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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 300 mg aripiprazole.
After reconstitution each ml of suspension contains 200 mg aripiprazole.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Powder and solvent for prolonged-release suspension for injection

Powder: white to off-white
Solvent: clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
ABILIFY MAINTENA is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

4.2 Posology and method of administration

Posology
For patients who have never taken aripiprazole, tolerability with oral aripiprazole must occur prior to initiating treatment with ABILIFY MAINTENA.

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

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

<table>
<thead>
<tr>
<th>Time Since Last Injection</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 4 weeks and &lt; 6 weeks</td>
<td>The injection should be administered as soon as possible and then resume monthly injection schedule.</td>
</tr>
<tr>
<td>&gt; 6 weeks</td>
<td>Concomitant oral aripiprazole should be restarted for 14 days with next administered injection and then resume monthly injection schedule.</td>
</tr>
</tbody>
</table>

**Special populations**

**Elderly patients**
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 done in patients taking concomitant strong CYP3A4 inhibitors or strong CYP2D6 inhibitors for more than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the dosage may need to be increased to the previous dose (see section 4.5). In case of adverse reactions despite dose adjustments of ABILIFY MAINTENA, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

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

**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**

<table>
<thead>
<tr>
<th>Patients taking 400 mg of ABILIFY MAINTENA</th>
<th>Adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 or strong CYP3A4 inhibitors</td>
<td>300 mg</td>
</tr>
<tr>
<td>Strong CYP2D6 and strong CYP3A4 inhibitors</td>
<td>200 mg</td>
</tr>
<tr>
<td>CYP3A4 inducers</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients taking 300 mg of ABILIFY MAINTENA</th>
<th>Adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 or strong CYP3A4 inhibitors</td>
<td>200 mg</td>
</tr>
<tr>
<td>Strong CYP2D6 and strong CYP3A4 inhibitors</td>
<td>160 mg</td>
</tr>
<tr>
<td>CYP3A4 inducers</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

**Paediatric population**
The safety and efficacy of ABILIFY MAINTENA in children and adolescents aged 0-17 years have not been established. No data are available.
Method of administration

ABILIFY MAINTENA is only intended for intramuscular use and should not be administered intravenously or subcutaneously. It should only be administered by a healthcare professional. The suspension should be injected immediately after reconstitution but can be stored below 25 °C for up to 4 hours in the vial. The suspension should be injected slowly as a single injection (doses must not be divided) into the gluteal muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Sites of injections should be rotated between the two gluteal muscles.

The recommended needle for administration is a 38 mm (1.5 inch), 21 gauge hypodermic safety needle. For obese patients (Body mass index > 28 kg/m²), a 50 mm (2 inch), 21 gauge hypodermic safety needle should be used (see section 6.6).

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ABILIFY MAINTENA and preventive measures undertaken (see section 4.8).

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

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

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including aripiprazole, must be discontinued (see section 4.8).

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

Elderly patients with dementia-related psychosis
Increased mortality
In three placebo-controlled trials of oral aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n = 938; mean age: 82.4 years; range: 56-99 years), patients treated with aripiprazole are at an increased risk of death compared to placebo. The rate of death in oral aripiprazole-treated patients was 3.5 % compared to 1.7 % in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8).

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

ABILIFY MAINTENA 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 specific interaction studies have been performed with ABILIFY MAINTENA. The information below is obtained from studies with oral aripiprazole.

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

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

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

Potential for other medicinal products to affect ABILIFY MAINTENA
Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes, but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

**Quinidine and other strong CYP2D6 inhibitors**
In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while Cmax was unchanged. The AUC and Cmax of dehydroaripiprazole, 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 Cmax by 63 % and 37 %, respectively. The AUC and Cmax of dehydroaripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolisers (see section 4.2).

When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should, therefore, be applied (see section 4.2).

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of ABILIFY MAINTENA should be increased to the dose prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g., diltiazem) or CYP2D6 (e.g., escitalopram) are used concomitantly with this medicinal product, modest increases in plasma aripiprazole concentrations may be expected.

**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 Cmax 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 Cmax and AUC after carbamazepine co-administration were 69% and 71% lower, respectively, than those following treatment with oral aripiprazole alone.

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

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

Potential for ABILIFY MAINTENA to affect other medicinal products

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

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

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

4.6 Fertility, pregnancy and lactation

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

Prescribers need to be aware of the long-acting properties of ABILIFY MAINTENA.

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

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

**Fertility**

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

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

#### Summary of the safety profile

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

#### Tabulated list of adverse reactions

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

All ADRs are listed by system organ class and frequency; very common (≥ 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".

<table>
<thead>
<tr>
<th>System Organs Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia</td>
<td>Anaemia, Thrombocytopenia, Neutrophil count decreased, White blood cell count decreased</td>
<td>Leukopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td></td>
<td>Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Blood prolactin decreased</td>
<td></td>
<td>Diabetic hyperosmolar coma, Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight increased, Diabetes</td>
<td>Hyperglycaemia, Hypercholesterolaemia, Hyperinsulinaemia</td>
<td>Anorexia, Hyponatraemia</td>
</tr>
<tr>
<td>Common/uncommon</td>
<td>Not known</td>
<td></td>
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<td>----------------------------------------</td>
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<tr>
<td>mellitus</td>
<td>Hyperlipidaemia</td>
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<tr>
<td>Weight decreased</td>
<td>Hypertriglyceridaemia</td>
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<td></td>
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<tr>
<td>Appetite disorder</td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
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<tr>
<td>Agitation</td>
<td>Suicidal ideation</td>
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<tr>
<td>Anxiety</td>
<td>Psychotic disorder</td>
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<tr>
<td>Restlessness</td>
<td>Hallucination</td>
<td></td>
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<tr>
<td>Insomnia</td>
<td>Delusion</td>
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<td></td>
<td>Hypersexuality</td>
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<td></td>
<td>Panic reaction</td>
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<td></td>
<td>Depression</td>
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<td>Affect lability</td>
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<td></td>
<td>Apathy</td>
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<td></td>
<td>Dysphoria</td>
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<td></td>
<td>Sleep disorder</td>
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<td></td>
<td>Bruxism</td>
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<td></td>
<td>Libido decreased</td>
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<tr>
<td></td>
<td>Mood altered</td>
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<td></td>
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<tr>
<td>Nervous system disorders</td>
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<tr>
<td>Extrapyramidal disorder</td>
<td>Dystonia</td>
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<tr>
<td>Akathisia</td>
<td>Tardive dyskinesia</td>
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<tr>
<td>Tremor</td>
<td>Parkinsonism</td>
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<tr>
<td>Dyskinesia</td>
<td>Movement disorder</td>
<td></td>
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<tr>
<td>Sedation</td>
<td>Psychomotor hyperactivity</td>
<td></td>
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</tr>
<tr>
<td>Somnolence</td>
<td>Restless legs syndrome</td>
<td></td>
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<tr>
<td>Dizziness</td>
<td>Cogwheel rigidity</td>
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<tr>
<td>Headache</td>
<td>Hypertonia</td>
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<tr>
<td></td>
<td>Bradykinesia</td>
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<tr>
<td></td>
<td>Drooling</td>
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<td></td>
<td>Dysgeusia</td>
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<tr>
<td></td>
<td>Parosmia</td>
<td></td>
<td></td>
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<tr>
<td>Eye disorders</td>
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<tr>
<td></td>
<td>Oculogyric crisis</td>
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<td></td>
<td>Vision blurred</td>
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<td></td>
<td>Eye pain</td>
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<tr>
<td>Cardiac disorders</td>
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<tr>
<td></td>
<td>Ventricular extrasystoles</td>
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<td></td>
<td>Bradycardia</td>
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<td></td>
<td>Tachycardia</td>
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<td></td>
<td>Electrocardiogram T wave amplitude decreased</td>
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<td></td>
<td>Electrocardiogram abnormal</td>
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<td></td>
<td>Electrocardiogram T wave inversion</td>
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<tr>
<td>Vascular disorders</td>
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<tr>
<td></td>
<td>Hypertension</td>
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<tr>
<td></td>
<td>Orthostatic hypotension</td>
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<td></td>
<td>Blood pressure increased</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<tr>
<td></td>
<td>Cough</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
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<td></td>
<td>Dry mouth</td>
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<tr>
<td></td>
<td>Gastrooesophageal reflux disease</td>
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<tr>
<td></td>
<td>Dyspepsia</td>
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Description of selected adverse reactions

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

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

Extrapyramidal Symptoms (EPS)
In trials in stable patients with schizophrenia, ABILIFY MAINTENA was associated with a higher frequency of EPS symptoms (18.4 %) than oral aripiprazole treatment (11.7 %). Akathisia was the most frequently observed symptom (8.2 %) and typically starts around day 10 after first injection, and lasts a median of 56 days.

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

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

Dystonia
Class effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

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

During the double-blind, placebo-controlled phase of the 52-week trial, the incidence of weight gain of ≥ 7 % from baseline to last visit was 6.4 % for the ABILIFY MAINTENA group and 5.2 % for the placebo group. The incidence of weight loss of ≥ 7 % from baseline to last visit was 6.4 % for the ABILIFY MAINTENA group and 6.7 % for the placebo group. During double-blind treatment, mean change in body weight from baseline to last visit was -0.2 kg for ABILIFY MAINTENA and -0.4 kg for placebo (p = 0.812).
Prolactin
In the double-blind active-controlled phase of the 38-week trial, from baseline to last visit there was a mean decrease in prolactin levels in the ABILIFY MAINTENA group (−0.33 ng/mL) compared with a mean increase in the oral aripiprazole tablets 10-30 mg group (0.79 ng/mL; p < 0.01). The incidence of ABILIFY MAINTENA patients with prolactin levels > 1 time the upper limit of normal range (ULN) at any assessment was 5.4 % compared with 3.5 % of the patients on oral aripiprazole tablets 10-30 mg. Male patients generally had a higher incidence than female patients in each treatment group.

In the double-blind placebo-controlled phase of the 52-week trial, from baseline to last visit there was a mean decrease in prolactin levels in the ABILIFY MAINTENA group (−0.38 ng/mL) compared with a mean increase in the placebo group (1.67 ng/mL).

The incidences of ABILIFY MAINTENA patients with prolactin levels > 1 time the upper limit of normal range (ULN) was 1.9 % compared to 7.1 % for placebo patients.

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 diarrhea. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence, transient loss of consciousness and extrapyramidal symptoms.

Management of overdose
Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple medicinal product involvement should be considered. Therefore, cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.
Haemodialysis
Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

It has been proposed that aripiprazole’s efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D2 and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2A receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties of dopaminergic hypoactivity. Aripiprazole exhibits high binding affinity in vitro for dopamine D2 and D3, serotonin 5-HT1A and 5-HT2A receptors and has moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, alpha-1 adrenergic, and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for cholinergic muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole oral doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of $^{11}$C-raclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Further information on clinical trials:

Maintenance treatment of schizophrenia in adults
The efficacy of ABILIFY MAINTENA in the maintenance treatment of patients with schizophrenia was established in two randomised, double-blind trials.

The 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 group to test assay sensitivity for the non-inferiority design.

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

The estimated relapse rate by end of Week 26 was 7.12 % in the ABILIFY MAINTENA group, and 7.76 % in the oral aripiprazole tablets 10-30 mg group, a difference of -0.64 %. The 95 % CI (-5.26, 3.99) for the difference in the estimated proportion of patients experiencing impending relapse by end of Week 26 excluded the predefined non-inferiority margin, 11.5 %. Therefore, ABILIFY MAINTENA is non-inferior to the aripiprazole oral tablets 10-30 mg formulation.
The estimated proportion of patients experiencing impending relapse by end of Week 26 for the ABILIFY MAINTENA group was 7.12%, which was statistically significantly lower than in the aripiprazole Long-Acting Injectable 50 mg/25 mg group (21.80%; p = 0.0006). Thus, superiority of ABILIFY MAINTENA over the aripiprazole Long-Acting Injectable 50 mg/25 mg was established and the validity of the trial design was confirmed.

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

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

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

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

**Table 1  PANSS Total Score – Change From Baseline to Week 38-LOCF: Randomised Efficacy Sample a,b**

<table>
<thead>
<tr>
<th></th>
<th>ABILIFY MAINTENA 400 mg/300 mg (n = 263)</th>
<th>Oral aripiprazole 10-30 mg/day (n = 266)</th>
<th>Aripiprazole Long-Acting Injectable 50 mg/25 mg (n = 131)</th>
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<tr>
<td><strong>Mean baseline (SD)</strong></td>
<td>57.9 (12.94)</td>
<td>56.6 (12.65)</td>
<td>56.1 (12.59)</td>
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<tr>
<td><strong>Mean change (SD)</strong></td>
<td>-1.8 (10.49)</td>
<td>0.7 (11.60)</td>
<td>3.2 (14.45)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>NA</td>
<td>0.0272</td>
<td>0.0002</td>
</tr>
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</table>

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 arm 39.6% of the patients had progressed to impending relapse, whilst in the ABILIFY MAINTENA 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.

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 Cmax values for the depot formulation were approximately 5% of Cmax from IM standard formulation.

After IM multiple dosing, the plasma concentrations of aripiprazole gradually rise and at steady state reach maximum plasma concentrations at a median Tmax of 5-7 days. Less than dose-proportional increases in aripiprazole and dehydro-aripiprazole concentrations and AUC parameters are observed after monthly ABILIFY MAINTENA injections of 300 mg to 400 mg.

Distribution
Based on results from trials with oral administration of aripiprazole, aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99% bound to serum proteins, binding primarily to albumin.

Biotransformation
Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in-vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. After multiple dose administration of ABILIFY MAINTENA, dehydro-aripiprazole, the active metabolite, represents about 29.1-32.5% of aripiprazole AUC in plasma.

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

Pharmacokinetics in special patient groups

CYP2D6 poor metabolisers
Based on population pharmacokinetic evaluation of ABILIFY MAINTENA, the total body clearance of aripiprazole was 3.71 L/h in extensive metabolisers of CYP2D6 and approximately 1.88 L/h (approximately 50 % lower) in poor metabolisers of CYP2D6 (for dose recommendation, see section 4.2).

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

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

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

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

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

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

### 5.3 Preclinical safety data

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

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

**Oral aripiprazole**
For oral aripiprazole, toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity in rats after 104 weeks of oral administration at approximately 3 to 10 times the mean steady-state AUC at the maximum recommended human dose and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at approximately 10 times the mean steady-state AUC at the maximum recommended human dose. The highest non-tumorigenic exposure in female rats was approximately 7 times the human exposure at the recommended dose.
An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy-metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day or approximately 16 to 81 times the maximum recommended human dose based on mg/m².

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

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

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in sub-therapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures approximately 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Carmellose sodium
Mannitol
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide

Solvent
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

After reconstitution
Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C. From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user. Shake the vial vigorously for at least 60 seconds to re-suspend prior to injection. Do not store the reconstituted suspension in the syringe.

6.4 Special precautions for storage

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.
6.5 Nature and contents of container

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

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

Single pack
Each single pack containing one vial of powder, 2 ml vial of solvent, one 3 ml luer lock syringe with pre-attached 38 mm (1.5 inch) 21 gauge, hypodermic safety needle with needle protection device, one 3 ml disposable syringe with luer lock tip, one vial adapter, one 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device and one 50 mm (2 inch) 21 gauge hypodermic safety needle for obese patients with needle protection device

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.

Step 1: Preparation prior to reconstitution of the powder.

(a) Lay out and confirm that components listed below are provided:
- 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
- One 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device
- One 50 mm (2 inch) 21 gauge hypodermic safety needle for obese patients with needle protection device

(b) Powder should be suspended using the solvent supplied in the carton.

(c) Select the amount of solvent needed for reconstitution.

300 mg vial: Add 1.5 ml solvent to reconstitute the powder

Important: the solvent vial contains an overfill.

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 (see figure 1). 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 (see figure 2).
Figure 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 figure 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.

Figure 3

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

Figure 4

(f) 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.

(g) 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.

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

Step 3: Preparation prior to injection

(a) Remove the cover, but not the adapter from the package (see figure 5).
(b) Using the vial adapter package to handle the vial adapter, attach the pre-packaged luer lock syringe to the vial adapter (see figure 6).

(c) Use the luer lock syringe to remove the vial adapter from the package and discard the vial adapter package (see figure 7). Do not touch the spike tip of the adapter at any time.

(d) Determine the recommended volume for injection.

<p>| <strong>ABILIFY MAINTENA reconstituted suspension volume to inject</strong> |
|--------------------------|--------------------------|
| <strong>300 mg Vial</strong>          |                          |</p>
<table>
<thead>
<tr>
<th>Dose</th>
<th>Volume to Inject</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>200 mg</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>160 mg</td>
<td>0.8 ml</td>
</tr>
</tbody>
</table>

(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 (see figure 8).
(g) Slowly withdraw the recommended volume from the vial into the luer lock syringe to allow for injection (see figure 9). A small amount of excess product will remain in the vial.

Step 4: Injection procedure

(a) Detach the luer lock syringe containing the recommended volume of reconstituted ABILIFY MAINTENA suspension from the vial.

(b) Select one of the following hypodermic safety needles depending on the 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 (see figure 10).

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

(c) Slowly inject the recommended volume as a single intramuscular injection into the gluteal 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.

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 powder and solvent vials are for single-use only.
(b) Remember to rotate sites of injections between the two gluteal muscles.
(c) Look for signs or symptoms of inadvertent intravenous administration.

7. MARKETING AUTHORITY

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

8. MARKETING AUTHORITY NUMBER(S)

EU/1/13/882/001

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{DD month YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT

ABILIFY MAINTENA 400 mg powder and solvent for prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection

Powder: white to off-white
Solvent: clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY MAINTENA is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

4.2 Posology and method of administration

Posology

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

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

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

<table>
<thead>
<tr>
<th>Time Since Last Injection</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 4 weeks and &lt; 6 weeks</td>
<td>The injection should be administered as soon as possible and then resume monthly injection schedule.</td>
</tr>
<tr>
<td>&gt; 6 weeks</td>
<td>Concomitant oral aripiprazole should be restarted for 14 days with next administered injection and then resume monthly injection schedule.</td>
</tr>
</tbody>
</table>

Special populations

**Elderly patients**
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 done in patients taking concomitant strong CYP3A4 inhibitors or strong CYP2D6 inhibitors for more than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the dosage may need to be increased to the previous dose (see section 4.5). In case of adverse reactions despite dose adjustments of ABILIFY MAINTENA, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

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

**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**

<table>
<thead>
<tr>
<th>Patients taking 400 mg of ABILIFY MAINTENA</th>
<th>Adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 or strong CYP3A4 inhibitors</td>
<td>300 mg</td>
</tr>
<tr>
<td>Strong CYP2D6 and strong CYP3A4 inhibitors</td>
<td>200 mg</td>
</tr>
<tr>
<td>CYP3A4 inducers</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients taking 300 mg of ABILIFY MAINTENA</th>
<th>Adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 or strong CYP3A4 inhibitors</td>
<td>200 mg</td>
</tr>
<tr>
<td>Strong CYP2D6 and strong CYP3A4 inhibitors</td>
<td>160 mg</td>
</tr>
<tr>
<td>CYP3A4 inducers</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

**Paediatric population**
The safety and efficacy of ABILIFY MAINTENA in children and adolescents aged 0-17 years have not been established. No data are available.
Method of administration

ABILIFY MAINTENA is only intended for intramuscular use and should not be administered intravenously or subcutaneously. It should only be administered by a healthcare professional. The suspension should be injected immediately after reconstitution but can be stored below 25 °C for up to 4 hours in the vial. The suspension should be injected slowly as a single injection (doses must not be divided) into the gluteal muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Sites of injections should be rotated between the two gluteal muscles.

The recommended needle for administration is a 38 mm (1.5 inch), 21 gauge hypodermic safety needle. For obese patients (Body mass index > 28 kg/m²), a 50 mm (2 inch), 21 gauge hypodermic safety needle should be used (see section 6.6).

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ABILIFY MAINTENA and preventive measures undertaken (see section 4.8).

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

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

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including aripiprazole, must be discontinued (see section 4.8).

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

Elderly patients with dementia-related psychosis
Increased mortality
In three placebo-controlled trials of oral aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n = 938; mean age: 82.4 years; range: 56-99 years), patients treated with aripiprazole are at an increased risk of death compared to placebo. The rate of death in oral aripiprazole-treated patients was 3.5% compared to 1.7% in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8).

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

ABILIFY MAINTENA 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 specific interaction studies have been performed with ABILIFY MAINTENA. The information below is obtained from studies with oral aripiprazole.

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

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

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

Potential for other medicinal products to affect ABILIFY MAINTENA
Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes, but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

**Quinidine and other strong CYP2D6 inhibitors**
In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while Cmax was unchanged. The AUC and Cmax 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 Cmax by 63 % and 37 %, respectively. The AUC and Cmax of dehydro-aripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolisers (see section 4.2).

When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should, therefore, be applied (see section 4.2).

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of ABILIFY MAINTENA should be increased to the dose prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g., diltiazem) or CYP2D6 (e.g., escitalopram) are used concomitantly with this medicinal product, modest increases in plasma aripiprazole concentrations may be expected.

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

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

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

Potential for ABILIFY MAINTENA to affect other medicinal products

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

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

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

4.6 Fertility, pregnancy and lactation

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

Prescribers need to be aware of the long-acting properties of ABILIFY MAINTENA.

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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

All ADRs are listed by system organ class and frequency; very common (≥ 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".

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia</td>
<td>Anaemia</td>
<td>Leukopenia</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Neutrophil count decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>White blood cell count</td>
<td>decreased</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td></td>
<td>Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Blood prolactin decreased</td>
<td></td>
<td>Diabetic hyperosmolar coma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight increased</td>
<td>Hyperglycaemia</td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>Hypercholesterolaemia</td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td></td>
<td>Hyperinsulinaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Uncommon</td>
<td>Not known</td>
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<td></td>
</tr>
<tr>
<td>mellitus</td>
<td>Hyperlipidaemia</td>
<td>Completed suicide</td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>Hypertriglyceridaemia</td>
<td>Suicide attempt</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appetite disorder</td>
<td>Pathological gambling</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nervousness</td>
<td></td>
</tr>
</tbody>
</table>

### 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
- Neuroleptic malignant syndrome
- Grand mal convulsion
- Serotonin syndrome
- Speech disorder

### 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
- Syncope
- Venous thromboembolism (including pulmonary embolism and deep vein thrombosis)

### Eye disorders
- Oculogyric crisis
- Vision blurred
- Eye pain

### 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
- Deep vein thrombosis

### Respiratory, thoracic and mediastinal disorders
- Cough
- Oropharyngeal spasm
- Laryngospasm
- Aspiration pneumonia

### Gastrointestinal disorders
- Dry mouth
- Gastrooesophageal reflux disease
- Dyspepsia
- Vomiting
- Pancreatitis
- Dysphagia
<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>Nausea</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>Abdominal discomfort</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Constipation</td>
<td>Frequent bowel movement</td>
<td>Hepatitis</td>
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<tr>
<td>Salivary hypersecretion</td>
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<td>Alkaline phosphatase increased</td>
</tr>
<tr>
<td></td>
<td>Liver function test abnormal</td>
<td></td>
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<tr>
<td></td>
<td>Hepatic enzyme increased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alanine aminotransferase increased</td>
<td></td>
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<tr>
<td></td>
<td>Gamma-glutamyl transferase increased</td>
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<tr>
<td></td>
<td>Blood bilirubin increased</td>
<td></td>
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<tr>
<td></td>
<td>Aspartate aminotransferase increased</td>
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<tr>
<td>Hepatobiliary disorders</td>
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<td></td>
<td>Liver function test abnormal</td>
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<td></td>
<td>Hepatic enzyme increased</td>
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<td></td>
<td>Alanine aminotransferase increased</td>
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<td></td>
<td>Gamma-glutamyl transferase increased</td>
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<tr>
<td></td>
<td>Blood bilirubin increased</td>
<td></td>
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<tr>
<td></td>
<td>Aspartate aminotransferase increased</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Acne</td>
<td>Rash</td>
</tr>
<tr>
<td>Acne</td>
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<td>Photosensitivity reaction</td>
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<tr>
<td>Rosacea</td>
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<td>Hyperhidrosis</td>
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<tr>
<td>Eczema</td>
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<tr>
<td>Skin induration</td>
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<tr>
<td></td>
<td>Rhabdomyolysis</td>
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<tr>
<td>Musculoskeletal and connective tissue</td>
<td></td>
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<tr>
<td>Musculoskeletal stiffness</td>
<td>Muscle rigidity</td>
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<tr>
<td></td>
<td>Muscle spasms</td>
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<td></td>
<td>Muscle twitching</td>
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<td></td>
<td>Muscle tightness</td>
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<td></td>
<td>Myalgia</td>
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<td></td>
<td>Pain in extremity</td>
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<td></td>
<td>Arthralgia</td>
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<td></td>
<td>Back pain</td>
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<td></td>
<td>Joint range of motion decreased</td>
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<tr>
<td></td>
<td>Nuchal rigidity</td>
<td></td>
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<tr>
<td></td>
<td>Trismus</td>
<td></td>
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<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td>Nephrolithiasis</td>
<td>Urinary retention,</td>
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<tr>
<td></td>
<td>Glycosuria</td>
<td>Urinary incontinence</td>
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<tr>
<td>Pregnancy, puerperium and perinatal</td>
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<td>Drug withdrawal</td>
</tr>
<tr>
<td></td>
<td>conditions</td>
<td>syndrome neonatal (see section 4.6)</td>
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<tr>
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<tr>
<td>Reproductive system and breast disorders</td>
<td>Erectile dysfunction</td>
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<tr>
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<td>Galactorrhoea</td>
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<td></td>
<td>Gynaecomastia</td>
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<td>Breast tenderness</td>
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<td>Vulvovaginal dryness</td>
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<td></td>
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<tr>
<td>General disorders and administration site</td>
<td>Injection site pain</td>
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<tr>
<td></td>
<td>Injection site induration</td>
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<tr>
<td></td>
<td>Fatigue</td>
<td></td>
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<tr>
<td></td>
<td>Pyrexia</td>
<td>Temperature regulation disorder</td>
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<tr>
<td></td>
<td>Asthenia</td>
<td>(e.g. hypothermia, pyrexia)</td>
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<tr>
<td></td>
<td>Gait disturbance</td>
<td></td>
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<tr>
<td></td>
<td>Chest discomfort</td>
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<tr>
<td></td>
<td>Injection site reaction</td>
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<tr>
<td></td>
<td>Injection site erythema</td>
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<tr>
<td></td>
<td>Injection site swelling</td>
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<tr>
<td></td>
<td>Injection site discomfort</td>
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<tr>
<td></td>
<td>Injection site pruritus</td>
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<tr>
<td></td>
<td>Thirst</td>
<td></td>
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<tr>
<td></td>
<td>Sluggishness</td>
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31
<table>
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<tr>
<th>Investigations</th>
<th>Common</th>
<th>Uncommon</th>
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<tr>
<td></td>
<td>Blood creatine phosphokinase increased</td>
<td>Blood glucose increased</td>
<td>Blood glucose fluctuation</td>
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<td></td>
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<td>Blood glucose decreased</td>
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<td></td>
<td></td>
<td>Glycosylated haemoglobin increased</td>
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<td></td>
<td></td>
<td>Waist circumference increased</td>
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<td></td>
<td></td>
<td>Blood cholesterol decreased</td>
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<tr>
<td></td>
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<td>Blood triglycerides decreased</td>
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</tr>
</tbody>
</table>

Description of selected adverse reactions

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

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

Extrapyramidal Symptoms (EPS)
In trials in stable patients with schizophrenia, ABILIFY MAINTENA was associated with a higher frequency of EPS symptoms (18.4 %) than oral aripiprazole treatment (11.7 %). Akathisia was the most frequently observed symptom (8.2 %) and typically starts around day 10 after first injection, and lasts a median of 56 days.

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

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

Dystonia
Class effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

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

During the double-blind, placebo-controlled phase of the 52-week trial, the incidence of weight gain of ≥ 7 % from baseline to last visit was 6.4 % for the ABILIFY MAINTENA group and 5.2 % for the placebo group. The incidence of weight loss of ≥ 7 % from baseline to last visit was 6.4 % for the ABILIFY MAINTENA group and 6.7 % for the placebo group. During double-blind treatment, mean change in body weight from baseline to last visit was -0.2 kg for ABILIFY MAINTENA and -0.4 kg for placebo (p = 0.812).
Prolactin
In the double-blind active-controlled phase of the 38-week trial, from baseline to last visit there was a mean decrease in prolactin levels in the ABILIFY MAINTENA group (−0.33 ng/mL) compared with a mean increase in the oral aripiprazole tablets 10-30 mg group (0.79 ng/mL; p < 0.01). The incidence of ABILIFY MAINTENA patients with prolactin levels > 1 time the upper limit of normal range (ULN) at any assessment was 5.4 % compared with 3.5 % of the patients on oral aripiprazole tablets 10-30 mg. Male patients generally had a higher incidence than female patients in each treatment group.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

It has been proposed that aripiprazole’s efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D2 and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2A receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties of dopaminergic hypoactivity. Aripiprazole exhibits high binding affinity in vitro for dopamine D2 and D3, serotonin 5-HT1A and 5-HT2A receptors and has moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, alpha-1 adrenergic, and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for cholinergic muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole oral doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Further information on clinical trials:

Maintenance treatment of schizophrenia in adults

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

The 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 group to test assay sensitivity for the non-inferiority design. The results of analysis of the primary efficacy endpoint, the estimated proportion of patients experiencing impending relapse by end of Week 26 of the Double-blind, Active-controlled Phase, showed that ABILIFY MAINTENA 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10-30 mg.

The estimated relapse rate by end of Week 26 was 7.12 % in the ABILIFY MAINTENA group, and 7.76 % in the oral aripiprazole tablets 10-30 mg group, a difference of -0.64 %. The 95 % CI (-5.26, 3.99) for the difference in the estimated proportion of patients experiencing impending relapse by end of Week 26 excluded the predefined non-inferiority margin, 11.5 %. Therefore, ABILIFY MAINTENA is non-inferior to the aripiprazole oral tablets 10-30 mg formulation.
The estimated proportion of patients experiencing impending relapse by end of Week 26 for the ABILIFY MAINTENA group was 7.12%, which was statistically significantly lower than in the aripiprazole Long-Acting Injectable 50 mg/25 mg group (21.80%; p = 0.0006). Thus, superiority of ABILIFY MAINTENA over the aripiprazole Long-Acting Injectable 50 mg/25 mg was established and the validity of the trial design was confirmed.

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

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

![Kaplan-Meier Plot](image)

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

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

**Table 1** PANSS Total Score – Change From Baseline to Week 38-LOCF: Randomised Efficacy Sample \(^a,b\)

<table>
<thead>
<tr>
<th></th>
<th>ABILIFY MAINTENA 400 mg/300 mg (n = 263)</th>
<th>Oral aripiprazole 10-30 mg/day (n = 266)</th>
<th>Aripiprazole Long-Acting Injectable 50 mg/25 mg (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean baseline (SD)</strong></td>
<td>57.9 (12.94)</td>
<td>56.6 (12.65)</td>
<td>56.1 (12.59)</td>
</tr>
<tr>
<td><strong>Mean change (SD)</strong></td>
<td>-1.8 (10.49)</td>
<td>0.7 (11.60)</td>
<td>3.2 (14.45)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>NA</td>
<td>0.0272</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

\(^a\): 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 arm 39.6% of the patients had progressed to impending relapse, whilst in the ABILIFY MAINTENA 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.

**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 \( C_{\text{max}} \) values for the depot formulation were approximately 5% of \( C_{\text{max}} \) from IM standard formulation.

After IM multiple dosing, the plasma concentrations of aripiprazole gradually rise and at steady state reach maximum plasma concentrations at a median \( T_{\text{max}} \) of 5-7 days. 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 \([^{14}\text{C}]\)-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

**Pharmacokinetics in special patient groups**

CYP2D6 poor metabolisers
Based on population pharmacokinetic evaluation of ABILIFY MAINTENA, the total body clearance of aripiprazole was 3.71 L/h in extensive metabolisers of CYP2D6 and approximately 1.88 L/h (approximately 50 % lower) in poor metabolisers of CYP2D6 (for dose recommendation, see section 4.2).

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

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

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

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

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

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

### 5.3 Preclinical safety data

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

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

**Oral aripiprazole**
For oral aripiprazole, toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity in rats after 104 weeks of oral administration at approximately 3 to 10 times the mean steady-state AUC at the maximum recommended human dose and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at approximately 10 times the mean steady-state AUC at the maximum recommended human dose. The highest non-tumorigenic exposure in female rats was approximately 7 times the human exposure at the recommended dose.
An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy-metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day or approximately 16 to 81 times the maximum recommended human dose based on mg/m².

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

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

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in sub-therapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures approximately 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
- Carmellose sodium
- Mannitol
- Sodium dihydrogen phosphate monohydrate
- Sodium hydroxide

Solvent
- Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

After reconstitution
Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C. From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user. Shake the vial vigorously for at least 60 seconds to re-suspend prior to injection. Do not store the reconstituted suspension in the syringe.

6.4 Special precautions for storage

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.
6.5 Nature and contents of container

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

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

Single pack
Each single pack containing one vial of powder, 2 ml vial of solvent, one 3 ml luer lock syringe with pre-attached 38 mm (1.5 inch) 21 gauge, hypodermic safety needle with needle protection device, one 3 ml disposable syringe with luer lock tip, one vial adapter, one 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device and one 50 mm (2 inch) 21 gauge hypodermic needle for obese patients with needle protection device

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.

Step 1: Preparation prior to reconstitution of the powder.

(a) Lay out and confirm that components listed below are provided:
- 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
- One 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device
- One 50 mm (2 inch) 21 gauge hypodermic safety needle for obese patients with needle protection device

(b) Powder should be suspended using the solvent supplied in the carton.

(c) Select the amount of solvent needed for reconstitution.
400 mg vial: Add 1.9 ml solvent to reconstitute the powder
Important: the solvent vial contains an overfill.

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 (see figure 1). A small amount of residual solvent will remain in the vial following withdrawal. Any excess should be discarded.

![Figure 1](image)

(c) Slowly inject the solvent into the vial containing the powder (see figure 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 figure 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.

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

(f) 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.

(g) 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.

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

Step 3: Preparation prior to injection

(a) Remove the cover, but not the adapter from the package (see figure 5).
Using the vial adapter package to handle the vial adapter, attach the pre-packaged luer lock syringe to the vial adapter (see figure 6).

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

Determine the recommended volume for injection.

<table>
<thead>
<tr>
<th>ABILIFY MAINTENA reconstituted suspension volume to inject</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>400 mg</td>
</tr>
<tr>
<td>300 mg</td>
</tr>
<tr>
<td>200 mg</td>
</tr>
<tr>
<td>160 mg</td>
</tr>
</tbody>
</table>

Wipe the top of the vial of the reconstituted suspension with a sterile alcohol swab. 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 (see figure 8).
(g) Slowly withdraw the recommended volume from the vial into the luer lock syringe to allow for injection (see figure 9). A small amount of excess product will remain in the vial.

Step 4: Injection procedure

(a) Detach the luer lock syringe containing the recommended volume of reconstituted ABILIFY MAINTENA suspension from the vial.

(b) Select one of the following hypodermic safety needles depending on the 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 (see figure 10).

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

(c) Slowly inject the recommended volume as a single intramuscular injection into the gluteal 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.

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 powder and solvent vials are for single-use only.
(b) Remember to rotate sites of injections between the two gluteal muscles.
(c) Look for signs or symptoms of inadvertent intravenous administration.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{DD month YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT
ABILIFY MAINTENA 300 mg powder and solvent for prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 300 mg aripiprazole.
After reconstitution each ml of suspension contains 200 mg aripiprazole.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Powder and solvent for prolonged-release suspension for injection
Powder: white to off-white
Solvent: clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
ABILIFY MAINTENA is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

4.2 Posology and method of administration
Posology
For patients who have never taken aripiprazole, tolerability with oral aripiprazole must occur prior to initiating treatment with ABILIFY MAINTENA.
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

<table>
<thead>
<tr>
<th>Missed doses</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 2nd or 3rd dose is missed and time since last injection is:</td>
<td></td>
</tr>
<tr>
<td>&gt; 4 weeks and &lt; 5 weeks</td>
<td>The injection should be administered as soon as possible and then resume monthly injection schedule.</td>
</tr>
<tr>
<td>&gt; 5 weeks</td>
<td>Concomitant oral aripiprazole should be restarted for 14 days with next administered injection and then resume monthly injection schedule.</td>
</tr>
<tr>
<td>If 4th or subsequent doses are</td>
<td></td>
</tr>
</tbody>
</table>

Missed doses
missed (i.e., after attainment of steady state) and time since last injection is:

<table>
<thead>
<tr>
<th>&gt; 4 weeks and &lt; 6 weeks</th>
<th>The injection should be administered as soon as possible and then resume monthly injection schedule.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6 weeks</td>
<td>Concomitant oral aripiprazole should be restarted for 14 days with next administered injection and then resume monthly injection schedule.</td>
</tr>
</tbody>
</table>

Special populations

Elderly patients
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 done in patients taking concomitant strong CYP3A4 inhibitors or strong CYP2D6 inhibitors for more than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the dosage may need to be increased to the previous dose (see section 4.5). In case of adverse reactions despite dose adjustments of ABILIFY MAINTENA, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

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

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

<table>
<thead>
<tr>
<th>Patients taking 400 mg of ABILIFY MAINTENA</th>
<th>Adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 or strong CYP3A4 inhibitors</td>
<td>300 mg</td>
</tr>
<tr>
<td>Strong CYP2D6 and strong CYP3A4 inhibitors</td>
<td>200 mg</td>
</tr>
<tr>
<td>CYP3A4 inducers</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients taking 300 mg of ABILIFY MAINTENA</th>
<th>Adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 or strong CYP3A4 inhibitors</td>
<td>200 mg</td>
</tr>
<tr>
<td>Strong CYP2D6 and strong CYP3A4 inhibitors</td>
<td>160 mg</td>
</tr>
<tr>
<td>CYP3A4 inducers</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

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

ABILIFY MAINTENA is only intended for intramuscular use and should not be administered intravenously or subcutaneously. It should only be administered by a healthcare professional. The suspension should be injected immediately after reconstitution but can be stored below 25 °C for up to 4 hours in the vial. The suspension should be injected slowly as a single injection (doses must not be divided) into the gluteal muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Sites of injections should be rotated between the two gluteal muscles.

The recommended needle for administration is a 38 mm (1.5 inch), 21 gauge hypodermic safety needle. For obese patients (Body mass index > 28 kg/m²), a 50 mm (2 inch), 21 gauge hypodermic safety needle should be used (see section 6.6).

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Suicidality

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

Cardiovascular disorders

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

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ABILIFY MAINTENA and preventive measures undertaken (see section 4.8).

QT prolongation

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

Tardive dyskinesia

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

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including aripiprazole, must be discontinued (see section 4.8).

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

Elderly patients with dementia-related psychosis
Increased mortality
In three placebo-controlled trials of oral aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n = 938; mean age: 82.4 years; range: 56-99 years), patients treated with aripiprazole are at an increased risk of death compared to placebo. The rate of death in oral aripiprazole-treated patients was 3.5 % compared to 1.7 % in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8).

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

ABILIFY MAINTENA 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 specific interaction studies have been performed with ABILIFY MAINTENA. The information below is obtained from studies with oral aripiprazole.

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

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

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

**Potential for other medicinal products to affect ABILIFY MAINTENA**
Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes, but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

**Quinidine and other strong CYP2D6 inhibitors**
In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while Cmax was unchanged. The AUC and Cmax of dehydroaripiprazole, 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 Cmax by 63 % and 37 %, respectively. The AUC and Cmax of dehydroaripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolisers (see section 4.2).
When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should, therefore, be applied (see section 4.2).
Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of ABILIFY MAINTENA should be increased to the dose prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g., diltiazem) or CYP2D6 (e.g., escitalopram) are used concomitantly with this medicinal product, modest increases in plasma aripiprazole concentrations may be expected.

**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 $C_{\text{max}}$ 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 $C_{\text{max}}$ and AUC after carbamazepine co-administration were 69% and 71% lower, respectively, than those following treatment with oral aripiprazole alone.

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

**Valproate and lithium**

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

**Potential for ABILIFY MAINTENA to affect other medicinal products**

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

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

**Serotonin syndrome**

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

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**

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

Prescribers need to be aware of the long-acting properties of ABILIFY MAINTENA.

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

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

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

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

**Summary of the safety profile**

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

**Tabulated list of adverse reactions**

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

All ADRs are listed by system organ class and frequency; very common (≥ 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".

| System Organ Class              | Common                                                                 | Uncommon                                                      | Not known                                      |
|---------------------------------|========================================================================|----------------------------------------------------------------|-----------------------------------------------|
| Blood and lymphatic system disorders | Neutropenia Anaemia Thrombocytopenia Neutrophil count decreased White blood cell count decreased | Hypersensitivity                                              | Leukopenia                                    |
| Immune system disorders         |                                                                        |                                                               |                                               |
| Endocrine disorders             | Blood prolactin decreased                                             |                                                               | Diabetic hyperosmolar coma                   |
| Metabolism and nutrition disorders | Weight increased Diabetes Hyperglycaemia Hypercholesterolaemia Hyperinsulinaemia |                                                               | Diabetic ketoacidosis Anorexia Hyponatraemia |

50
<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidaemia</td>
<td>Hypertriglyceridaemia</td>
<td>Appetite disorder</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Agitation</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Psychotic disorder</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>Hallucination</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>Delusion</td>
<td></td>
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<tr>
<td></td>
<td>Hypersexuality</td>
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<tr>
<td></td>
<td>Panic reaction</td>
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<tr>
<td></td>
<td>Depression</td>
<td></td>
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<tr>
<td></td>
<td>Affect lability</td>
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<tr>
<td></td>
<td>Apathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysphoria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bruxism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Libido decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mood altered</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Extrapyramidal disorder</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Akathisia</td>
<td>Tardive dyskinesia</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>Parkinsonism</td>
<td></td>
</tr>
<tr>
<td>Dykesesia</td>
<td>Movement disorder</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>Psychomotor hyperactivity</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>Restless legs syndrome</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>Cogwheel rigidity</td>
<td></td>
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<tr>
<td>Headache</td>
<td>Hypertonia</td>
<td></td>
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<tr>
<td></td>
<td>Bradykinesia</td>
<td></td>
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<tr>
<td></td>
<td>Drooling</td>
<td></td>
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<tr>
<td></td>
<td>Dysgeusia</td>
<td></td>
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<tr>
<td></td>
<td>Parosmia</td>
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<tr>
<td>Eye disorders</td>
<td>Oculogyric crisis</td>
<td>Sudden unexplained death</td>
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<td></td>
<td>Vision blurred</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>Eye pain</td>
<td>Torsades de pointes</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Ventricular extrasystoles</td>
<td>Sudden unexplained death</td>
</tr>
<tr>
<td>Bradycardia</td>
<td></td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
<td>Torsades de pointes</td>
</tr>
<tr>
<td>Electrocardiogram T wave amplitude decreased</td>
<td></td>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td>Electrocardiogram abnormal</td>
<td></td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Electrocardiogram T wave inversion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>Syncope</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td></td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td></td>
<td>(including pulmonary embolism and deep vein thrombosis)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>Oropharyngeal spasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laryngospasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dry mouth</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Gastrooesophageal reflux disease</td>
<td></td>
<td>Dysphagia</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td><strong>Uncommon</strong></td>
<td><strong>Not known</strong></td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Liver function test abnormal</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Nausea</td>
<td>Hepatic enzyme increased</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>Alanine aminotransferase increased</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>Gamma-glutamyl transferase increased</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>Constipation</td>
<td>Blood bilirubin increased</td>
<td>increased</td>
</tr>
<tr>
<td>Frequent bowel movement</td>
<td>Aspartate aminotransferase increased</td>
<td></td>
</tr>
<tr>
<td>Salivary hypersecretion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hepatobiliary disorders**

- Alopecia
- Acne
- Rosacea
- Eczema
- Skin induration

**Skin and subcutaneous tissue disorders**

- Muscle stiffness
- Muscle rigidity
- Muscle spasms
- Muscle twitching
- Muscle tightness
- Myalgia
- Pain in extremity
- Arthralgia
- Back pain
- Joint range of motion decreased
- Nuchal rigidity
- Trismus

**Musculoskeletal and connective tissue disorders**

- Nephrolithiasis
- Glycosuria

**Renal and urinary disorders**

- Erectile dysfunction
- Galactorrhoea
- Gynaecomastia
- Breast tenderness
- Vulvovaginal dryness

**Reproductive system and breast disorders**

- Injection site pain
- Injection site induration
- Fatigue

**General disorders and administration site conditions**

- 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
<table>
<thead>
<tr>
<th>Investigations</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
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<tr>
<td></td>
<td>Blood creatine phosphokinase increased</td>
<td>Blood glucose increased</td>
<td>Blood glucose fluctuation</td>
</tr>
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<td></td>
<td></td>
<td>Blood glucose decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glycosylated haemoglobin increased</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Waist circumference increased</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Blood cholesterol decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood triglycerides decreased</td>
<td></td>
</tr>
</tbody>
</table>

Description of selected adverse reactions

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

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

Extrapyramidal Symptoms (EPS)
In trials in stable patients with schizophrenia, ABILIFY MAINTENA was associated with a higher frequency of EPS symptoms (18.4 %) than oral aripiprazole treatment (11.7 %). Akathisia was the most frequently observed symptom (8.2 %) and typically starts around day 10 after first injection, and lasts a median of 56 days.

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

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

Dystonia
Class effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

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

During the double-blind, placebo-controlled phase of the 52-week trial, the incidence of weight gain of ≥7 % from baseline to last visit was 6.4 % for the ABILIFY MAINTENA group and 5.2 % for the placebo group. The incidence of weight loss of ≥7 % from baseline to last visit was 6.4 % for the ABILIFY MAINTENA group and 6.7 % for the placebo group. During double-blind treatment, mean change in body weight from baseline to last visit was -0.2 kg for ABILIFY MAINTENA and -0.4 kg for placebo (p = 0.812).
Prolactin
In the double-blind active-controlled phase of the 38-week trial, from baseline to last visit there was a mean decrease in prolactin levels in the ABILIFY MAINTENA group (−0.33 ng/mL) compared with a mean increase in the oral aripiprazole tablets 10-30 mg group (0.79 ng/mL; p < 0.01). The incidence of ABILIFY MAINTENA patients with prolactin levels > 1 time the upper limit of normal range (ULN) at any assessment was 5.4 % compared with 3.5 % of the patients on oral aripiprazole tablets 10-30 mg. Male patients generally had a higher incidence than female patients in each treatment group.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continuous 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 D2 and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2A receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties of dopaminergic hypoactivity. Aripiprazole exhibits high binding affinity in vitro for dopamine D2 and D3, serotonin 5-HT1A and 5-HT2A receptors and has moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, alpha-1 adrenergic, and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for cholinergic muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole oral doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of \(^{11}\text{C}\)-raclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Further information on clinical trials:

Maintenance treatment of schizophrenia in adults
The efficacy of ABILIFY MAINTENA in the maintenance treatment of patients with schizophrenia was established in two randomised, double-blind trials.

The 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 group to test assay sensitivity for the non-inferiority design. The results of analysis of the primary efficacy endpoint, the estimated proportion of patients experiencing impending relapse by end of Week 26 of the Double-blind, Active-controlled Phase, showed that ABILIFY MAINTENA 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10-30 mg.

The estimated relapse rate by end of Week 26 was 7.12 % in the ABILIFY MAINTENA group, and 7.76 % in the oral aripiprazole tablets 10-30 mg group, a difference of -0.64 %. The 95 % CI (-5.26, 3.99) for the difference in the estimated proportion of patients experiencing impending relapse by end of Week 26 excluded the predefined non-inferiority margin, 11.5 %. Therefore, ABILIFY MAINTENA is non-inferior to the aripiprazole oral tablets 10-30 mg formulation.
The estimated proportion of patients experiencing impending relapse by end of Week 26 for the ABILIFY MAINTENA group was 7.12 %, which was statistically significantly lower than in the aripiprazole Long-Acting Injectable 50 mg/25 mg group (21.80 %; \( p = 0.0006 \)). Thus, superiority of ABILIFY MAINTENA over the aripiprazole Long-Acting Injectable 50 mg/25 mg was established and the validity of the trial design was confirmed.

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

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

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**TABLE 1** PANSS Total Score – Change From Baseline to Week 38-LOCF: Randomised Efficacy Sample \(^{a,b}\)

<table>
<thead>
<tr>
<th></th>
<th>ABILIFY MAINTENA 400 mg/300 mg (n = 263)</th>
<th>Oral aripiprazole 10-30 mg/day (n = 266)</th>
<th>Aripiprazole Long-Acting Injectable 50 mg/25 mg (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean baseline (SD)</strong></td>
<td>57.9 (12.94)</td>
<td>56.6 (12.65)</td>
<td>56.1 (12.59)</td>
</tr>
<tr>
<td><strong>Mean change (SD)</strong></td>
<td>-1.8 (10.49)</td>
<td>0.7 (11.60)</td>
<td>3.2 (14.45)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>NA</td>
<td>0.0272</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

\(^{a}\): 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.

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

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 arm 39.6% of the patients had progressed to impending relapse, whilst in the ABILIFY MAINTENA 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.

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. After IM multiple dosing, the plasma concentrations of aripiprazole gradually rise and at steady state reach maximum plasma concentrations at a median Tmax of 5-7 days. Less than dose-proportional increases in aripiprazole and dehydro-aripiprazole concentrations and AUC parameters are observed after monthly ABILIFY MAINTENA injections of 300 mg to 400 mg.

Distribution
Based on results from trials with oral administration of aripiprazole, aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99 % bound to serum proteins, binding primarily to albumin.

Biotransformation
Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in-vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. After multiple dose administration of ABILIFY MAINTENA, dehydro-aripiprazole, the active metabolite, represents about 29.1-32.5 % of aripiprazole AUC in plasma.

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

Pharmacokinetics in special patient groups

CYP2D6 poor metabolisers
Based on population pharmacokinetic evaluation of ABILIFY MAINTENA, the total body clearance of aripiprazole was 3.71 L/h in extensive metabolisers of CYP2D6 and approximately 1.88 L/h (approximately 50 % lower) in poor metabolisers of CYP2D6 (for dose recommendation, see section 4.2).

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

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

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

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

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

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

### 5.3 Preclinical safety data

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

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

**Oral aripiprazole**
For oral aripiprazole, toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity in rats after 104 weeks of oral administration at approximately 3 to 10 times the mean steady-state AUC at the maximum recommended human dose and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at approximately 10 times the mean steady-state AUC at the maximum recommended human dose. The highest non-tumorigenic exposure in female rats was approximately 7 times the human exposure at the recommended dose.
An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy-metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day or approximately 16 to 81 times the maximum recommended human dose based on mg/m².

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

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

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in sub-therapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures approximately 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Carmellose sodium
Mannitol
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide

Solvent
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

After reconstitution
Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C. From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user. Shake the vial vigorously for at least 60 seconds to re-suspend prior to injection. Do not store the reconstituted suspension in the syringe.

6.4 Special precautions for storage

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.
6.5 Nature and contents of container

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

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

Multipack
Bundle pack of 3 single packs.

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

6.6 Special precautions for disposal and other handling.

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

Step 1: Preparation prior to reconstitution of the powder

(a) Lay out and confirm that components listed below are provided:
   - 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
   - One 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device
   - One 50 mm (2 inch) 21 gauge hypodermic safety needle for obese patients with needle protection device

(b) Powder should be suspended using the solvent supplied in the carton.

(c) Select the amount of solvent needed for reconstitution.
   300 mg vial: Add 1.5 ml solvent to reconstitute the powder
   **Important:** the solvent vial contains an overfill.

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 (see figure 1). 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 (see figure 2).
Figure 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 figure 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.

Figure 3

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

Figure 4

(f) 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.

(g) 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.

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

Step 3: Preparation prior to injection

(a) Remove the cover, but not the adapter from the package (see figure 5).
(b) Using the vial adapter package to handle the vial adapter, attach the pre-packaged luer lock syringe to the vial adapter (see figure 6).

(c) Use the luer lock syringe to remove the vial adapter from the package and discard the vial adapter package (see figure 7). Do not touch the spike tip of the adapter at any time.

(d) Determine the recommended volume for injection.

**ABILIFY MAINTENA reconstituted suspension volume to inject**

<table>
<thead>
<tr>
<th>300 mg Vial</th>
<th>Volume to Inject</th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>300 mg</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>200 mg</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>160 mg</td>
<td>0.8 ml</td>
</tr>
</tbody>
</table>

(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 (see figure 8).
(g) Slowly withdraw the recommended volume from the vial into the luer lock syringe to allow for injection (see figure 9). A small amount of excess product will remain in the vial.

Step 4: Injection procedure

(a) Detach the luer lock syringe containing the recommended volume of reconstituted ABILIFY MAINTENA suspension from the vial.
(b) Select one of the following hypodermic safety needles depending on the 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 (see figure 10).

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

(c) Slowly inject the recommended volume as a single intramuscular injection into the gluteal 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.

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 powder and solvent vials are for single-use only.
(b) Remember to rotate sites of injections between the two gluteal muscles.
(c) Look for signs or symptoms of inadvertent intravenous administration.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER(S)

EU/1/13/882/003

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{DD month YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT

ABILIFY MAINTENA 400 mg powder and solvent for prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection

Powder: white to off-white
Solvent: clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY MAINTENA is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

4.2 Posology and method of administration

Posology
For patients who have never taken aripiprazole, tolerability with oral aripiprazole must occur prior to initiating treatment with ABILIFY MAINTENA.

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

<table>
<thead>
<tr>
<th>Missed doses</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>If 2\textsuperscript{nd} or 3\textsuperscript{rd} dose is missed and time since last injection is:</td>
<td></td>
</tr>
<tr>
<td>&gt; 4 weeks and &lt; 5 weeks</td>
<td>The injection should be administered as soon as possible and then resume monthly injection schedule.</td>
</tr>
<tr>
<td>&gt; 5 weeks</td>
<td>Concomitant oral aripiprazole should be restarted for 14 days with next administered injection and then resume monthly injection schedule.</td>
</tr>
<tr>
<td>If 4\textsuperscript{th} or subsequent doses are</td>
<td></td>
</tr>
</tbody>
</table>

65
missed (i.e., after attainment of steady state) and time since last injection is:

<table>
<thead>
<tr>
<th>Time since last injection</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 4 weeks and &lt; 6 weeks</td>
<td>The injection should be administered as soon as possible and then resume monthly injection schedule.</td>
</tr>
<tr>
<td>&gt; 6 weeks</td>
<td>Concomitant oral aripiprazole should be restarted for 14 days with next administered injection and then resume monthly injection schedule.</td>
</tr>
</tbody>
</table>

Special populations

**Elderly patients**
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 done in patients taking concomitant strong CYP3A4 inhibitors or strong CYP2D6 inhibitors for more than 14 days. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the dosage may need to be increased to the previous dose (see section 4.5). In case of adverse reactions despite dose adjustments of ABILIFY MAINTENA, the necessity of concomitant use of CYP2D6 or CYP3A4 inhibitor should be reassessed.

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

**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**

<table>
<thead>
<tr>
<th>Patients taking 400 mg of ABILIFY MAINTENA</th>
<th>Adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 or strong CYP3A4 inhibitors</td>
<td>300 mg</td>
</tr>
<tr>
<td>Strong CYP2D6 and strong CYP3A4 inhibitors</td>
<td>200 mg</td>
</tr>
<tr>
<td>CYP3A4 inducers</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients taking 300 mg of ABILIFY MAINTENA</th>
<th>Adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP2D6 or strong CYP3A4 inhibitors</td>
<td>200 mg</td>
</tr>
<tr>
<td>Strong CYP2D6 and strong CYP3A4 inhibitors</td>
<td>160 mg</td>
</tr>
<tr>
<td>CYP3A4 inducers</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

**Paediatric population**
The safety and efficacy of ABILIFY MAINTENA in children and adolescents aged 0-17 years have not been established. No data are available.
Method of administration

ABILIFY MAINTENA is only intended for intramuscular use and should not be administered intravenously or subcutaneously. It should only be administered by a healthcare professional. The suspension should be injected immediately after reconstitution but can be stored below 25 °C for up to 4 hours in the vial. The suspension should be injected slowly as a single injection (doses must not be divided) into the gluteal muscle. Care should be taken to avoid inadvertent injection into a blood vessel. Sites of injections should be rotated between the two gluteal muscles.

The recommended needle for administration is a 38 mm (1.5 inch), 21 gauge hypodermic safety needle. For obese patients (Body mass index > 28 kg/m²), a 50 mm (2 inch), 21 gauge hypodermic safety needle should be used (see section 6.6).

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ABILIFY MAINTENA and preventive measures undertaken (see section 4.8).

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

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

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including aripiprazole, must be discontinued (see section 4.8).

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

Elderly patients with dementia-related psychosis
Increased mortality
In three placebo-controlled trials of oral aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n = 938; mean age: 82.4 years; range: 56-99 years), patients treated with aripiprazole are at an increased risk of death compared to placebo. The rate of death in oral aripiprazole-treated patients was 3.5 % compared to 1.7 % in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8).

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

ABILIFY MAINTENA 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 specific interaction studies have been performed with ABILIFY MAINTENA. The information below is obtained from studies with oral aripiprazole.

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

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

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

**Potential for other medicinal products to affect ABILIFY MAINTENA**
Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes, but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

**Quinidine and other strong CYP2D6 inhibitors**
In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while $C_{\text{max}}$ was unchanged. The AUC and $C_{\text{max}}$ 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 $C_{\text{max}}$ by 63 % and 37 %, respectively. The AUC and $C_{\text{max}}$ of dehydro-aripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolisers (see section 4.2).

When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should, therefore, be applied (see section 4.2).

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of ABILIFY MAINTENA should be increased to the dose prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g., diltiazem) or CYP2D6 (e.g., escitalopram) are used concomitantly with this medicinal product, modest increases in plasma aripiprazole concentrations may be expected.

**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 $C_{\text{max}}$ 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 $C_{\text{max}}$ and AUC after carbamazepine co-administration were 69% and 71% lower, respectively, than those following treatment with oral aripiprazole alone.

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

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

Potential for ABILIFY MAINTENA to affect other medicinal products

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

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

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

4.6 Fertility, pregnancy and lactation

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

Prescribers need to be aware of the long-acting properties of ABILIFY MAINTENA.

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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

All ADRs are listed by system organ class and frequency; very common (≥ 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".

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia</td>
<td>Anaemia</td>
<td>Leukopenia</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Neutrophil count decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>White blood cell count decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td></td>
<td>Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Blood prolactin decreased</td>
<td></td>
<td>Diabetic hyperosmolar coma</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight increased</td>
<td>Hyperglycaemia</td>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>Hypercholesterolaemia</td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperinsulinaemia</td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td>Common</td>
<td>Uncommon</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>----------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>mellitus</td>
<td>Hyperlipidaemia</td>
<td>Completed suicide</td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>Hypertriglyceridaemia</td>
<td>Suicide attempt</td>
<td></td>
</tr>
<tr>
<td>Appetite disorder</td>
<td></td>
<td>Pathological gambling</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nervousness</td>
<td></td>
</tr>
</tbody>
</table>

**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
- Neuroleptic malignant syndrome
- Grand mal convulsion
- Serotonin syndrome
- Speech disorder

**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

**Eye disorders**
- Oculogyric crisis
- Vision blurred
- Eye pain

**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
- Oropharyngeal spasm
- Laryngospasm
- Aspiration pneumonia

**Gastrointestinal disorders**
- Dry mouth
- Gastrooesophageal reflux disease
- Dyspepsia
- Vomiting
- Pancreatitis
- Dysphagia
<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>Nausea</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>Abdominal discomfort</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Constipation</td>
<td>Frequent bowel movement</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Salivary hypersecretion</td>
<td>Liver function test abnormal</td>
<td>Alkaline phosphatase increased</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatic enzyme increased</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>Gamma-glutamyl transferase increased</td>
<td></td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>Aspartate aminotransferase increased</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia</td>
<td>Rash</td>
</tr>
<tr>
<td>Acne</td>
<td>Photosensitivity reaction</td>
<td></td>
</tr>
<tr>
<td>Rosacea</td>
<td>Eczema</td>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Skin induration</td>
<td>Skin induration</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>Muscle rigidity</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>Muscle twitching</td>
<td></td>
</tr>
<tr>
<td>Muscle tightness</td>
<td>Myalgia</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>Arthralgia</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>Joint range of motion decreased</td>
<td></td>
</tr>
<tr>
<td>Nuchal rigidity</td>
<td>Trismus</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Nephrolithiasis</td>
<td>Urinary retention,</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>Urinary incontinence</td>
<td></td>
</tr>
<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td>Erectile dysfunction</td>
<td>Drug withdrawal</td>
</tr>
<tr>
<td>Galactorrhoea</td>
<td>syndrome neonatal</td>
<td>(see section 4.6)</td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td>Breast tenderness</td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal dryness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Injection site pain</td>
<td>Priapism</td>
</tr>
<tr>
<td>Injection site induration</td>
<td>Pyrexia</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Asthenia</td>
<td></td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>Chest discomfort</td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>Injection site erythema</td>
<td></td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>Injection site discomfort</td>
<td></td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>Thirst</td>
<td></td>
</tr>
<tr>
<td>Temperature regulation disorder</td>
<td>Sluggishness</td>
<td>(e.g. hypothermia,</td>
</tr>
<tr>
<td>(e.g. hypothermia, pyrexia)</td>
<td></td>
<td>pyrexia)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Peripheral oedema</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Uncommon</td>
<td>Not known</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Blood creatine</td>
<td>Blood glucose increased</td>
<td>Blood glucose fluctuation</td>
</tr>
<tr>
<td>phosphokinase increased</td>
<td>Blood glucose decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glycosylated haemoglobin increased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Waist circumference increased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood cholesterol decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood triglycerides decreased</td>
<td></td>
</tr>
</tbody>
</table>

**Description of selected adverse reactions**

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

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

*Extrapyramidal Symptoms (EPS)*
In trials in stable patients with schizophrenia, ABILIFY MAINTENA was associated with a higher frequency of EPS symptoms (18.4 %) than oral aripiprazole treatment (11.7 %). Akathisia was the most frequently observed symptom (8.2 %) and typically starts around day 10 after first injection, and lasts a median of 56 days.

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

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

*Dystonia*
Class effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

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

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

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

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

**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 D2 and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2A receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties of dopaminergic hypoactivity. Aripiprazole exhibits high binding affinity in vitro for dopamine D2 and D3, serotonin 5-HT1A and 5-HT2A receptors and has moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, alpha-1 adrenergic, and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for cholinergic muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole oral doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of $^{11}$C-raclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

**Further information on clinical trials:**

*Maintenance treatment of schizophrenia in adults*

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

The 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 group to test assay sensitivity for the non-inferiority design. The results of analysis of the primary efficacy endpoint, the estimated proportion of patients experiencing impending relapse by end of Week 26 of the Double-blind, Active-controlled Phase, showed that ABILIFY MAINTENA 400 mg/300 mg is non-inferior to aripiprazole oral tablets 10-30 mg.

The estimated relapse rate by end of Week 26 was 7.12 % in the ABILIFY MAINTENA group, and 7.76 % in the oral aripiprazole tablets 10-30 mg group, a difference of -0.64 %. The 95 % CI (-5.26, 3.99) for the difference in the estimated proportion of patients experiencing impending relapse by end of Week 26 excluded the predefined non-inferiority margin, 11.5 %. Therefore, ABILIFY MAINTENA is non-inferior to the aripiprazole oral tablets 10-30 mg formulation.
The estimated proportion of patients experiencing impending relapse by end of Week 26 for the ABILIFY MAINTENA group was 7.12%, which was statistically significantly lower than in the aripiprazole Long-Acting Injectable 50 mg/25 mg group (21.80%; p = 0.0006). Thus, superiority of ABILIFY MAINTENA over the aripiprazole Long-Acting Injectable 50 mg/25 mg was established and the validity of the trial design was confirmed.

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

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

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

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

Table 1  PANSS Total Score – Change From Baseline to Week 38-LOCF: Randomised Efficacy Sample a,b

<table>
<thead>
<tr>
<th></th>
<th>ABILIFY MAINTENA 400 mg/300 mg (n = 263)</th>
<th>Oral aripiprazole 10-30 mg/day (n = 266)</th>
<th>Aripiprazole Long-Acting Injectable 50 mg/25 mg (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline (SD)</td>
<td>57.9 (12.94)</td>
<td>56.6 (12.65)</td>
<td>56.1 (12.59)</td>
</tr>
<tr>
<td>Mean change (SD)</td>
<td>-1.8 (10.49)</td>
<td>0.7 (11.60)</td>
<td>3.2 (14.45)</td>
</tr>
<tr>
<td>P-value</td>
<td>NA</td>
<td>0.0272</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

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-
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 arm 39.6% of the patients had progressed to impending relapse, whilst in the ABILIFY MAINTENA 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.

**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 $C_{\text{max}}$ values for the depot formulation were approximately 5% of $C_{\text{max}}$ from IM standard formulation.

After IM multiple dosing, the plasma concentrations of aripiprazole gradually rise and at steady state reach maximum plasma concentrations at a median $T_{\text{max}}$ of 5-7 days. 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 $[^{14}\text{C}]$-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

**Pharmacokinetics in special patient groups**

CYP2D6 poor metabolisers
Based on population pharmacokinetic evaluation of ABILIFY MAINTENA, the total body clearance of aripiprazole was 3.71 L/h in extensive metabolisers of CYP2D6 and approximately 1.88 L/h (approximately 50% lower) in poor metabolisers of CYP2D6 (for dose recommendation, see section 4.2).

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

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

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

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

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

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

### 5.3 Preclinical safety data

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

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

**Oral aripiprazole**
For oral aripiprazole, toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity in rats after 104 weeks of oral administration at approximately 3 to 10 times the mean steady-state AUC at the maximum recommended human dose and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at approximately 10 times the mean steady-state AUC at the maximum recommended human dose. The highest non-tumorigenic exposure in female rats was approximately 7 times the human exposure at the recommended dose.
An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy-metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day or approximately 16 to 81 times the maximum recommended human dose based on mg/m².

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

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

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in sub-therapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures approximately 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Carmellose sodium
Mannitol
Sodium dihydrogen phosphate monohydrate
Sodium hydroxide

Solvent
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

After reconstitution
Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C. From a microbiological point of view, unless the method of opening/ reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user. Shake the vial vigorously for at least 60 seconds to re-suspend prior to injection. Do not store the reconstituted suspension in the syringe.

6.4 Special precautions for storage

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.
6.5 **Nature and contents of container**

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

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

**Multipack**
Bundle pack of 3 single packs.

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

6.6 **Special precautions for disposal and other handling.**

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

**Step 1: Preparation prior to reconstitution of the powder.**

(a) Lay out and confirm that components listed below are provided:
- 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
- One 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device
- One 50 mm (2 inch) 21 gauge hypodermic safety needle for obese patients with needle protection device

(b) Powder should be suspended using the solvent supplied in the carton.

(c) Select the amount of solvent needed for reconstitution.

400 mg vial: Add 1.9 ml solvent to reconstitute the powder
**Important:** the solvent vial contains an overfill.

**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 (see figure 1). 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 (see figure 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 figure 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.

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

(f) 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.

(g) 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.

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

Step 3: Preparation prior to injection

(a) Remove the cover, but not the adapter from the package (see figure 5).
(b) Using the vial adapter package to handle the vial adapter, attach the pre-packaged luer lock syringe to the vial adapter (see figure 6).

(c) Use the luer lock syringe to remove the vial adapter from the package and discard the vial adapter package (see figure 7). Do not touch the spike tip of the adapter at any time.

(d) Determine the recommended volume for injection.

**ABILIFY MAINTENA reconstituted suspension volume to inject**

<table>
<thead>
<tr>
<th>400 mg Vial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Volume to Inject</td>
</tr>
<tr>
<td>400 mg</td>
<td>2.0 ml</td>
</tr>
<tr>
<td>300 mg</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>200 mg</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>160 mg</td>
<td>0.8 ml</td>
</tr>
</tbody>
</table>

(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 (see figure 8).
Figure 8

(g) Slowly withdraw the recommended volume from the vial into the luer lock syringe to allow for injection (see figure 9). A small amount of excess product will remain in the vial.

Figure 9

Step 4: Injection procedure

(a) Detach the luer lock syringe containing the recommended volume of reconstituted ABILIFY MAINTENA suspension from the vial.

(b) Select one of the following hypodermic safety needles depending on the 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 (see figure 10).

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

Figure 10

(c) Slowly inject the recommended volume as a single intramuscular injection into the gluteal 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.

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 powder and solvent vials are for single-use only.
(b) Remember to rotate sites of injections between the two gluteal muscles.
(c) Look for signs or symptoms of inadvertent intravenous administration.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/882/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

{DD month 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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

- Periodic safety update reports

The marketing authorisation holder shall submit PSURs for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton - Single pack

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
Two 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 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.
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**Vial Powder**

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
<td>ABILIFY MAINTENA 300 mg powder for prolonged-release suspension for injection</td>
</tr>
<tr>
<td></td>
<td>aripiprazole</td>
</tr>
<tr>
<td></td>
<td>Intramuscular use only</td>
</tr>
<tr>
<td><strong>2. METHOD OF ADMINISTRATION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
<td>EXP</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
<td>300 mg</td>
</tr>
<tr>
<td><strong>6. OTHER</strong></td>
<td></td>
</tr>
</tbody>
</table>
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

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
Two 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 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
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 APPLICABLE

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, Framwood 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.
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial Powder</td>
</tr>
</tbody>
</table>

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

   ABILIFY MAINTENA 400 mg powder for prolonged-release suspension for injection
   aripiprazole
   Intramuscular use only

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

<table>
<thead>
<tr>
<th>1. Name of the Medicinal Product and Route(s) of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent for ABILIFY MAINTENA</td>
</tr>
<tr>
<td>Water for injections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Method of Administration</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3. Expiry Date</th>
</tr>
</thead>
</table>

<table>
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<tr>
<th>4. Batch Number</th>
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</table>

<table>
<thead>
<tr>
<th>5. Contents by Weight, by Volume or by Unit</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>6. Other</th>
</tr>
</thead>
</table>

2 ml
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer label (with blue box) - Multipack

### 1. NAME OF THE MEDICINAL PRODUCT

ABILIFY MAINTENA 300 mg powder and solvent for prolonged-release suspension for injection
apeliprazole

### 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
- Two 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 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

**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
Two 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 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.
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**Vial Powder**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<tbody>
<tr>
<td>ABILIFY MAINTENA 300 mg powder for prolonged-release suspension for injection</td>
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<tr>
<td>aripiprazole</td>
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<td>Intramuscular use only</td>
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<th>2. METHOD OF ADMINISTRATION</th>
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<table>
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<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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</thead>
<tbody>
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<td>300 mg</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
</table>
## 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 label (with blue box) - Multipack

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
Two 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 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 AUTHORITY HOLIDER**

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

12. **MARKETING AUTHORIZATION 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

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY MAINTENA 400 mg powder and solvent for prolonged-release suspension for injection

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
Two 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 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

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

ABILIFY MAINTENA 400 mg powder for prolonged-release suspension for injection

aripiprazole

Intramuscular use only

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

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent for ABILIFY MAINTENA</td>
</tr>
<tr>
<td>Water for injections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
</table>

<table>
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<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
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<td>EXP</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
</table>
B. PACKAGE LEAFLET
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.

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 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
• pain killers (such as tramadol and pethidine) used for pain relief
• triptans (such as sumatriptan and zolmitriptan) 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, and sleepiness have been reported as potential side effects of this medicine.

3. How ABILIFY MAINTENA is given

Your doctor will decide how much ABILIFY MAINTENA you need.

This medicine is given in doses of 400 mg as a single injection into the gluteal muscle (buttock) every month unless your doctor tells you otherwise. The interval between the two injections (doses) should not be shorter than 26 days. 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.

This medicine comes as a powder which your doctor or nurse will make into a suspension that will then be injected into the muscle in your buttock. You may feel a little pain during the injection.

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 of 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
• increased sexual activity, decreased sexual activity
• 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
• fixation of the eyeballs in one position, blurred vision, eye pain
• 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, muscle pain (myalgia), pain in extremity, gait disturbance, joint pain (arthritis), 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
• 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.
- 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, one vial of solvent, one 3 mL sterile syringe with a 38 mm (1.5 inch) 21 gauge needle with needle protection device for reconstitution, one sterile syringe without needle, one 38 mm (1.5 inch) and one 50 mm (2 inch) 21 gauge sterile safety needle with needle protection device for injection and one vial adapter.

Marketing Authorisation Holder

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

Manufacturer

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

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:
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.

**Step 1: Preparation prior to reconstitution of the powder.**

(a) Lay out and confirm that components listed below are provided:
   - 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
   - One 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device
   - One 50 mm (2 inch) 21 gauge hypodermic safety needle for obese patients with needle protection device

(b) Powder should be suspended using the solvent supplied in the carton.

(c) Select the amount of solvent needed for reconstitution.
   - 300 mg vial: Add 1.5 ml solvent to reconstitute the powder

   **Important:** the solvent vial contains an overfill.

**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 (see figure 1). 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 (see figure 2).

**Figure 1**

**Figure 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 figure 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.

![Figure 3](image)

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

![Figure 4](image)

(f) 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.

(g) 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.

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

Step 3: Preparation prior to injection

(a) Remove the cover, but not the adapter from the package (see figure 5).

![Figure 5](image)

(b) Using the vial adapter package to handle the vial adapter, attach the pre-packaged luer lock syringe to the vial adapter (see figure 6).

![Figure 6](image)
(c) Use the luer lock syringe to remove the vial adapter from the package and discard the vial adapter package (see figure 7). Do not touch the spike tip of the adapter at any time.

![Figure 7](image)

(d) Determine the recommended volume for injection.

**ABILIFY MAINTENA reconstituted suspension volume to inject**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Volume to Inject</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>200 mg</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>160 mg</td>
<td>0.8 ml</td>
</tr>
</tbody>
</table>

(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 (see figure 8).

![Figure 8](image)

(g) Slowly withdraw the recommended volume from the vial into the luer lock syringe to allow for injection (see figure 9). A small amount of excess product will remain in the vial.

![Figure 9](image)

Step 4: Injection procedure
(a) Detach the luer lock syringe containing the recommended volume of reconstituted ABILIFY MAINTENA suspension from the vial.

(b) Select one of the following hypodermic safety needles depending on the 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 (see figure 10).

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

![Figure 10](image)

(c) Slowly inject the recommended volume as a single intramuscular injection into the gluteal 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.

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

(b) Remember to rotate sites of injections between the two gluteal muscles.

(c) Look for signs or symptoms of inadvertent intravenous administration.
What is in this leaflet

1. What ABILIFY MAINTENA is and what it is used for
2. What you need to know before you are given ABILIFY MAINTENA
3. How ABILIFY MAINTENA is given
4. Possible side effects
5. How to store ABILIFY MAINTENA
6. Contents of the pack and other information

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 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
• pain killers (such as tramadol and pethidine) used for pain relief
• triptans (such as sumatriptan and zolmitriptan) 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, and sleepiness have been reported as potential side effects of this medicine.

3. **How ABILIFY MAINTENA is given**

Your doctor will decide how much ABILIFY MAINTENA you need.

This medicine is given in doses of 400 mg as a single injection into the gluteal muscle (buttock) every month unless your doctor tells you otherwise. The interval between the two injections (doses) should not be shorter than 26 days.

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.

This medicine comes as a powder which your doctor or nurse will make into a suspension that will then be injected into the muscle in your buttock. You may feel a little pain during the injection.

**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 of 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
- increased sexual activity, decreased sexual activity
- 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
- fixation of the eyeballs in one position, blurred vision, eye pain
- 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
- 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 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

ABLEIFY MAINTENA is a powder and solvent for prolonged-release suspension for injection.

ABLEIFY 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, one vial of solvent, one 3 mL sterile syringe with a 38 mm (1.5 inch) 21 gauge needle with needle protection device for reconstitution, one sterile syringe without needle, one 38 mm (1.5 inch) and one 50 mm (2 inch) 21 gauge sterile safety needle with needle protection device for injection and one vial adapter.

**Marketing Authorisation Holder**

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

**Manufacturer**

H. Lundbeck A/S
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Denmark

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
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.

Step 1: Preparation prior to reconstitution of the powder.

(a) Lay out and confirm that components listed below are provided:
   - 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
   - One 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device
   - One 50 mm (2 inch) 21 gauge hypodermic safety needle for obese patients with needle protection device

(b) Powder should be suspended using the solvent supplied in the carton.

(c) Select the amount of solvent needed for reconstitution.
   400 mg vial: Add 1.9 ml solvent to reconstitute the powder
   **Important:** the solvent vial contains an overfill.

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 (see figure 1). A small amount of residual solvent will remain in the vial following withdrawal. Any excess should be discarded.

![Figure 1](image1.png)

(c) Slowly inject the solvent into the vial containing the powder (see figure 2).

![Figure 2](image2.png)

(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 figure 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.

![Figure 3](image)

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

![Figure 4](image)

(f) 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.

(g) 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.

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

**Step 3: Preparation prior to injection**

(a) Remove the cover, but not the adapter from the package (see figure 5).

![Figure 5](image)

(b) Using the vial adapter package to handle the vial adapter, attach the pre-packaged luer lock syringe to the vial adapter (see figure 6).

![Figure 6](image)
(c) Use the luer lock syringe to remove the vial adapter from the package and discard the vial adapter package (see figure 7). Do not touch the spike tip of the adapter at any time.

![Figure 7](image)

(d) Determine the recommended volume for injection.

**ABILIFY MAINTENA reconstituted suspension volume to inject**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Volume to Inject</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg</td>
<td>2.0 ml</td>
</tr>
<tr>
<td>300 mg</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>200 mg</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>160 mg</td>
<td>0.8 ml</td>
</tr>
</tbody>
</table>

(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 (see figure 8).

![Figure 8](image)

(g) Slowly withdraw the recommended volume from the vial into the luer lock syringe to allow for injection (see figure 9). A small amount of excess product will remain in the vial.

![Figure 9](image)

**Step 4: Injection procedure**
(a) Detach the luer lock syringe containing the recommended volume of reconstituted ABILIFY MAINTENA suspension from the vial.

(b) Select one of the following hypodermic safety needles depending on the 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 (see figure 10).

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

![Figure 10](image)

(c) Slowly inject the recommended volume as a single intramuscular injection into the gluteal 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.

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

(b) Remember to rotate sites of injections between the two gluteal muscles.

(c) Look for signs or symptoms of inadvertent intravenous administration.
Package leaflet: Information for the user

ABIephy MAINTENA 300 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 ABIephy MAINTENA is and what it is used for
2. What you need to know before you are given ABIephy MAINTENA
3. How ABIephy MAINTENA is given
4. Possible side effects
5. How to store ABIephy MAINTENA
6. Contents of the pack and other information

1. What ABIephy MAINTENA is and what it is used for

ABIephy 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.

ABIephy 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 ABIephy MAINTENA

Do not use ABIephy 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 ABIephy 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 ABIephy 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 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
• pain killers (such as tramadol and pethidine) used for pain relief
• triptans (such as sumatriptan and zolmitriptan) 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, and sleepiness have been reported as potential side effects of this medicine.

3. How ABILIFY MAINTENA is given

Your doctor will decide how much ABILIFY MAINTENA you need.

This medicine is given in doses of 400 mg as a single injection into the gluteal muscle (buttock) every month unless your doctor tells you otherwise. The interval between the two injections (doses) should not be shorter than 26 days. 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.

This medicine comes as a powder which your doctor or nurse will make into a suspension that will then be injected into the muscle in your buttock. You may feel a little pain during the injection.

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 of 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
- increased sexual activity, decreased sexual activity
- 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
- fixation of the eyeballs in one position, blurred vision, eye pain
- 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, muscle 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
- 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.
- 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.

Multipack
Bundle pack of 3 single packs.
Each single pack containing one vial of powder, one vial of solvent, one 3 mL sterile syringe with a 38 mm (1.5 inch) 21 gauge needle with needle protection device for reconstitution, one sterile syringe without needle, one 38 mm (1.5 inch) and one 50 mm (2 inch) 21 gauge sterile safety needle with needle protection device for injection and one vial adapter.

Marketing Authorisation Holder

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

Manufacturer

H. Lundbeck A/S
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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.

**Step 1: Preparation prior to reconstitution of the powder.**

(a) Lay out and confirm that components listed below are provided:
- 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
- One 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device
- One 50 mm (2 inch) 21 gauge hypodermic safety needle for obese patients with needle protection device
(b) Powder should be suspended using the solvent supplied in the carton.
(c) Select the amount of solvent needed for reconstitution. 300 mg vial: Add 1.5 ml solvent to reconstitute the powder

**Important:** the solvent vial contains an overfill.

**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 (see figure 1). A small amount of residual solvent will remain in the vial following withdrawal. Any excess should be discarded.

![Figure 1](image1)

(c) Slowly inject the solvent into the vial containing the powder (see figure 2).

![Figure 2](image2)

(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 figure 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.

Figure 3

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

Figure 4

(f) 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.

(g) 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.

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

Step 3: Preparation prior to injection

(a) Remove the cover, but not the adapter from the package (see figure 5).

Figure 5

(b) Using the vial adapter package to handle the vial adapter, attach the pre-packaged luer lock syringe to the vial adapter (see figure 6).

Figure 6
(c) Use the luer lock syringe to remove the vial adapter from the package and discard the vial adapter package (see figure 7). Do not touch the spike tip of the adapter at any time.

Figure 7

(d) Determine the recommended volume for injection.

**ABILIFY MAINTENA reconstituted suspension volume to inject**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Volume to Inject</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>200 mg</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>160 mg</td>
<td>0.8 ml</td>
</tr>
</tbody>
</table>

(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 (see figure 8).

Figure 8

(g) Slowly withdraw the recommended volume from the vial into the luer lock syringe to allow for injection (see figure 9). A small amount of excess product will remain in the vial.

Figure 9

Step 4: Injection procedure
(a) Detach the luer lock syringe containing the recommended volume of reconstituted ABILIFY MAINTENA suspension from the vial.

(b) Select one of the following hypodermic safety needles depending on the 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 (see figure 10).

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

Figure 10

(c) Slowly inject the recommended volume as a single intramuscular injection into the gluteal 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.

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 powder and solvent vials are for single-use only.

(b) Remember to rotate sites of injections between the two gluteal muscles.

(c) Look for signs or symptoms of inadvertent intravenous administration.
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
2. What you need to know before you are given ABILIFY MAINTENA
3. How ABILIFY MAINTENA is given
4. Possible side effects
5. How to store ABILIFY MAINTENA
6. Contents of the pack and other information

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 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)
• 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
• pain killers (such as tramadol and pethidine) used for pain relief
• triptans (such as sumatriptan and zolmitriptan) 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, and sleepiness have been reported as potential side effects of this medicine.

**3. How ABILIFY MAINTENA is given**

Your doctor will decide how much ABILIFY MAINTENA you need.

This medicine is given in doses of 400 mg as a single injection into the gluteal muscle (buttock) every month unless your doctor tells you otherwise. The interval between the two injections (doses) should not be shorter than 26 days. 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.

This medicine comes as a powder which your doctor or nurse will make into a suspension that will then be injected into the muscle in your buttock. You may feel a little pain during the injection.

**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 of 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
• increased sexual activity, decreased sexual activity
• 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
• fixation of the eyeballs in one position, blurred vision, eye pain
• 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, muscle pain (myalgia), pain in extremity, gait disturbance, joint pain (arthritis), 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
• 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 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.

**Multipack**
Bundle pack of 3 single packs.
Each single pack containing one vial of powder, one vial of solvent, one 3 mL sterile syringe with a 38 mm (1.5 inch) 21 gauge needle with needle protection device for reconstitution, one sterile syringe without needle, one 38 mm (1.5 inch) and one 50 mm (2 inch) 21 gauge sterile safety needle with needle protection device for injection and one vial adapter.

**Marketing Authorisation Holder**

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

**Manufacturer**

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

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Contact Information</th>
</tr>
</thead>
</table>
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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.
INSTRUCTIONS FOR HEALTH CARE PROFESSIONALS

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

Step 1: Preparation prior to reconstitution of the powder.

(a) Lay out and confirm that components listed below are provided:
   - 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
   - One 38 mm (1.5 inch) 21 gauge hypodermic safety needle with needle protection device
   - One 50 mm (2 inch) 21 gauge hypodermic safety needle for obese patients with needle protection device
(b) Powder should be suspended using the solvent supplied in the carton.
(c) Select the amount of solvent needed for reconstitution.
   400 mg vial: Add 1.9 ml solvent to reconstitute the powder
   **Important**: the solvent vial contains an overfill.

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 (see figure 1). 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 (see figure 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 figure 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.

Figure 3

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

Figure 4

(f) 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.

(g) 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.

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

Step 3: Preparation prior to injection

(a) Remove the cover, but not the adapter from the package (see figure 5).

Figure 5

(b) Using the vial adapter package to handle the vial adapter, attach the pre-packaged luer lock
syringe to the vial adapter (see figure 6).

Figure 6
(c) Use the luer lock syringe to remove the vial adapter from the package and discard the vial adapter package (see figure 7). Do not touch the spike tip of the adapter at any time.

![Figure 7](image)

(d) Determine the recommended volume for injection.

**ABILIFY MAINTENA reconstituted suspension volume to inject**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Volume to Inject</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg</td>
<td>2.0 ml</td>
</tr>
<tr>
<td>300 mg</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>200 mg</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>160 mg</td>
<td>0.8 ml</td>
</tr>
</tbody>
</table>

(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 (see figure 8).

![Figure 8](image)

(g) Slowly withdraw the recommended volume from the vial into the luer lock syringe to allow for injection (see figure 9). A small amount of excess product will remain in the vial.

![Figure 9](image)

**Step 4: Injection procedure**
(a) Detach the luer lock syringe containing the recommended volume of reconstituted ABILIFY MAINTENA suspension from the vial.

(b) Select one of the following hypodermic safety needles depending on the 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 (see figure 10).

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

![Figure 10](image)

(c) Slowly inject the recommended volume as a single intramuscular injection into the gluteal 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.

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 powder and solvent vials are for single-use only.

(b) Remember to rotate sites of injections between the two gluteal muscles.

(c) Look for signs or symptoms of inadvertent intravenous administration.