 39, 57, and 61 nM, respectively). Aripiprazole also

exhibited moderate binding affinity for the serotonin reuptake site ($K_i$ value of 98 nM) but no appreciable affinity for muscarinic receptors ($IC_{50}$>1000 nM).

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

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

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

**Pharmacokinetics**

***Absorption***

Aripiprazole absorption into the systemic circulation is slow and prolonged following Abilify Maintena administration due to the low solubility of aripiprazole particles. Following a single intramuscular dose, the plasma concentrations of aripiprazole gradually rise and at steady state reach their maximum values at a median $T_{max}$ of 5-7 days. Dose-proportional increases in aripiprazole and dehydro-aripiprazole concentrations and AUC parameters are observed after monthly Abilify Maintena injections of 400 mg and 300 mg and steady state aripiprazole plasma concentrations were attained by the fourth monthly injection.

***Distribution***

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

***Metabolism***

Aripiprazole undergoes minimal pre-systemic metabolism at the site of injection. Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are primarily responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant drug moiety in systemic circulation. After multiple dose administration of Abilify Maintena, dehydro-aripiprazole, the active metabolite represents about 29.1-32.5% of aripiprazole AUC in plasma.

***Excretion***

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

**Special Populations**

***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 recommendations see DOSAGE & ADMINISTRATION. Subjects were entered into clinical studies without knowledge of their metaboliser status and, therefore, the safety profile reflects experience in both EMs and PMs.

***Elderly Patients***

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

***Gender***

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

***Race***

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

***Renal Impairment***

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

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

***Hepatic Impairment***

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

***Smoking***

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

## CLINICAL TRIALS

The efficacy and safety of Abilify Maintena in the treatment of patients with schizophrenia was established, in part, on one pivotal, randomised double-blind, placebo-controlled trial.

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

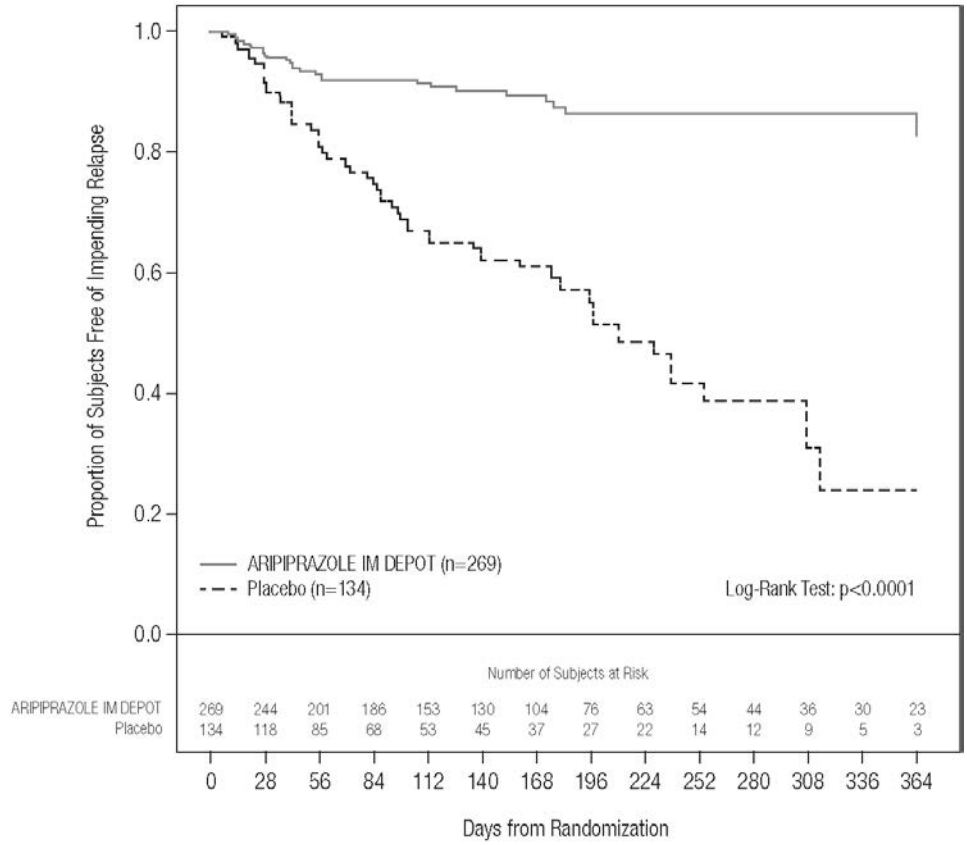
The final efficacy analysis included 403 randomised patients and 80 exacerbations of psychotic symptoms/impending relapse events. The trial was terminated early because efficacy was demonstrated by the pre-specified interim analysis. The hazard ratio from the Cox proportional hazard model for the placebo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

The Kaplan-Meier curves of the time from randomisation to impending relapse during the 52-week, double-blind treatment phase for Abilify Maintena and placebo groups are shown in Figure 1.

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

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

**Figure 1 Kaplan-Meier Product Limit Plot of Time to Impending Relapse (Double-blind, Placebo-controlled Phase Efficacy Sample)**




IM = Intramuscular

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

## INDICATIONS

For maintenance of clinical improvement in the treatment of schizophrenia.

## CONTRAINDICATIONS

Hypersensitivity to aripiprazole or any of the excipients (See DESCRIPTION).

## PRECAUTIONS

### Elderly patients with dementia-related psychosis

***Increased mortality***

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo

group. Although the causes of death varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

In three placebo-controlled trials with oral aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n= 938; mean age: 82.4 years; range: 56- 99 years), patients treated with aripiprazole were at an increased risk of death compared to placebo. The rate of death in the aripiprazole-treated patients was 3.5% compared with 1.7% in the placebo group.

***Cerebrovascular adverse events***

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

**General**

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

**Suicide**

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

**Tardive dyskinesia**

In clinical trials of one year or less duration, there were uncommon reports of treatment-emergent tardive dyskinesia during treatment with aripiprazole. The risk of tardive dyskinesia increases with long-term exposure to antipsychotic treatment. If signs and symptoms of tardive dyskinesia appear in a patient on Abilify Maintena, dose reduction or discontinuation of treatment should be considered (see DOSAGE & ADMINISTRATION). These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

**Neuroleptic malignant syndrome**

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

**Seizure**

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

**Hyperglycaemia and diabetes mellitus**

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

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

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes), who are starting treatment with atypical antipsychotics, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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

**Cardiovascular disorders**

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

**QT interval**

In clinical trials of treatment with Abilify Maintena and oral aripiprazole, the incidence of QT prolongation was uncommon. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation. See also ADVERSE EFFECTS, QT interval.

**Orthostatic hypotension**

Aripiprazole may be associated with orthostatic hypotension, potentially due to its α1-adrenergic receptor antagonism. Aripiprazole may induce orthostatic hypotension, tachycardia, dizziness and

sometimes syncope, especially at the initiation of treatment. In the double-blind controlled phase of the clinical trials using Abilify Maintena, orthostasis-related events were reported in 2/534 (0.4%) patients.

**Venous thromboembolism**

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

**Body temperature regulation**

Disruption of the body's ability to increase or reduce core body temperature has been attributed to antipsychotic agents, including aripiprazole. Appropriate care is advised when prescribing Abilify Maintena for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity or being subject to dehydration.

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

**Dysphagia**

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

**Akathisia**

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

**Leukopenia, neutropenia and agranulocytosis**

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

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

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

**Potential for cognitive and motor impairment**

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

**Weight gain**

Antipsychotic drugs have been associated with metabolic changes, including weight gain. In clinical trials there was no clinically relevant difference in the incidence of weight gain between Abilify Maintena and placebo (See ADVERSE EFFECTS, Weight).

**Effects on fertility**

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

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

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

**Use in pregnancy**

Category: C

There are no adequate and well-controlled studies of aripiprazole in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits. Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 9 times the oral Maximum Recommended Human Dose [MRHD] of 30 mg/day on a $mg/m^2$ basis) of aripiprazole during the period of organogenesis. At 30 mg/kg in the rat, treatment was associated with slightly prolonged gestation, and a slight delay in fetal development, as evidenced by decreased fetal weight, undescended testes, and delayed skeletal ossification. There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights, and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses and increased post implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at the oral MRHD of 30 mg/day based on AUC) of aripiprazole during the period of

organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 100 mg/kg), and minor skeletal variations (100 mg/kg).

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

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

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

Patients must be advised to notify their doctors if they become pregnant or intend to become pregnant.

**Use in labour and delivery**

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

**Use in lactation**

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

In rats, there were adverse effects in dams and offspring following daily oral administration of aripiprazole from late gestation through weaning (see Use in pregnancy).

**Paediatric use**

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

**Use in the elderly**

There are no data on the safety and efficacy of Abilify Maintena in patients ≥ 61 years of age.

**Effects on laboratory tests**

Drug interaction with laboratory tests has not been established.

**Animal Toxicology**

The toxicological profile for aripiprazole administered to experimental animals by intramuscular injection is generally similar to that seen following oral administration at comparable plasma levels of the drug. With intramuscular injection, however, injection-site tissue reactions are observed that consist of localised inflammation, swelling, scabbing and foreign-body reactions to deposited drug. These effects gradually resolved with discontinuation of dosing.

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

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

***Carcinogenicity***

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

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

***Genotoxicity***

Aripiprazole was tested for genotoxic potential in a standard range of assays for gene mutation, chromosomal damage, and DNA damage and repair. Aripiprazole was nongenotoxic in the *in vitro* bacterial reverse mutation assay, in vitro forward gene mutation assay in mouse lymphoma cells, *in vitro* bacterial DNA repair assay, and the unscheduled DNA synthesis assay in rat hepatocytes.

However, aripiprazole and its minor metabolite 2,3-DCPP were clastogenic in the *in vitro* chromosomal aberration assay in Chinese hamster lung cells with and without metabolic activation. A positive response in 1 of 6 *in vivo* mouse micronucleus tests was likely due to a mechanism not relevant to humans.

## INTERACTIONS WITH OTHER MEDICINES

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

**Potential for other medicinal products to affect aripiprazole**

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

***Inhibitors and Inducers of CYP2D6 and CYP3A4***

***Quinidine and other strong CYP2D6 inhibitors***

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

***Ketoconazole and other strong CYP3A4 inhibitors***

In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) decreased oral clearance of aripiprazole by 38%, increased aripiprazole AUC and $C_{max}$ by 63% and 37%, respectively. The AUC and $C_{max}$ of dehydro-aripiprazole increased by 77% and 43%, respectively. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should, therefore, be applied (see DOSAGE & ADMINISTRATION, Dose Adjustments due to Interactions). When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with Abilify Maintena, potential benefits should outweigh the potential risks to the patient.

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dose of Abilify Maintena should be increased to the dose prior to the initiation of the concomitant therapy.

***Carbamazepine and other CYP3A4 inducers***

In a clinical study in patients with schizophrenia or schizo-affective disorder, co-administration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, with aripiprazole (30 mg daily) resulted in an approximate 70% decrease in AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. Concomitant administration of Abilify 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.

***Valproate and lithium***

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

***Inhibitors and inducers of CYP1A1, CYP1A2, CYP2C9 and CYP2C19***

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

**Potential for aripiprazole to affect other medicinal products**

***CNS Drugs (including Alcohol)***

Given the primary CNS effects of aripiprazole, caution should be used when Abilify Maintena is administered in combination with alcohol or other CNS drugs with overlapping adverse reactions, such as sedation. See ADVERSE EFFECTS.

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

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

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

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

***Antihypertensive agents***

Due to its $\alpha_1$-adrenergic receptor antagonistic activity, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

***Medicines which cause QT prolongation or electrolyte imbalance***

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

## ADVERSE EFFECTS

Abilify Maintena administered once monthly has been evaluated for safety in clinical trials in adult patients with schizophrenia. Of the 1,624 adult patients exposed to aripiprazole long-acting injectable, 1,539 patients have been treated with Abilify Maintena.

The most frequently observed adverse drug reactions (ADRs) reported in ≥5 % of patients in two double-blind clinical trials of Abilify Maintena were weight increased (9%), akathisia (7.9%), insomnia (5.8%), and injection site pain (5.1%). Overall, these adverse drug reactions were similar to placebo and were mild to moderate in severity. The following table lists the adverse drug reactions in clinical trials with Abilify Maintena that occurred at the frequency of 2% or greater.

**Table 3 Potentially Trial Medication-related Treatment–Emergent Adverse Events Reported for 2% or More Subjects in Any Double-blind Treatment Group (Controlled Trials)**

| System / Organ Class<br><br>MedDRA Preferred Term | Abilify Maintena<br><br>(N = 534) | Oral Aripiprazole 10-30 mg (N = 266) | Aripiprazole Long-Acting Injectable 50 mg/25 mg (N = 131) | Placebo (N=134) |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) |
| Any Treatment-Emergent Adverse Event (TEAE) | 262 (49.1) | 128 (48.1) | 61 (46.6) | 52 (38.8) |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue | 9 (1.7) | 8 (3.0) | 1 (0.8) | 1 (0.7) |
| Injection site pain | 27 (5.1) | 6 (2.3) | 1 (0.8) | 4 (3.0) |
| **Investigations** | | | | |
| Blood creatine phosphokinase increased | 6 (1.1) | 5 (1.9) | 5 (3.8) | 1 (0.7) |
| Weight decreased | 20 (3.7) | 8 (3.0) | 7 (5.3) | 1 (0.7) |
| Weight increased | 48 (9.0) | 27 (10.2) | 7 (5.3) | 12 (9.0) |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 4 (0.7) | 1 (0.4) | 3 (2.3) | 0 (0.0) |
| **Nervous system disorders** | | | | |
| Akathisia | 42 (7.9) | 17 (6.4) | 10 (7.6) | 7 (5.2) |
| Headache | 16 (3.0) | 8 (3.0) | 3 (2.3) | 0 (0.0) |
| Sedation | 12 (2.2) | 3 (1.1) | 1 (0.8) | 0 (0.0) |
| Somnolence | 10 (1.9) | 8 (3.0) | 2 (1.5) | 1 (0.7) |
| Tremor | 24 (4.5) | 9 (3.4) | 5 (3.8) | 2 (1.5) |
| **Psychiatric disorders** | | | | |
| Anxiety | 14 (2.6) | 8 (3.0) | 6 (4.6) | 8 (6.0) |
| Insomnia | 31 (5.8) | 22 (8.3) | 9 (6.9) | 8 (6.0) |
| Psychotic disorder | 4 (0.7) | 1 (0.4) | 1 (0.8) | 3 (2.2) |
| Restlessness | 16 (3.0) | 2 (0.8) | 2 (1.5) | 2 (1.5) |

**Injection Site Adverse Events**

Injection site assessments were completed after all injections during the double-blind, controlled phases of the two Abilify Maintena trials. Analyses of injection site assessments (investigator-rated and subject reported VAS) were performed to evaluate the safety/tolerability of Abilify Maintena, see Table 4. In both controlled trials, infrequent injection site reactions were observed; those seen were generally mild to moderate in severity, and resolved over time. Injection site pain (incidence 5.1 %), has a median onset on day 2 after the injection and a median duration of 4 days.

**Table 4 Investigator Assessments of Pain, Swelling and Induration at the Injection Site and Patient VAS scores**

| Treatment Group Dose (n) | Absence of Investigator Rated Pain, Redness, Swelling, and Induration at the Injection Site (% of patients)* | | Mean VAS (patient rated pain from 0 mm (no pain) – 100mm (unbearably painful) (N=134) | |
|---|---|---|---|---|
| | First Injection | Last Injection | First Injection | Last Injection |
| **38-week double-blind, active-controlled trial** | | | | |
| **Double-blind, Active-controlled Phase** | | | | |
| **Abilify Maintena** (n=265) | 81.4 – 98.1 | 88.3 – 98.9 | 5.6 | 3.7 |
| Oral aripiprazole 10-30 mg (n=266) | 83.3 – 98.5 | 90.2 – 99.6 | 4.9 | 3.5 |
| Aripiprazole Long-Acting Injectable 50 mg/25 mg (n=131) | 90.7 – 99.2 | 90.0 – 99.2 | 3.3 | 2.4 |
| **52-week double-blind, placebo-controlled trial** | | | | |
| **Long-Acting Injectable Stabilisation Phase (Open Label)**** | | | | |
| **Abilify Maintena** (n=403) | 75.3 – 96.2 | 77.3 – 97.0 | 6.0 | 4.5 |
| **Double-blind, Placebo-controlled Phase** | | | | |
| **Abilify Maintena** (n=269) | 80.1 – 98.1 | 84.4 – 98.5 | 5.1 | 4.0 |
| Placebo (n=134) | 72.2 – 97.7 | 77.3 – 97.7 | 5.1 | 4.9 |

VAS = Visual Analogue Scale.
IM – Intramuscular.
*Range of per-cent is based on rating in the 4 domains (pain, redness, swelling, and induration)
**The open-label analyses were done to understand the injection site reaction parameters after initiation of Abilify Maintena as well as during its continued use in the double-blind, placebo-controlled phase.

### Leukopenia

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

### Extrapyramidal Symptoms (EPS)

During the double-blind phases of the 38- and 52-week trials, treatment-emergent EPS and EPS-related events were reported for Abilify Maintena (18.4%) and oral aripiprazole tablets 10-30 mg (11.7%). The most commonly reported EPS and EPS-related events in each group were akathisia events (Abilify Maintena: 8.2%; oral aripiprazole tablets 10-30 mg group: 6.8%; and placebo: 6.0%), followed by parkinsonism events (6.9%; 4.1% and 3.0; respectively). Akathisia typically starts around day 10 after first injection, and lasts a median of 56 days.

There was minimal variation in EPS symptoms during the double-blind phases as assessed by mean changes from baseline in the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS) and Barnes Akathisia Rating Scale (BARS) rating scales. The mean changes were not considered to be clinically relevant.

### Dystonia

*Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of

the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

**Weight**

During the double-blind, active-controlled phase of the 38-week trial, the incidence of weight gain of ≥7% from baseline to last visit was 9.5% for the Abilify Maintena group and 11.7% for the oral aripiprazole tablets 10-30 mg group. The incidence of weight loss of ≥7% from baseline to last visit was 10.2% for Abilify Maintena and 4.5% for oral aripiprazole tablets 10-30 mg. During double-blind treatment, mean change in body weight from baseline to last visit was -0.2kg for Abilify Maintena, +0.7kg for oral aripiprazole tablets.

During the double-blind, placebo-controlled phase of the 52-week aripiprazole trial, the incidence of weight gain of ≥7% from baseline to last visit was similar between Abilify Maintena and placebo: 6.4% for the Abilify Maintena group and 5.2% for the placebo group. The incidence of weight loss of ≥7% from baseline to last visit was 6.4% for the Abilify Maintena group and 6.7% for the placebo group. During double-blind treatment, mean change in body weight from baseline to last visit was -0.2kg for Abilify Maintena and -0.4kg for placebo (p=0.812).

**Laboratory Tests**

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

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

***QT Interval***

During double-blind treatment, 1/534 (0.2%) Abilify Maintena subjects had a Treatment-Emergent Adverse Event (TEAE) related to QT interval change (prolonged ECG QT).

***Prolactin***

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

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

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

***Lipid Parameters***

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

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

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

***Blood and Lymphatic System Disorders***

Anaemia, bicytopenia, lymphadenopathy, neutropenia, thrombocytopenia.

***Cardiac Disorders***

Acute myocardial infarction, first degree atrioventricular blocks, cardiac failure congestive, ventricular extrasystoles.

***Ear and Labyrinth disorders***

Deafness, vertigo.

***Eye Disorders***

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

***Gastrointestinal disorders***

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

***General disorders and administration site conditions***

Asthenia, chest discomfort, gait disturbance, influenza-like illness, infusion site haematoma, infusion site swelling, injection site discomfort, injection site pruritus, injection site induration, injection site reaction, injection site swelling, pain, sluggishness, suprapubic pain, thirst, vessel puncture site haematoma, vessel puncture site pain.

***Hepatobiliary disorders***

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

***Immune System Disorders***

Drug hypersensitivity.

***Infections and Infestations***

Acrodermatitis, anal abscess, appendicitis perforated, cellulitis, cystitis, ear infection, Escherichia UTI, folliculitis, fungal infection, fungal skin infection, furuncle, gastroenteritis, gastroenteritis viral, herpes virus infection, herpes zoster, hordeoleum, impetigo, lice infestation, localised infection, mastitis, oral candidiasis, pharyngitis, pharyngitis streptococcal, pilonidal cyst, pneumonia, respiratory tract infection, viral rhinitis, subcutaneous abscess, tinea pedis, tooth abscess, tooth infection, urinary tract infections, vaginal infection, varicella, viral infection, viral upper respiratory tract infection, vulvovaginal mycotic infection.

***Injury, poisoning and procedural complications***

Accident, ankle fracture, carbon monoxide poisoning, contusion, drug toxicity, excoriation, face injury, fall, foot fracture, gunshot wound, injury, joint dislocation, joint sprain, multiple injuries, muscle injury, muscle strain, procedural pain, radius fracture, skeletal injury, skin laceration, thermal burn, tooth fracture, wound.

***Investigations***

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

***Metabolism and nutrition disorders***

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

***Musculoskeletal and connective tissue disorders***

Arthritis, joint swelling, muscle rigidity, muscle spasm, muscle tightness, muscle twitching, musculoskeletal pain, myalgia, nuchal rigidity, rotator cuff syndrome, trismus.

***Neoplasms benign malignant and unspecified***

Basal cell carcinoma, breast fibroma, pancreatic carcinoma.

***Nervous system disorders***

Bradykinesia, cogwheel rigidity, disturbance in attention, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypersomnia, hypoaesthesia, migraine, movement disorder, parkinsonism, parosmia, poor quality sleep, psychomotor hyperactivity, restless leg syndrome, sinus headache, syncope, tension headache.

***Psychiatric Disorders***

Abnormal dreams, affect lability, apathy, bruxism, bulimia nervosa, delusion, dysphoria, hallucination auditory, hypersexuality, hyposomnia, libido decreased, middle insomnia, mood altered, nightmare, panic attack, panic reaction, sleep disorder, suicidal ideation, suicide attempt, tension.

***Renal and Urinary Disorders***

Glycosuria, micturition urgency, nephrolithiasis, pollakiuria.

***Reproductive system and breast disorders***

Adnexa uteri pain, breast mass, breast tenderness, erectile dysfunction, galactorrhoea, gynaecomastia, ovarian cyst, vulvovaginal dryness.

***Respiratory Thoracic and Mediastinal disorders***

Acute respiratory distress syndrome, dysphonia, dyspnoea, epistaxis, nasal septum deviation, oropharyngeal pain, paranasal sinus hypersecretion, respiratory tract congestion, rhinalgia, rhinitis allergic, sinus congestion, wheezing.

***Skin and Subcutaneous tissue disorders***

Acne, blister, dry skin, eczema, erythema, hyperkeratosis, pruritus, psoriasis, rash macula, rosacea, skin induration, skin lesion, skin striae, urticaria.

***Vascular Disorders***

Orthostatic hypertension.

**Post-Market Adverse Drug Reactions**

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

***Blood and lymphatic system disorders***

Leukopenia, neutropenia, thrombocytopenia.

***Endocrine disorders***

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

***Metabolism and nutrition disorders***

Anorexia, hyponatraemia.

***Psychiatric disorders***

Agitation.

***Nervous system disorders***

Speech disorder, grand mal convulsion.

***Vascular disorders***

Syncope, hypertension.

***Respiratory, thoracic and mediastinal disorders***

Aspiration pneumonia.

***Gastrointestinal disorders***

Pancreatitis, dysphagia, diarrhoea.

***Hepato-biliary disorders***

Jaundice, hepatitis.

***Skin and subcutaneous tissue disorders***

Allergic reaction (e.g. anaphylactic reaction, angioedema, pruritus, or urticaria, rash, laryngospasm), hyperhidrosis.

***Musculoskeletal and connective tissue disorders***

Rhabdomyolysis, myalgia, musculoskeletal stiffness.

***Renal and urinary disorders***

Urinary incontinence, urinary retention.

***Reproductive system and breast disorders***

Priapism.

***General disorders and administration site conditions***

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

***Investigations***

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

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

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

## DOSAGE AND ADMINISTRATION

### Recommended Dosage and Dosage Adjustment

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

The recommended starting and maintenance dose of Abilify Maintena is 400 mg. Titration of the dose of Abilify Maintena is not required. Abilify Maintena should be administered by a healthcare professional once-monthly as a single injection (no sooner than 26 days after the previous injection). After the first Abilify Maintena injection, treatment with oral aripiprazole (10 mg to 20 mg), or other oral antipsychotic, should be continued for 14 consecutive days to maintain therapeutic antipsychotic concentrations during initiation of therapy.

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

**Switching from oral antipsychotics**

For patients who have never taken oral or injectable aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with Abilify Maintena. When switching from oral antipsychotics, patients may continue their current oral antipsychotic (oral aripiprazole or prescribed dose of other oral antipsychotic) for 14 days following the first dose of Abilify Maintena to maintain therapeutic plasma concentrations during the initiation of Abilify Maintena. Abilify Maintena should then be administered once monthly as described above.

**Switching from long-acting injectable antipsychotics**

For patients who have never taken oral or injectable aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with Abilify Maintena. When switching patients from previous long-acting injectable antipsychotics, initiate Abilify Maintena therapy in place of the next scheduled injection, with 14 days of concurrent oral aripiprazole. Abilify Maintena should then be continued monthly.

**Discontinuation of Abilify Maintena**

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

**Missed doses**

**Table 5 Management of 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 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. |

**Dosage in Special Populations**

***Elderly Population***

The effectiveness and safety of Abilify Maintena in the treatment of schizophrenia in patients 61 years of age or older has not been evaluated.

***Renal Impairment***

No dosage adjustment of Abilify Maintena is required for patients with renal impairment. See PHARMACOLOGY, Pharmacokinetics, Special Populations.

***Hepatic Impairment***

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

***Other Special Populations***

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

***Known CYP2D6 Poor Metabolisers***

In patients who are known to be CYP2D6 poor metabolisers, the starting and maintenance dose of Abilify Maintena should be 300 mg. If Abilify Maintena is taken concomitantly with strong CYP3A4 inhibitors, the dose of Abilify Maintena should be reduced to 200 mg. See INTERACTIONS WITH OTHER MEDICINES.

***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.

***Dose Adjustments due to Interactions***

Dosage adjustments are recommended 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 Abilify Maintena dose may need to be increased. Refer to Table 6.

Avoid the concomitant use of CYP3A4 inducers with Abilify Maintena for more than 14 days, because the blood levels of aripiprazole will be decreased and may fall below the effective levels. Refer to Table 6.

**Table 6 Dose Adjustments of Abilify Maintena in patients who are known CYP2D6 poor metabolisers and patients 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 |

**Administration**

Abilify Maintena is available in a convenience kit which contains one vial of lyophilised powder, one vial of diluent (water for injections), one 3 mL sterile syringe with a 21 gauge needle for reconstitution, one sterile syringe without a needle, one 1.5-inch (38 mm) and one 2-inch (50 mm) 21 gauge sterile safety needle for injection and one vial adapter.

***For deep intramuscular gluteal injection only: do not administer intravenously or subcutaneously.***

**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 should be administered by a healthcare professional once-monthly. The injection should be injected slowly as a single injection (doses must not be divided) into the gluteal muscle.**

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

**Reconstitution**

***Step 1: Preparation Prior to Reconstitution of the Lyophilised Abilify Maintena Powder.***

a) Lay out the contents of the package and confirm that all components listed below are provided:

- Vial of Abilify Maintena (aripiprazole) powder for reconstitution;
- 2.0 mL vial of water for injections;
- One 3 mL luer lock syringe with pre-attached 21 gauge, 1.5-inch (38 mm) hypodermic safety needle with needle protection device;
- One 3 mL disposable syringe with luer lock tip;
- One vial adapter;
- One 21 gauge, 1.5-inch (38 mm) hypodermic safety needle for non-obese patients with needle protection device; and
- One 21 gauge, 2-inch (50 mm) hypodermic safety needle for obese patients with needle protection device.

b) Abilify Maintena should be suspended using the water for injections supplied in the carton.

c) The water for injections and Abilify Maintena vials are for single-use only.

d) Use appropriate aseptic techniques throughout the reconstitution and reconstitute at room temperature.

e) Select the amount of water for injections needed for reconstitution at room temperature.

| **400 mg Vial** | | **300 mg Vial** | |
|---|---|---|---|
| Dose | Water for Injections | Dose | Water for Injections |
| 400 mg | 1.9 mL | 300 mg | 1.5 mL |

**It is important to note that there is more water for injections in the vial than is needed to reconstitute Abilify Maintena (aripiprazole) for prolonged-release suspension for injection.**

***Step 2: Reconstitution of the Lyophilised Powder***

a) Remove the cap of the vial of water for injections and remove the cap of the vial containing Abilify Maintena lyophilised powder and wipe the tops with a sterile alcohol swab.

b) Using the syringe with pre-attached hypodermic safety needle, withdraw the pre-determined water for injections volume from the vial of water for injections into the syringe (see Diagram 1). A small amount of residual water for injections will remain in the vial following withdrawal.

Diagram 1

c) Slowly inject the water for injections into the vial containing the Abilify Maintena lyophilised powder (see Diagram 2).

Diagram 2

d) Withdraw air to equalise the pressure in the vial by pulling back slightly on the plunger. Subsequently, remove the needle from the vial. Engage the needle safety device by using the one-handed technique (see Diagram 3). 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.

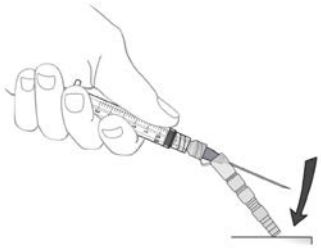


Diagram 3

e) Shake the vial vigorously for 30 seconds until the suspension appears uniform (see Diagram 4).

Diagram 4

f) Visually inspect the reconstituted suspension for particulate matter and discolouration prior to administration. The reconstituted Abilify Maintena is a uniform, homogeneous suspension that is opaque and milky-white in colour.

g) If the injection is not performed immediately after reconstitution, keep the vial below 25°C for up to 4 hours and shake the vial vigorously for at least 60 seconds to re-suspend prior to injection.

h) Do not store the reconstituted suspension in the syringe.

***Step 3: Preparation Prior to Injection***

a) Use appropriate aseptic techniques throughout injection of the reconstituted Abilify Maintena suspension.

b) Remove the cover from the vial adapter package (see Diagram 5). Do not remove the vial adapter from the package.

Diagram 5

c) Using the vial adapter package to handle the vial adapter, attach the pre-packaged disposable syringe to the vial adapter (see Diagram 6).

Diagram 6

d) Use the disposable syringe to remove the vial adapter from the package and discard the vial adapter package (see Diagram 7). Do not touch the spike tip of the adapter at any time.

Diagram 7

e) Determine the recommended volume for injection.

**Abilify Maintena Reconstituted Suspension Volume to Inject**

| **400 mg Vial** | | **300 mg Vial** | |
|---|---|---|---|
| Dose | Volume to Inject | Dose | Volume to Inject |
| 400 mg | 2.0 mL | --- | --- |
| 300 mg | 1.5 mL | 300 mg | 1.5 mL |
| 200 mg | 1.0 mL | 200 mg | 1.0 mL |
| 160 mg | 0.8 mL | 160 mg | 0.8 mL |

f) Wipe the top of the vial of the reconstituted Abilify Maintena suspension with a sterile alcohol swab.

g) Place and hold the vial of the reconstituted Abilify Maintena 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 (see Diagram 8).

Diagram 8

h) Slowly withdraw the recommended volume from the vial into the disposable syringe to allow for injection (see Diagram 9). A small amount of excess product will remain in the vial.

Diagram 9

***Step 4: Injection Procedure***

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

b) Select one of the following hypodermic safety needles and attach the needle to the disposable syringe containing the suspension for injection. To avoid subcutaneous drug administration, examine the depth of subcutaneous fat at the injection site and select the appropriate needle size. Ensure the needle is firmly seated on the needle safety device with a push and clockwise twist and then pull the needle cap straight away from the needle (see Diagram 10).

- 21 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for non-obese patients.
- 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for obese patients.

Diagram 10

c) Slowly inject the recommended volume as a single intramuscular injection into the gluteal muscle. Do not massage the injection site. Do not administer intravenously or subcutaneously.

***Step 5: Procedures After Injection***

a) Engage the needle safety device as described in Step 2 (d). Dispose of the vials, adapter, needles, and syringe appropriately after injection. **The water for injections and Abilify Maintena vials are for single-use only**.

b) Rotate sites of injections between the two gluteal muscles.

## OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre (Tel: 13 11 26 for Australia).

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 which corresponds to 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 (42 times higher than the recommended daily aripiprazole dose, 30 mg) 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.

## PRESENTATION AND STORAGE CONDITIONS

Abilify Maintena is provided as a lyophilised powder for reconstitution in two dosage strengths, 400 mg and 300 mg, in one-month convenience kits.

Each convenience kit contains one vial of (400 mg or 300 mg) powder, one vial containing 2 mL of water for injections, one 3 mL sterile syringe with a 21 gauge needle for reconstitution, one sterile syringe without a needle, one 1.5-inch (38 mm) and one 2-inch (50 mm) 21 gauge sterile safety needle for injection and one vial adapter.

**Storage conditions**

Lyophilised Abilify Maintena is stable up to the expiration date stamped on the vial.

Store in the original packaging below 30°C. Do not freeze.

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

***Reconstituted Abilify Maintena***

The reconstituted suspension should be used immediately, but may be stored below 25°C for up to 4 hours. Shake the vial vigorously for at least 60 seconds to re-suspend prior to injection.

## NAME AND ADDRESS OF THE SPONSOR

Lundbeck Australia Pty Ltd
Ground Floor
1 Innovation Rd
North Ryde NSW 2113
Ph: +61 2 8669 1000

## POISON SCHEDULE OF THE MEDICINE

S4 - Prescription only medicine

## DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

25 July 2014

Abilify Maintena is a trademark of Otsuka Pharmaceutical Company.