

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of aripiprazole.

Excipient: 67 mg lactose per tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Rectangular and blue, engraved with "A-007" and "5" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

4.2 Posology and method of administration

Posology

Adults:

Schizophrenia: the recommended starting dose for ABILIFY is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals.

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes: the recommended starting dose for ABILIFY is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population:

Schizophrenia in adolescents 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be

administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents although individual patients may benefit from a higher dose.

ABILIFY is not recommended for use in patients below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Elderly: the effectiveness of ABILIFY in the treatment of schizophrenia and Bipolar I Disorder in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status: according to the metabolic pathway of ABILIFY no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY tablets are for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.

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

accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.

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

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

Conduction abnormalities: In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

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, dose reduction or discontinuation should be considered. 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 ABILIFY, must be discontinued.

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.

Elderly patients with dementia-related psychosis:

Increased mortality: in three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in 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.

Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6% of placebo-treated patients in these trials. 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.

ABILIFY is not indicated for the treatment of 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 agents, including ABILIFY. 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 ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, 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.

Hypersensitivity: as with other medicinal products, hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ABILIFY. 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 5.1).

Dysphagia: oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including ABILIFY. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Lactose: ABILIFY tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1 -adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken 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:

A gastric acid blocker, the H2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

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

In a clinical trial in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole

increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent 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.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with ABILIFY, modest increases in aripiprazole concentrations might be expected.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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 aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

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

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses 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, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Fertility, pregnancy and lactation

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 should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. 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.

Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions in placebo-controlled trials are akathisia and nausea each occurring in more than 3% of patients treated with oral aripiprazole.

The following adverse reactions occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse reactions (*):

The frequency listed below is defined using the following convention: common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

<p>Psychiatric disorders <i>Common:</i> restlessness, insomnia, anxiety <i>Uncommon:</i> depression*</p>
<p>Nervous system disorders <i>Common:</i> extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache</p>
<p>Eye disorders <i>Common:</i> blurred vision</p>
<p>Cardiac disorders <i>Uncommon:</i> tachycardia*</p>
<p>Vascular disorders <i>Uncommon:</i> orthostatic hypotension*</p>
<p>Gastrointestinal disorders <i>Common:</i> dyspepsia, vomiting, nausea, constipation, salivary hypersecretion</p>
<p>General disorders and administration site conditions <i>Common:</i> fatigue</p>

Extrapyramidal symptoms (EPS): *Schizophrenia* - in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%). In a long term 26-week placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8% for aripiprazole-treated patients and 15.1% for olanzapine-treated patients. *Manic episodes in Bipolar I Disorder* - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium. In the long term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1% with aripiprazole and 3.2% with placebo. In schizophrenia patients the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

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

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no

medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5% of aripiprazole treated patients as compared to 2.0% of patients who received placebo.

Other findings:

Adverse reactions known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse reactions and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Paediatric population:

In a short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and type of undesirable effects were similar to those in adults except for the following events that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo): somnolence/sedation and extrapyramidal disorder were reported very commonly ($\geq 1/10$), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly ($\geq 1/100$, $< 1/10$).

The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (< 3 ng/ml) and males (< 2 ng/ml) was 29.5% and 48.3%, respectively.

Post-Marketing:

The following adverse reactions have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:	leukopenia, neutropenia, thrombocytopenia
Immune system disorders:	allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders:	hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma
Metabolism and nutrition disorders:	weight gain, weight decreased, anorexia, hyponatremia
Psychiatric disorders:	agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)
Nervous system disorders:	speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion
Cardiac disorders:	QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia
Vascular disorders:	syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders:	oropharyngeal spasm, laryngospasm, aspiration pneumonia
Gastrointestinal disorders:	pancreatitis, dysphagia, abdominal discomfort, stomach discomfort, diarrhoea

Hepato-biliary disorders:	jaundice, hepatitis, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST), increased Gamma Glutamyl Transferase (GGT), increased alkaline phosphatase
Skin and subcutaneous tissue disorders:	rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders:	rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders:	urinary incontinence, urinary retention
Reproductive system and breast disorders:	priapism
General disorders and administration site conditions:	temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema
Investigations:	increased Creatine Phosphokinase, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased

4.9 Overdose

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 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 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.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

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: other antipsychotics, ATC code: N05AX12

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic

hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole 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:

Schizophrenia in adults:

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Paediatric population:

Schizophrenia in adolescents: in a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13-17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74% of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

Irritability associated with autistic disorder in paediatric patients (see section 4.2): aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Weight gain:

In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N= 18, or 13% of evaluable patients), compared to olanzapine (N= 45, or 33% of evaluable patients).

Lipid parameters:

In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL.

-Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (≥ 6.22 mmol/l) was 2.5% for aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo.

-Fasting triglycerides: incidence of changes in levels from normal (<1.69 mmol/l) to high (≥ 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for placebo and mean change from baseline was -0.11 mmol/l (95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo.

-HDL: incidence of changes in levels from normal (≥ 1.04 mmol/l) to low (<1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l (95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo.

-Fasting LDL: incidence of changes in levels from normal (<2.59 mmol/l) to high (≥ 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo.

Manic episodes in Bipolar I Disorder:

In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomization, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores ≤ 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania).

In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer.

Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate.

The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16% in aripiprazole + lithium and 18% in aripiprazole + valproate compared to 45% in placebo + lithium and 19% in placebo + valproate.

5.2 Pharmacokinetic properties

Absorption:

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:

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.

Metabolism:

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. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination:

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

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

Paediatric population:

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 13 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Elderly:

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:

There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:

A single-dose study in 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

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

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 (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (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 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 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 (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 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 effects 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 subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 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

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate

Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium perforated unit dose blisters in cartons of 14 x 1, 28 x 1, 49 x 1, 56 x 1, 98 x 1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/001-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 June 2004

Date of latest renewal: 4 June 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of aripiprazole.

Excipient: 62.18 mg lactose per tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Rectangular and pink, engraved with "A-008" and "10" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

4.2 Posology and method of administration

Posology

Adults:

Schizophrenia: the recommended starting dose for ABILIFY is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals.

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes: the recommended starting dose for ABILIFY is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population:

Schizophrenia in adolescents 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be

administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents although individual patients may benefit from a higher dose.

ABILIFY is not recommended for use in patients below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Elderly: the effectiveness of ABILIFY in the treatment of schizophrenia and Bipolar I Disorder in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status: according to the metabolic pathway of ABILIFY no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY tablets are for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.

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

accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.

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

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

Conduction abnormalities: In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

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, dose reduction or discontinuation should be considered. 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 ABILIFY, must be discontinued.

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.

Elderly patients with dementia-related psychosis:

Increased mortality: in three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in 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.

Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6% of placebo-treated patients in these trials. 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.

ABILIFY is not indicated for the treatment of 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 agents, including ABILIFY. 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 ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, 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.

Hypersensitivity: as with other medicinal products, hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ABILIFY. 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 5.1).

Dysphagia: oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including ABILIFY. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Lactose: ABILIFY tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1 -adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken 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:

A gastric acid blocker, the H2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

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

In a clinical trial in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole

increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent 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.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with ABILIFY, modest increases in aripiprazole concentrations might be expected.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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 aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

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

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses 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, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Fertility, pregnancy and lactation

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 should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. 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.

Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions in placebo-controlled trials are akathisia and nausea each occurring in more than 3% of patients treated with oral aripiprazole.

The following adverse reactions occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse reactions (*):

The frequency listed below is defined using the following convention: common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

Psychiatric disorders <i>Common:</i> restlessness, insomnia, anxiety <i>Uncommon:</i> depression*
Nervous system disorders <i>Common:</i> extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache
Eye disorders <i>Common:</i> blurred vision
Cardiac disorders <i>Uncommon:</i> tachycardia*
Vascular disorders <i>Uncommon:</i> orthostatic hypotension*
Gastrointestinal disorders <i>Common:</i> dyspepsia, vomiting, nausea, constipation, salivary hypersecretion
General disorders and administration site conditions <i>Common:</i> fatigue

Extrapyramidal symptoms (EPS): *Schizophrenia* - in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%). In a long term 26-week placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8% for aripiprazole-treated patients and 15.1% for olanzapine-treated patients. *Manic episodes in Bipolar I Disorder* - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium. In the long term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1% with aripiprazole and 3.2% with placebo. In schizophrenia patients the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

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

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no

medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5% of aripiprazole treated patients as compared to 2.0% of patients who received placebo.

Other findings:

Adverse reactions known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse reactions and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Paediatric population:

In a short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and type of undesirable effects were similar to those in adults except for the following events that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo): somnolence/sedation and extrapyramidal disorder were reported very commonly ($\geq 1/10$), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly ($\geq 1/100$, $< 1/10$).

The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 29.5% and 48.3%, respectively.

Post-Marketing:

The following adverse reactions have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:	leukopenia, neutropenia, thrombocytopenia
Immune system disorders:	allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders:	hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma
Metabolism and nutrition disorders:	weight gain, weight decreased, anorexia, hyponatremia
Psychiatric disorders:	agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)
Nervous system disorders:	speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion
Cardiac disorders:	QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia
Vascular disorders:	syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders:	oropharyngeal spasm, laryngospasm, aspiration pneumonia
Gastrointestinal disorders:	pancreatitis, dysphagia, abdominal discomfort, stomach discomfort, diarrhoea

Hepato-biliary disorders:	jaundice, hepatitis, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST), increased Gamma Glutamyl Transferase (GGT), increased alkaline phosphatase
Skin and subcutaneous tissue disorders:	rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders:	rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders:	urinary incontinence, urinary retention
Reproductive system and breast disorders:	priapism
General disorders and administration site conditions:	temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema
Investigations:	increased Creatine Phosphokinase, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased

4.9 Overdose

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 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 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.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

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: other antipsychotics, ATC code: N05AX12

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic

hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole 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:

Schizophrenia in adults:

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Paediatric population:

Schizophrenia in adolescents: in a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13-17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74% of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

Irritability associated with autistic disorder in paediatric patients (see section 4.2): aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Weight gain:

In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N= 18, or 13% of evaluable patients), compared to olanzapine (N= 45, or 33% of evaluable patients).

Lipid parameters:

In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL.

-Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (\geq 6.22 mmol/l) was 2.5% for aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo.

-Fasting triglycerides: incidence of changes in levels from normal (<1.69 mmol/l) to high (\geq 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for placebo and mean change from baseline was -0.11 mmol/l (95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo.

-HDL: incidence of changes in levels from normal (\geq 1.04 mmol/l) to low (<1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l (95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo.

-Fasting LDL: incidence of changes in levels from normal (<2.59 mmol/l) to high (\geq 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo.

Manic episodes in Bipolar I Disorder:

In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomization, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores \leq 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania).

In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer.

Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate.

The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16% in aripiprazole + lithium and 18% in aripiprazole + valproate compared to 45% in placebo + lithium and 19% in placebo + valproate.

5.2 Pharmacokinetic properties

Absorption:

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:

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.

Metabolism:

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. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination:

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

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

Paediatric population:

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 13 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Elderly:

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:

There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:

A single-dose study in 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

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

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 (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (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 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 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 (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 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 effects 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 subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 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

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium perforated unit dose blisters in cartons of 14 x 1, 28 x 1, 49 x 1, 56 x 1, 98 x 1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/006-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 June 2004

Date of latest renewal: 4 June 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 15 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg of aripiprazole.

Excipient: 57 mg lactose per tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Round and yellow, engraved with "A-009" and "15" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

4.2 Posology and method of administration

Posology

Adults:

Schizophrenia: the recommended starting dose for ABILIFY is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals.

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes: the recommended starting dose for ABILIFY is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population:

Schizophrenia in adolescents 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be

administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents although individual patients may benefit from a higher dose.

ABILIFY is not recommended for use in patients below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Elderly: the effectiveness of ABILIFY in the treatment of schizophrenia and Bipolar I Disorder in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status: according to the metabolic pathway of ABILIFY no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY tablets are for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.

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

accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.

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

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

Conduction abnormalities: In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

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, dose reduction or discontinuation should be considered. 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 ABILIFY, must be discontinued.

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.

Elderly patients with dementia-related psychosis:

Increased mortality: in three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in 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.

Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6% of placebo-treated patients in these trials. 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.

ABILIFY is not indicated for the treatment of 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 agents, including ABILIFY. 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 ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, 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.

Hypersensitivity: as with other medicinal products, hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ABILIFY. 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 5.1).

Dysphagia: oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including ABILIFY. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Lactose: ABILIFY tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1 -adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken 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:

A gastric acid blocker, the H2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

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

In a clinical trial in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole

increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent 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.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with ABILIFY, modest increases in aripiprazole concentrations might be expected.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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 aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

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

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses 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, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Fertility, pregnancy and lactation

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 should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. 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.

Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions in placebo-controlled trials are akathisia and nausea each occurring in more than 3% of patients treated with oral aripiprazole.

The following adverse reactions occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse reactions (*):

The frequency listed below is defined using the following convention: common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

Psychiatric disorders <i>Common:</i> restlessness, insomnia, anxiety <i>Uncommon:</i> depression*
Nervous system disorders <i>Common:</i> extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache
Eye disorders <i>Common:</i> blurred vision
Cardiac disorders <i>Uncommon:</i> tachycardia*
Vascular disorders <i>Uncommon:</i> orthostatic hypotension*
Gastrointestinal disorders <i>Common:</i> dyspepsia, vomiting, nausea, constipation, salivary hypersecretion
General disorders and administration site conditions <i>Common:</i> fatigue

Extrapyramidal symptoms (EPS): *Schizophrenia* - in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%). In a long term 26-week placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8% for aripiprazole-treated patients and 15.1% for olanzapine-treated patients. *Manic episodes in Bipolar I Disorder* - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium. In the long term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1% with aripiprazole and 3.2% with placebo. In schizophrenia patients the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

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

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no

medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5% of aripiprazole treated patients as compared to 2.0% of patients who received placebo.

Other findings:

Adverse reactions known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse reactions and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Paediatric population:

In a short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and type of undesirable effects were similar to those in adults except for the following events that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo): somnolence/sedation and extrapyramidal disorder were reported very commonly ($\geq 1/10$), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly ($\geq 1/100$, $< 1/10$).

The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 29.5% and 48.3%, respectively.

Post-Marketing:

The following adverse reactions have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:	leukopenia, neutropenia, thrombocytopenia
Immune system disorders:	allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders:	hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma
Metabolism and nutrition disorders:	weight gain, weight decreased, anorexia, hyponatremia
Psychiatric disorders:	agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)
Nervous system disorders:	speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion
Cardiac disorders:	QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia
Vascular disorders:	syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders:	oropharyngeal spasm, laryngospasm, aspiration pneumonia
Gastrointestinal disorders:	pancreatitis, dysphagia, abdominal discomfort, stomach discomfort, diarrhoea

Hepato-biliary disorders:	jaundice, hepatitis, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST), increased Gamma Glutamyl Transferase (GGT), increased alkaline phosphatase
Skin and subcutaneous tissue disorders:	rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders:	rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders:	urinary incontinence, urinary retention
Reproductive system and breast disorders:	priapism
General disorders and administration site conditions:	temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema
Investigations:	increased Creatine Phosphokinase, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased

4.9 Overdose

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 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 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.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

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: other antipsychotics, ATC code: N05AX12

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic

hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole 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:

Schizophrenia in adults:

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Paediatric population:

Schizophrenia in adolescents: in a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13-17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74% of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

Irritability associated with autistic disorder in paediatric patients (see section 4.2): aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Weight gain:

In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N= 18, or 13% of evaluable patients), compared to olanzapine (N= 45, or 33% of evaluable patients).

Lipid parameters:

In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL.

-Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (≥ 6.22 mmol/l) was 2.5% for aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo.

-Fasting triglycerides: incidence of changes in levels from normal (<1.69 mmol/l) to high (≥ 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for placebo and mean change from baseline was -0.11 mmol/l (95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo.

-HDL: incidence of changes in levels from normal (≥ 1.04 mmol/l) to low (<1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l (95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo.

-Fasting LDL: incidence of changes in levels from normal (<2.59 mmol/l) to high (≥ 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo.

Manic episodes in Bipolar I Disorder:

In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomization, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores ≤ 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania).

In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer.

Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate.

The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16% in aripiprazole + lithium and 18% in aripiprazole + valproate compared to 45% in placebo + lithium and 19% in placebo + valproate.

5.2 Pharmacokinetic properties

Absorption:

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:

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.

Metabolism:

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. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination:

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

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

Paediatric population:

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 13 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Elderly:

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:

There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:

A single-dose study in 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

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

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 (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (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 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 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 (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 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 effects 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 subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 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

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate

Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium perforated unit dose blisters in cartons of 14 x 1, 28 x 1, 49 x 1, 56 x 1, 98 x 1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/011-015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 June 2004

Date of latest renewal: 4 June 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30 mg of aripiprazole.

Excipient: 186.54 mg lactose per tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Round and pink, engraved with "A-011" and "30" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

4.2 Posology and method of administration

Posology

Adults:

Schizophrenia: the recommended starting dose for ABILIFY is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals.

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes: the recommended starting dose for ABILIFY is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population:

Schizophrenia in adolescents 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be

administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents although individual patients may benefit from a higher dose.

ABILIFY is not recommended for use in patients below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Elderly: the effectiveness of ABILIFY in the treatment of schizophrenia and Bipolar I Disorder in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status: according to the metabolic pathway of ABILIFY no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY tablets are for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.

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

accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.

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

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

Conduction abnormalities: In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

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, dose reduction or discontinuation should be considered. 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 ABILIFY, must be discontinued.

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.

Elderly patients with dementia-related psychosis:

Increased mortality: in three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in 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.

Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6% of placebo-treated patients in these trials. 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.

ABILIFY is not indicated for the treatment of 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 agents, including ABILIFY. 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 ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, 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.

Hypersensitivity: as with other medicinal products, hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ABILIFY. 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 5.1).

Dysphagia: oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including ABILIFY. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Lactose: ABILIFY tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1 -adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken 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:

A gastric acid blocker, the H2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

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

In a clinical trial in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole

increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent 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.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with ABILIFY, modest increases in aripiprazole concentrations might be expected.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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 aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

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

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses 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, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Fertility, pregnancy and lactation

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 should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. 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.

Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions in placebo-controlled trials are akathisia and nausea each occurring in more than 3% of patients treated with oral aripiprazole.

The following adverse reactions occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse reactions (*):

The frequency listed below is defined using the following convention: common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

Psychiatric disorders <i>Common:</i> restlessness, insomnia, anxiety <i>Uncommon:</i> depression*
Nervous system disorders <i>Common:</i> extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache
Eye disorders <i>Common:</i> blurred vision
Cardiac disorders <i>Uncommon:</i> tachycardia*
Vascular disorders <i>Uncommon:</i> orthostatic hypotension*
Gastrointestinal disorders <i>Common:</i> dyspepsia, vomiting, nausea, constipation, salivary hypersecretion
General disorders and administration site conditions <i>Common:</i> fatigue

Extrapyramidal symptoms (EPS): *Schizophrenia* - in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%). In a long term 26-week placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8% for aripiprazole-treated patients and 15.1% for olanzapine-treated patients. *Manic episodes in Bipolar I Disorder* - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium. In the long term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1% with aripiprazole and 3.2% with placebo. In schizophrenia patients the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

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

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no

medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5% of aripiprazole treated patients as compared to 2.0% of patients who received placebo.

Other findings:

Adverse reactions known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse reactions and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Paediatric population:

In a short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and type of undesirable effects were similar to those in adults except for the following events that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo): somnolence/sedation and extrapyramidal disorder were reported very commonly ($\geq 1/10$), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly ($\geq 1/100$, $< 1/10$).

The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (< 3 ng/ml) and males (< 2 ng/ml) was 29.5% and 48.3%, respectively.

Post-Marketing:

The following adverse reactions have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:	leukopenia, neutropenia, thrombocytopenia
Immune system disorders:	allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders:	hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma
Metabolism and nutrition disorders:	weight gain, weight decreased, anorexia, hyponatremia
Psychiatric disorders:	agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)
Nervous system disorders:	speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion
Cardiac disorders:	QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia
Vascular disorders:	syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders:	oropharyngeal spasm, laryngospasm, aspiration pneumonia
Gastrointestinal disorders:	pancreatitis, dysphagia, abdominal discomfort, stomach discomfort, diarrhoea

Hepato-biliary disorders:	jaundice, hepatitis, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST), increased Gamma Glutamyl Transferase (GGT), increased alkaline phosphatase
Skin and subcutaneous tissue disorders:	rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders:	rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders:	urinary incontinence, urinary retention
Reproductive system and breast disorders:	priapism
General disorders and administration site conditions:	temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema
Investigations:	increased Creatine Phosphokinase, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased

4.9 Overdose

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 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 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.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

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: other antipsychotics, ATC code: N05AX12

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic

hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole 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:

Schizophrenia in adults:

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Paediatric population:

Schizophrenia in adolescents: in a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13-17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74% of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

Irritability associated with autistic disorder in paediatric patients (see section 4.2): aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Weight gain:

In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N= 18, or 13% of evaluable patients), compared to olanzapine (N= 45, or 33% of evaluable patients).

Lipid parameters:

In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL.

-Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (\geq 6.22 mmol/l) was 2.5% for aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo.

-Fasting triglycerides: incidence of changes in levels from normal (<1.69 mmol/l) to high (\geq 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for placebo and mean change from baseline was -0.11 mmol/l (95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo.

-HDL: incidence of changes in levels from normal (\geq 1.04 mmol/l) to low (<1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l (95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo.

-Fasting LDL: incidence of changes in levels from normal (<2.59 mmol/l) to high (\geq 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo.

Manic episodes in Bipolar I Disorder:

In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomization, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores \leq 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania).

In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer.

Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate.

The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16% in aripiprazole + lithium and 18% in aripiprazole + valproate compared to 45% in placebo + lithium and 19% in placebo + valproate.

5.2 Pharmacokinetic properties

Absorption:

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:

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.

Metabolism:

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. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination:

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

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

Paediatric population:

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 13 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Elderly:

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:

There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:

A single-dose study in 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

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

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 (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (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 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 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 (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 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 effects 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 subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 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

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium perforated unit dose blisters in cartons of 14 x 1, 28 x 1, 49 x 1, 56 x 1, 98 x 1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/016-020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 June 2004

Date of latest renewal: 4 June 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 10 mg of aripiprazole.

Excipient: 2 mg aspartame (E951) per orodispersible tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Round and pink, marked with "A" over "640" on one side and "10" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

4.2 Posology and method of administration

Posology

Adults:

Schizophrenia: the recommended starting dose for ABILIFY is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals.

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes: the recommended starting dose for ABILIFY is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population:

Schizophrenia in adolescents 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be

administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents although individual patients may benefit from a higher dose.

ABILIFY is not recommended for use in patients below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Elderly: the effectiveness of ABILIFY in the treatment of schizophrenia and Bipolar I Disorder in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status: according to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY orodispersible tablets are for oral use.

The orodispersible tablet should be placed in the mouth on the tongue, where it will rapidly disperse in saliva. It can be taken with or without liquid. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, disperse the tablet in water and drink the resulting suspension.

The orodispersible tablets may be used as an alternative to ABILIFY tablets for patients who have difficulty to swallow ABILIFY tablets (see also section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.

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

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

Conduction abnormalities: In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

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, dose reduction or discontinuation should be considered. 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 ABILIFY, must be discontinued.

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.

Elderly patients with dementia-related psychosis:

Increased mortality: in three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in 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.

Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions

compared with 0.6% of placebo-treated patients in these trials. 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. ABILIFY is not indicated for the treatment of 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 agents, including ABILIFY. 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 ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, 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.

Hypersensitivity: as with other medicinal products, hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ABILIFY. 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 5.1).

Dysphagia: oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including ABILIFY. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Phenylketonurics: ABILIFY orodispersible tablets contain aspartame, a source of phenylalanine which may be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1 -adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken 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:

A gastric acid blocker, the H₂ antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

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

In a clinical trial in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active

metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent 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.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with ABILIFY, modest increases in aripiprazole concentrations might be expected.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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 aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

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

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses 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, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Fertility, pregnancy and lactation

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 should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. 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.

Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions in placebo-controlled trials are akathisia and nausea each occurring in more than 3% of patients treated with oral aripiprazole.

The following adverse reactions occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse reactions (*):

The frequency listed below is defined using the following convention: common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

<p>Psychiatric disorders <i>Common:</i> restlessness, insomnia, anxiety <i>Uncommon:</i> depression*</p>
<p>Nervous system disorders <i>Common:</i> extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache</p>
<p>Eye disorders <i>Common:</i> blurred vision</p>
<p>Cardiac disorders <i>Uncommon:</i> tachycardia*</p>
<p>Vascular disorders <i>Uncommon:</i> orthostatic hypotension*</p>
<p>Gastrointestinal disorders <i>Common:</i> dyspepsia, vomiting, nausea, constipation, salivary hypersecretion</p>
<p>General disorders and administration site conditions <i>Common:</i> fatigue</p>

Extrapyramidal symptoms (EPS): *Schizophrenia* - in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%). In a long term 26-week placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8% for aripiprazole-treated patients and 15.1% for olanzapine-treated patients. *Manic episodes in Bipolar I Disorder* - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium. In the long term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1% with aripiprazole and 3.2% with placebo. In schizophrenia patients the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

Dystonia: *Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at

low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5% of aripiprazole treated patients as compared to 2.0% of patients who received placebo.

Other findings:

Adverse reactions known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse reactions and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Paediatric population:

In a short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and type of undesirable effects were similar to those in adults except for the following events that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo): somnolence/sedation and extrapyramidal disorder were reported very commonly ($\geq 1/10$), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly ($\geq 1/100$, $< 1/10$).

The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 29.5% and 48.3%, respectively.

Post-Marketing:

The following adverse reactions have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:	leukopenia, neutropenia, thrombocytopenia
Immune system disorders:	allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders:	hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma
Metabolism and nutrition disorders:	weight gain, weight decreased, anorexia, hyponatremia
Psychiatric disorders:	agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)
Nervous system disorders:	speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion
Cardiac disorders:	QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia
Vascular disorders:	syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)

Respiratory, thoracic and mediastinal disorders:	oropharyngeal spasm, laryngospasm, aspiration pneumonia
Gastrointestinal disorders:	pancreatitis, dysphagia, abdominal discomfort, stomach discomfort, diarrhoea
Hepato-biliary disorders:	jaundice, hepatitis, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST), increased Gamma Glutamyl Transferase (GGT), increased alkaline phosphatase
Skin and subcutaneous tissue disorders:	rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders:	rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders:	urinary incontinence, urinary retention
Reproductive system and breast disorders:	priapism
General disorders and administration site conditions:	temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema
Investigations:	increased Creatine Phosphokinase, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased

4.9 Overdose

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 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 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.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

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: other antipsychotics, ATC code: N05AX12

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole 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:

Schizophrenia in adults:

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Paediatric population:

Schizophrenia in adolescents: in a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13-17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74% of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

Irritability associated with autistic disorder in paediatric patients (see section 4.2): aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Weight gain:

In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included

314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N= 18, or 13% of evaluable patients), compared to olanzapine (N= 45, or 33% of evaluable patients).

Lipid parameters:

In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL.

-Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (\geq 6.22 mmol/l) was 2.5% for aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo.

-Fasting triglycerides: incidence of changes in levels from normal (<1.69 mmol/l) to high (\geq 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for placebo and mean change from baseline was -0.11 mmol/l (95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo.

-HDL: incidence of changes in levels from normal (\geq 1.04 mmol/l) to low (<1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l (95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo.

-Fasting LDL: incidence of changes in levels from normal (<2.59 mmol/l) to high (\geq 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo.

Manic episodes in Bipolar I Disorder:

In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomization, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores \leq 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania).

In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer.

Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate.

The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16% in aripiprazole + lithium and 18% in aripiprazole + valproate compared to 45% in placebo + lithium and 19% in placebo + valproate.

5.2 Pharmacokinetic properties

Aripiprazole orodispersible tablet is bioequivalent to aripiprazole tablets, with a similar rate and extent of absorption. Aripiprazole orodispersible tablets may be used as an alternative to aripiprazole tablets.

Absorption:

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:

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.

Metabolism:

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. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination:

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

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

Paediatric population:

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 13 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Elderly:

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:

There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:

A single-dose study in 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

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

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 (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (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 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 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 (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 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 effects 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 subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 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

Calcium silicate
Croscarmellose sodium
Crospovidone
Silicon dioxide
Xylitol
Microcrystalline cellulose
Aspartame (E951)
Acesulfame potassium
Vanilla flavour (including vanillin and ethyl vanillin)
Tartaric acid
Magnesium stearate

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Carton of 14 x 1 tablets in cold-formed aluminium perforated unit dose blisters.
Carton of 28 x 1 tablets in cold-formed aluminium perforated unit dose blisters.
Carton of 49 x 1 tablets in cold-formed aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/024-026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 June 2004
Date of latest renewal: 4 June 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 15 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 15 mg of aripiprazole.

Excipient: 3 mg aspartame (E951) per orodispersible tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Round and yellow, marked with "A" over "641" on one side and "15" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

4.2 Posology and method of administration

Posology

Adults:

Schizophrenia: the recommended starting dose for ABILIFY is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals.

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes: the recommended starting dose for ABILIFY is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population:

Schizophrenia in adolescents 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be

administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents although individual patients may benefit from a higher dose.

ABILIFY is not recommended for use in patients below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Elderly: the effectiveness of ABILIFY in the treatment of schizophrenia and Bipolar I Disorder in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status: according to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY orodispersible tablets are for oral use.

The orodispersible tablet should be placed in the mouth on the tongue, where it will rapidly disperse in saliva. It can be taken with or without liquid. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, disperse the tablet in water and drink the resulting suspension.

The orodispersible tablets may be used as an alternative to ABILIFY tablets for patients who have difficulty to swallow ABILIFY tablets (see also section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.

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

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

Conduction abnormalities: In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

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, dose reduction or discontinuation should be considered. 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 ABILIFY, must be discontinued.

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.

Elderly patients with dementia-related psychosis:

Increased mortality: in three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in 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.

Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions

compared with 0.6% of placebo-treated patients in these trials. 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. ABILIFY is not indicated for the treatment of 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 agents, including ABILIFY. 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 ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, 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.

Hypersensitivity: as with other medicinal products, hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ABILIFY. 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 5.1).

Dysphagia: oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including ABILIFY. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Phenylketonurics: ABILIFY orodispersible tablets contain aspartame, a source of phenylalanine which may be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1 -adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken 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:

A gastric acid blocker, the H₂ antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

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

In a clinical trial in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active

metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent 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.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with ABILIFY, modest increases in aripiprazole concentrations might be expected.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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 aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

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

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses 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, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Fertility, pregnancy and lactation

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 should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. 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.

Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions in placebo-controlled trials are akathisia and nausea each occurring in more than 3% of patients treated with oral aripiprazole.

The following adverse reactions occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse reactions (*):

The frequency listed below is defined using the following convention: common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

<p>Psychiatric disorders <i>Common:</i> restlessness, insomnia, anxiety <i>Uncommon:</i> depression*</p>
<p>Nervous system disorders <i>Common:</i> extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache</p>
<p>Eye disorders <i>Common:</i> blurred vision</p>
<p>Cardiac disorders <i>Uncommon:</i> tachycardia*</p>
<p>Vascular disorders <i>Uncommon:</i> orthostatic hypotension*</p>
<p>Gastrointestinal disorders <i>Common:</i> dyspepsia, vomiting, nausea, constipation, salivary hypersecretion</p>
<p>General disorders and administration site conditions <i>Common:</i> fatigue</p>

Extrapyramidal symptoms (EPS): *Schizophrenia* - in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%). In a long term 26-week placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8% for aripiprazole-treated patients and 15.1% for olanzapine-treated patients. *Manic episodes in Bipolar I Disorder* - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium. In the long term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1% with aripiprazole and 3.2% with placebo. In schizophrenia patients the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

Dystonia: *Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at

low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5% of aripiprazole treated patients as compared to 2.0% of patients who received placebo.

Other findings:

Adverse reactions known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse reactions and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Paediatric population:

In a short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and type of undesirable effects were similar to those in adults except for the following events that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo): somnolence/sedation and extrapyramidal disorder were reported very commonly ($\geq 1/10$), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly ($\geq 1/100$, $< 1/10$).

The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 29.5% and 48.3%, respectively.

Post-Marketing:

The following adverse reactions have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:	leukopenia, neutropenia, thrombocytopenia
Immune system disorders:	allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders:	hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma
Metabolism and nutrition disorders:	weight gain, weight decreased, anorexia, hyponatremia
Psychiatric disorders:	agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)
Nervous system disorders:	speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion
Cardiac disorders:	QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia
Vascular disorders:	syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)

Respiratory, thoracic and mediastinal disorders:	oropharyngeal spasm, laryngospasm, aspiration pneumonia
Gastrointestinal disorders:	pancreatitis, dysphagia, abdominal discomfort, stomach discomfort, diarrhoea
Hepato-biliary disorders:	jaundice, hepatitis, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST), increased Gamma Glutamyl Transferase (GGT), increased alkaline phosphatase
Skin and subcutaneous tissue disorders:	rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders:	rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders:	urinary incontinence, urinary retention
Reproductive system and breast disorders:	priapism
General disorders and administration site conditions:	temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema
Investigations:	increased Creatine Phosphokinase, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased

4.9 Overdose

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 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 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.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

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: other antipsychotics, ATC code: N05AX12

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole 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:

Schizophrenia in adults:

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Paediatric population:

Schizophrenia in adolescents: in a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13-17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74% of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

Irritability associated with autistic disorder in paediatric patients (see section 4.2): aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Weight gain:

In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included

314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N= 18, or 13% of evaluable patients), compared to olanzapine (N= 45, or 33% of evaluable patients).

Lipid parameters:

In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL.

-Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (\geq 6.22 mmol/l) was 2.5% for aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo.

-Fasting triglycerides: incidence of changes in levels from normal (<1.69 mmol/l) to high (\geq 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for placebo and mean change from baseline was -0.11 mmol/l (95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo.

-HDL: incidence of changes in levels from normal (\geq 1.04 mmol/l) to low (<1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l (95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo.

-Fasting LDL: incidence of changes in levels from normal (<2.59 mmol/l) to high (\geq 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo.

Manic episodes in Bipolar I Disorder:

In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomization, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores \leq 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania).

In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer.

Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate.

The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16% in aripiprazole + lithium and 18% in aripiprazole + valproate compared to 45% in placebo + lithium and 19% in placebo + valproate.

5.2 Pharmacokinetic properties

Aripiprazole orodispersible tablet is bioequivalent to aripiprazole tablets, with a similar rate and extent of absorption. Aripiprazole orodispersible tablets may be used as an alternative to aripiprazole tablets.

Absorption:

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:

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.

Metabolism:

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. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination:

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

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

Paediatric population:

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 13 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Elderly:

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:

There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:

A single-dose study in 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

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

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 (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (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 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 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 (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 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 effects 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 subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 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

Calcium silicate
Croscarmellose sodium
Crospovidone
Silicon dioxide
Xylitol
Microcrystalline cellulose
Aspartame (E951)
Acesulfame potassium
Vanilla flavour (including vanillin and ethyl vanillin)
Tartaric acid
Magnesium stearate

Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Carton of 14 x 1 tablets in cold-formed aluminium perforated unit dose blisters.
Carton of 28 x 1 tablets in cold-formed aluminium perforated unit dose blisters.
Carton of 49 x 1 tablets in cold-formed aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/027-029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 June 2004
Date of latest renewal: 4 June 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 30 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 30 mg of aripiprazole.

Excipient: 6 mg aspartame (E951) per orodispersible tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Round and pink, marked with "A" over "643" on one side and "30" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

4.2 Posology and method of administration

Posology

Adults:

Schizophrenia: the recommended starting dose for ABILIFY is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals.

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes: the recommended starting dose for ABILIFY is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population:

Schizophrenia in adolescents 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be

administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents although individual patients may benefit from a higher dose.

ABILIFY is not recommended for use in patients below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Elderly: the effectiveness of ABILIFY in the treatment of schizophrenia and Bipolar I Disorder in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status: according to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY orodispersible tablets are for oral use.

The orodispersible tablet should be placed in the mouth on the tongue, where it will rapidly disperse in saliva. It can be taken with or without liquid. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, disperse the tablet in water and drink the resulting suspension.

The orodispersible tablets may be used as an alternative to ABILIFY tablets for patients who have difficulty to swallow ABILIFY tablets (see also section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.

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

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

Conduction abnormalities: In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

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, dose reduction or discontinuation should be considered. 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 ABILIFY, must be discontinued.

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.

Elderly patients with dementia-related psychosis:

Increased mortality: in three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in 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.

Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions

compared with 0.6% of placebo-treated patients in these trials. 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. ABILIFY is not indicated for the treatment of 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 agents, including ABILIFY. 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 ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, 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.

Hypersensitivity: as with other medicinal products, hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ABILIFY. 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 5.1).

Dysphagia: oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including ABILIFY. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Phenylketonurics: ABILIFY orodispersible tablets contain aspartame, a source of phenylalanine which may be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1 -adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken 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:

A gastric acid blocker, the H₂ antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

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

In a clinical trial in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active

metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent 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.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with ABILIFY, modest increases in aripiprazole concentrations might be expected.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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 aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

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

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses 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, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Fertility, pregnancy and lactation

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 should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. 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.

Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions in placebo-controlled trials are akathisia and nausea each occurring in more than 3% of patients treated with oral aripiprazole.

The following adverse reactions occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse reactions (*):

The frequency listed below is defined using the following convention: common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

<p>Psychiatric disorders <i>Common:</i> restlessness, insomnia, anxiety <i>Uncommon:</i> depression*</p>
<p>Nervous system disorders <i>Common:</i> extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache</p>
<p>Eye disorders <i>Common:</i> blurred vision</p>
<p>Cardiac disorders <i>Uncommon:</i> tachycardia*</p>
<p>Vascular disorders <i>Uncommon:</i> orthostatic hypotension*</p>
<p>Gastrointestinal disorders <i>Common:</i> dyspepsia, vomiting, nausea, constipation, salivary hypersecretion</p>
<p>General disorders and administration site conditions <i>Common:</i> fatigue</p>

Extrapyramidal symptoms (EPS): *Schizophrenia* - in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%). In a long term 26-week placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8% for aripiprazole-treated patients and 15.1% for olanzapine-treated patients. *Manic episodes in Bipolar I Disorder* - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium. In the long term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1% with aripiprazole and 3.2% with placebo. In schizophrenia patients the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

Dystonia: *Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at

low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5% of aripiprazole treated patients as compared to 2.0% of patients who received placebo.

Other findings:

Adverse reactions known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse reactions and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Paediatric population:

In a short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and type of undesirable effects were similar to those in adults except for the following events that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo): somnolence/sedation and extrapyramidal disorder were reported very commonly ($\geq 1/10$), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly ($\geq 1/100$, $< 1/10$).

The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 29.5% and 48.3%, respectively.

Post-Marketing:

The following adverse reactions have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:	leukopenia, neutropenia, thrombocytopenia
Immune system disorders:	allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders:	hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma
Metabolism and nutrition disorders:	weight gain, weight decreased, anorexia, hyponatremia
Psychiatric disorders:	agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)
Nervous system disorders:	speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion
Cardiac disorders:	QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia
Vascular disorders:	syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)

Respiratory, thoracic and mediastinal disorders:	oropharyngeal spasm, laryngospasm, aspiration pneumonia
Gastrointestinal disorders:	pancreatitis, dysphagia, abdominal discomfort, stomach discomfort, diarrhoea
Hepato-biliary disorders:	jaundice, hepatitis, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST), increased Gamma Glutamyl Transferase (GGT), increased alkaline phosphatase
Skin and subcutaneous tissue disorders:	rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders:	rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders:	urinary incontinence, urinary retention
Reproductive system and breast disorders:	priapism
General disorders and administration site conditions:	temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema
Investigations:	increased Creatine Phosphokinase, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased

4.9 Overdose

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 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 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.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

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: other antipsychotics, ATC code: N05AX12

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole 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:

Schizophrenia in adults:

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Paediatric population:

Schizophrenia in adolescents: in a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13-17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74% of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

Irritability associated with autistic disorder in paediatric patients (see section 4.2): aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was 27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Weight gain:

In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included

314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N= 18, or 13% of evaluable patients), compared to olanzapine (N= 45, or 33% of evaluable patients).

Lipid parameters:

In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL.

-Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (\geq 6.22 mmol/l) was 2.5% for aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo.

-Fasting triglycerides: incidence of changes in levels from normal (<1.69 mmol/l) to high (\geq 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for placebo and mean change from baseline was -0.11 mmol/l (95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo.

-HDL: incidence of changes in levels from normal (\geq 1.04 mmol/l) to low (<1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l (95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo.

-Fasting LDL: incidence of changes in levels from normal (<2.59 mmol/l) to high (\geq 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo.

Manic episodes in Bipolar I Disorder:

In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomization, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores \leq 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania).

In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer.

Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate.

The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16% in aripiprazole + lithium and 18% in aripiprazole + valproate compared to 45% in placebo + lithium and 19% in placebo + valproate.

5.2 Pharmacokinetic properties

Aripiprazole orodispersible tablet is bioequivalent to aripiprazole tablets, with a similar rate and extent of absorption. Aripiprazole orodispersible tablets may be used as an alternative to aripiprazole tablets.

Absorption:

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:

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.

Metabolism:

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. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination:

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

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

Paediatric population:

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 13 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Elderly:

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:

There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:

A single-dose study in 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

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

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 (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (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 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 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 (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 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 effects 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 subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 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

Calcium silicate
Croscarmellose sodium
Crospovidone
Silicon dioxide
Xylitol
Microcrystalline cellulose
Aspartame (E951)
Acesulfame potassium
Vanilla flavour (including vanillin and ethyl vanillin)
Tartaric acid
Magnesium stearate

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Carton of 14 x 1 tablets in cold-formed aluminium perforated unit dose blisters.
Carton of 28 x 1 tablets in cold-formed aluminium perforated unit dose blisters.
Carton of 49 x 1 tablets in cold-formed aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/030-032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 June 2004
Date of latest renewal: 4 June 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 1 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 1 mg of aripiprazole.

Excipients: 200 mg fructose per ml
400 mg sucrose per ml
1.8 mg methyl parahydroxybenzoate (E218) per ml
0.2 mg propyl parahydroxybenzoate (E216) per ml

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution
Clear, colourless to light yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

4.2 Posology and method of administration

Posology

Adults:

Schizophrenia: the recommended starting dose for ABILIFY is 10 or 15 mg/day (i.e. 10 or 15 ml solution/day) with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals. A calibrated measuring cup and a 2 ml calibrated dropper are included in the carton.

ABILIFY is effective in a dose range of 10 to 30 mg/day (i.e. 10 to 30 ml solution/day). Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes: the recommended starting dose for ABILIFY is 15 mg (i.e. 15 ml solution/day) administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg (i.e. 30 ml solution/day).

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population:

Schizophrenia in adolescents 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).

ABILIFY is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated in adolescents although individual patients may benefit from a higher dose.

ABILIFY is not recommended for use in patients below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Elderly: the effectiveness of ABILIFY in the treatment of schizophrenia and Bipolar I Disorder in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see sections 4.4 and 5.2).

Smoking status: according to the metabolic pathway of ABILIFY no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY oral solution is for oral use.

ABILIFY oral solution may be used as an alternative to ABILIFY tablets for patients who have difficulty swallowing ABILIFY tablets (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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.

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.

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

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

Conduction abnormalities: In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

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, dose reduction or discontinuation should be considered. 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 ABILIFY, must be discontinued.

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.

Elderly patients with dementia-related psychosis:

Increased mortality: in three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in 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.

Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions

compared with 0.6% of placebo-treated patients in these trials. 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. ABILIFY is not indicated for the treatment of 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 agents, including ABILIFY. 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 ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, 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.

Hypersensitivity: as with other medicinal products, hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ABILIFY. 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 5.1).

Dysphagia: oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including ABILIFY. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Intolerance:

The oral solution contains fructose. Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

The oral solution contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

The oral solution contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take the oral solution.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1 -adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken 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:

A gastric acid blocker, the H2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

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

In a clinical trial in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent 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.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with ABILIFY, modest increases in aripiprazole concentrations might be expected.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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 aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

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

Potential for ABILIFY to affect other medicinal products:

In clinical studies, 10-30 mg/day doses 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, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Fertility, pregnancy and lactation

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 should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. 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.

Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions in placebo-controlled trials are akathisia and nausea each occurring in more than 3% of patients treated with oral aripiprazole.

The following adverse reactions occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse reactions (*):

The frequency listed below is defined using the following convention: common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

Psychiatric disorders <i>Common:</i> restlessness, insomnia, anxiety <i>Uncommon:</i> depression*
Nervous system disorders <i>Common:</i> extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache
Eye disorders <i>Common:</i> blurred vision
Cardiac disorders <i>Uncommon:</i> tachycardia*
Vascular disorders <i>Uncommon:</i> orthostatic hypotension*
Gastrointestinal disorders <i>Common:</i> dyspepsia, vomiting, nausea, constipation, salivary hypersecretion
General disorders and administration site conditions <i>Common:</i> fatigue

Extrapyramidal symptoms (EPS): *Schizophrenia* - in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%). In a long term 26-week placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8% for aripiprazole-treated patients and 15.1% for olanzapine-treated patients. *Manic episodes in Bipolar I Disorder* - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium. In the long term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1% with aripiprazole and 3.2% with placebo. In schizophrenia patients the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

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

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5% of aripiprazole treated patients as compared to 2.0% of patients who received placebo.

Other findings:

Adverse reactions known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse reactions and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Paediatric population:

In a short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and type of undesirable effects were similar to those in adults except for the following events that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo): somnolence/sedation and extrapyramidal disorder were reported very commonly ($\geq 1/10$), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly ($\geq 1/100$, $< 1/10$).

The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (< 3 ng/ml) and males (< 2 ng/ml) was 29.5% and 48.3%, respectively.

Post-Marketing:

The following adverse reactions have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:	leukopenia, neutropenia, thrombocytopenia
Immune system disorders:	allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders:	hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma
Metabolism and nutrition disorders:	weight gain, weight decreased, anorexia, hyponatremia
Psychiatric disorders:	agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)
Nervous system disorders:	speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion
Cardiac disorders:	QT prolongation, ventricular arrhythmias, sudden unexplained

	death, cardiac arrest, torsades de pointes, bradycardia
Vascular disorders:	syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders:	oropharyngeal spasm, laryngospasm, aspiration pneumonia
Gastrointestinal disorders:	pancreatitis, dysphagia, abdominal discomfort, stomach discomfort, diarrhoea
Hepato-biliary disorders:	jaundice, hepatitis, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST), increased Gamma Glutamyl Transferase (GGT), increased alkaline phosphatase
Skin and subcutaneous tissue disorders:	rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders:	rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders:	urinary incontinence, urinary retention
Reproductive system and breast disorders:	priapism
General disorders and administration site conditions:	temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema
Investigations:	increased Creatine Phosphokinase, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased

4.9 Overdose

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 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 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.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

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: other antipsychotics, ATC code: N05AX12

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole 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:

Schizophrenia in adults:

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on aripiprazole (43%) than for haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34% in aripiprazole group and 57% in placebo.

Paediatric population:

Schizophrenia in adolescents: in a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13-17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74% of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

Irritability associated with autistic disorder in paediatric patients (see section 4.2): aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2-15 mg/day) and one fixed-dose (5, 10, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75% of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) in aripiprazole-treated patients was

27/46 (58.7%) and 258/298 (86.6%), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Weight gain:

In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (N = 18, or 13% of evaluable patients), compared to olanzapine (N = 45, or 33% of evaluable patients).

Lipid parameters:

In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL.

-Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (\geq 6.22 mmol/l) was 2.5% for aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo.

-Fasting triglycerides: incidence of changes in levels from normal (<1.69 mmol/l) to high (\geq 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for placebo and mean change from baseline was -0.11 mmol/l (95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo.

-HDL: incidence of changes in levels from normal (\geq 1.04 mmol/l) to low (<1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l (95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo.

-Fasting LDL: incidence of changes in levels from normal (<2.59 mmol/l) to high (\geq 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo.

Manic episodes in Bipolar I Disorder:

In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomization, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores \leq 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive

aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania).

In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer.

Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate.

The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16% in aripiprazole + lithium and 18% in aripiprazole + valproate compared to 45% in placebo + lithium and 19% in placebo + valproate.

5.2 Pharmacokinetic properties

Absorption:

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:

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.

Metabolism:

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. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination:

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

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.

Oral Solution:

Aripiprazole is well absorbed when administered orally as the solution. At equivalent doses, the peak plasma concentrations of aripiprazole (C_{max}) from the solution were somewhat higher but the systemic exposure (AUC) was equivalent to tablets. In a relative bioavailability study comparing the pharmacokinetics of 30 mg aripiprazole as the oral solution to 30 mg aripiprazole tablets in healthy subjects, the solution to the tablet ratio of geometric mean C_{max} values was 122% (N = 30). The single-dose pharmacokinetics of aripiprazole were linear and dose-proportional.

Pharmacokinetics in special patient groups

Paediatric population:

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 13 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Elderly:

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:

There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:

A single-dose study in 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

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

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 (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (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 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 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 (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 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 effects 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 subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 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

Disodium edetate
Fructose
Glycerin
Lactic acid
Methyl parahydroxybenzoate (E218)
Propylene glycol
Propyl parahydroxybenzoate (E216)
Sodium hydroxide
Sucrose
Purified water

Natural orange cream with other natural flavours

6.2 Incompatibilities

The oral solution should not be diluted with other liquids or mixed with any food prior to administration.

6.3 Shelf life

3 years
After first opening: 6 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PET-bottles with polypropylene child-resistant closure containing 50, 150 or 480 ml per bottle. Each carton contains 1 bottle and both a calibrated polypropylene measuring cup and a calibrated polypropylene low-density polyethylene dropper.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/033-035

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 June 2004

Date of latest renewal: 4 June 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 7.5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 7.5 mg of aripiprazole.

Each vial contains 9.75 mg aripiprazole.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY solution for injection is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate.

Treatment with aripiprazole solution for injection should be discontinued as soon as clinically appropriate and the use of oral aripiprazole should be initiated.

4.2 Posology and method of administration

Posology

The recommended initial dose for aripiprazole solution for injection is 9.75 mg (1.3 ml), administered as a single intramuscular injection. The effective dose range of aripiprazole solution for injection is 5.25-15 mg as a single injection. A lower dose of 5.25 mg (0.7 ml) may be given, on the basis of individual clinical status, which should also include consideration of medicinal products already administered either for maintenance or acute treatment (see section 4.5). A second injection may be administered 2 hours after the first injection, on the basis of individual clinical status and no more than three injections should be given in any 24-hour period.

The maximum daily dose of aripiprazole is 30 mg (including all formulations of aripiprazole).

If continued treatment is indicated with oral aripiprazole, see the Summary of Product Characteristics for ABILIFY tablets, ABILIFY orodispersible tablets, or ABILIFY oral solution.

Paediatric population: there is no experience in children and adolescents under 18 years of age.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Elderly: the effectiveness of ABILIFY solution for injection in patients who are 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status: according to the metabolic pathway of ABILIFY no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY solution for injection is for intramuscular use.

To enhance absorption and minimise variability, injection into the deltoid or deep within the gluteus maximus muscle, avoiding adipose regions, is recommended.

ABILIFY solution for injection should not be administered intravenously or subcutaneously. ABILIFY solution for injection is ready to use and intended for short-term use only (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

The efficacy of aripiprazole solution for injection in patients with agitation and disturbed behaviours has not been established related to conditions other than schizophrenia and manic episodes in Bipolar I Disorder.

Simultaneous administration of injectable antipsychotics and parenteral benzodiazepine may be associated with excessive sedation and cardiorespiratory depression. If parenteral benzodiazepine therapy is deemed necessary in addition to aripiprazole solution for injection, patients should be monitored for excessive sedation and for orthostatic hypotension (see section 4.5).

Patients receiving aripiprazole solution for injection should be observed for orthostatic hypotension. Blood pressure, pulse, respiratory rate and level of consciousness should be monitored regularly.

The safety and efficacy of aripiprazole solution for injection has not been evaluated in patients with alcohol or medicinal product intoxication (either with prescribed or illicit medicinal products).

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.

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no

increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.

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

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

Conduction abnormalities: In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

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, dose reduction or discontinuation should be considered. 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 ABILIFY, must be discontinued.

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.

Elderly patients with dementia-related psychosis:

Increased mortality: in three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in 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.

Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6% of placebo-treated patients in these trials. 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.

ABILIFY is not indicated for the treatment of 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 agents, including ABILIFY. 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 ABILIFY and with other atypical antipsychotic agents are not available to allow direct comparisons. Patients treated with any antipsychotic agents, including ABILIFY, 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.

Hypersensitivity: as with other medicinal products, hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ABILIFY. 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 5.1).

Dysphagia: oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including ABILIFY. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1 -adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken 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:

The administration of lorazepam solution for injection had no effect on the pharmacokinetics of aripiprazole solution for injection when administered concomitantly. However, in a single-dose, intramuscular study of aripiprazole (dose 15 mg) in healthy subjects, administered simultaneously with intramuscular lorazepam (dose 2 mg), the intensity of sedation was greater with the combination as compared to that observed with aripiprazole alone.

A gastric acid blocker, the H₂ antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant.

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

In a clinical trial in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%. ABILIFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ABILIFY with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ABILIFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY dose should be reduced to approximately one-half of its prescribed dose. Other potent 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.

Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with ABILIFY, modest increases in aripiprazole concentrations might be expected.

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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 aripiprazole alone.

ABILIFY dose should be doubled when concomitant administration of ABILIFY occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of potent CYP3A4 inducers, the dosage of ABILIFY should be reduced to the recommended dose.

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

Potential for ABILIFY to affect other medicinal products:

The administration of aripiprazole solution for injection had no effect on the pharmacokinetics of lorazepam solution for injection when administered concomitantly. However, in a single-dose, intramuscular study of aripiprazole (dose 15 mg) in healthy subjects, administered simultaneously with intramuscular lorazepam (dose 2 mg), the orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone.

In clinical studies, 10-30 mg/day doses 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, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Fertility, pregnancy and lactation

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 should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. 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.

Aripiprazole was excreted in the milk of treated rats during lactation. It is not known whether aripiprazole is excreted in human milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely (see section 4.8).

4.8 Undesirable effects

The most commonly reported adverse reactions in placebo-controlled trials are nausea, dizziness and somnolence each occurring in more than 3% of patients treated with aripiprazole solution for injection.

The following adverse reactions occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse reactions (*) in clinical trials with aripiprazole solution for injection (see section 5.1):

The frequency listed below is defined using the following convention: common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

Nervous system disorders <i>Common:</i> somnolence, dizziness, headache, akathisia
Cardiac disorders <i>Uncommon:</i> tachycardia*
Vascular disorders <i>Uncommon:</i> orthostatic hypotension*, increased diastolic blood pressure*
Gastrointestinal disorders <i>Common:</i> nausea, vomiting <i>Uncommon:</i> dry mouth*
General disorders and administration site conditions <i>Uncommon:</i> fatigue*

The following undesirable effects occurred more often ($\geq 1/100$) than placebo, or were identified as possibly medically relevant adverse reactions (*) in clinical trials with oral formulations of aripiprazole (see section 5.1):

Psychiatric disorders <i>Common:</i> restlessness, insomnia, anxiety <i>Uncommon:</i> depression*
Nervous system disorders <i>Common:</i> extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache
Eye disorders <i>Common:</i> blurred vision
Cardiac disorders <i>Uncommon:</i> tachycardia*
Vascular disorders <i>Uncommon:</i> orthostatic hypotension*
Gastrointestinal disorders <i>Common:</i> dyspepsia, vomiting, nausea, constipation, salivary hypersecretion
General disorders and administration site conditions <i>Common:</i> fatigue

Extrapyramidal symptoms (EPS): *Schizophrenia* - in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%). In a long term 26-week placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8% for aripiprazole-treated patients and 15.1% for olanzapine-treated patients. *Manic episodes in Bipolar I Disorder* - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium. In the long term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1% with aripiprazole and 3.2% with placebo. In schizophrenia patients the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

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

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5% of aripiprazole treated patients as compared to 2.0% of patients who received placebo.

Other findings:

Adverse reactions known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse reactions and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus (see section 4.4).

Paediatric population:

In a short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and type of undesirable effects were similar to those in adults except for the following events that were reported more frequently in adolescents receiving oral aripiprazole than in adults receiving oral aripiprazole (and more frequently than placebo): somnolence/sedation and extrapyramidal disorder were reported very commonly ($\geq 1/10$), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly ($\geq 1/100$, $< 1/10$).

The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 29.5% and 48.3%, respectively.

Post-Marketing:

The following adverse reactions have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders: leukopenia, neutropenia, thrombocytopenia

Immune system disorders: allergic reaction (e.g. anaphylactic reaction, angioedema including

	swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders:	hyperglycaemia, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma
Metabolism and nutrition disorders:	weight gain, weight decreased, anorexia, hyponatremia
Psychiatric disorders:	agitation, nervousness; suicide attempt, suicidal ideation, and completed suicide (see section 4.4)
Nervous system disorders:	speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion
Cardiac disorders:	QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest, torsades de pointes, bradycardia
Vascular disorders:	syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal disorders:	oropharyngeal spasm, laryngospasm, aspiration pneumonia
Gastrointestinal disorders:	pancreatitis, dysphagia, abdominal discomfort, stomach discomfort, diarrhoea
Hepato-biliary disorders:	jaundice, hepatitis, increased Alanine Aminotransferase (ALT), increased Aspartate Aminotransferase (AST), increased Gamma Glutamyl Transferase (GGT), increased alkaline phosphatase
Skin and subcutaneous tissue disorders:	rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders:	rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders:	urinary incontinence, urinary retention
Reproductive system and breast disorders:	priapism
General disorders and administration site conditions:	temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain, peripheral oedema
Investigations:	increased Creatine Phosphokinase, blood glucose increased, blood glucose fluctuation, glycosylated haemoglobin increased

4.9 Overdose

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 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 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.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

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: other antipsychotics, ATC code: N05AX12

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole 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:

Agitation in schizophrenia and Bipolar I Disorder in adults with aripiprazole solution for injection: In two short-term (24-hour) placebo-controlled trials involving 554 schizophrenic adult patients presenting with agitation and disturbed behaviours, aripiprazole solution for injection was associated with statistically significant greater improvements in agitation/behavioural symptoms compared to placebo and was similar to haloperidol. In one short-term (24-hour) placebo-controlled trial involving 291 patients with bipolar disorder presenting with agitation and disturbed behaviours, aripiprazole solution for injection was associated with statistically significant greater improvements in agitation/behavioural symptoms compared to placebo and was similar to the reference arm lorazepam. The observed mean improvement from baseline on the PANSS Excitement Component score at the primary 2-hour endpoint was 5.8 for placebo, 9.6 for lorazepam, and 8.7 for aripiprazole. In subpopulation analyses on patients with mixed episodes or on patients with severe agitation, a similar pattern of efficacy to the overall population was observed but statistical significance could not be established due to a reduced sample size.

Schizophrenia in adults with oral aripiprazole:

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, oral aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

ABILIFY is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (oral aripiprazole 77% and haloperidol 73%). The overall completion rate was significantly higher for patients on oral aripiprazole (43%) than for oral haloperidol (30%). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in stabilised patients with chronic schizophrenia, oral aripiprazole had significantly greater reduction in relapse rate, 34% in oral aripiprazole group and 57% in placebo.

Paediatric population:

Schizophrenia in adolescents with oral aripiprazole: in a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13-17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74% of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

Weight gain:

In clinical trials oral aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 patients and where the primary end-point was weight gain, significantly less patients had at least 7% weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on oral aripiprazole (N= 18, or 13% of evaluable patients), compared to oral olanzapine (N= 45, or 33% of evaluable patients).

Lipid parameters:

In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL.

-Total cholesterol: incidence of changes in levels from normal (<5.18 mmol/l) to high (\geq 6.22 mmol/l) was 2.5% for aripiprazole and 2.8% for placebo and mean change from baseline was -0.15 mmol/l (95% CI: -0.182, -0.115) for aripiprazole and -0.11 mmol/l (95% CI: -0.148, -0.066) for placebo.

-Fasting triglycerides: incidence of changes in levels from normal (<1.69 mmol/l) to high (\geq 2.26 mmol/l) was 7.4% for aripiprazole and 7.0% for placebo and mean change from baseline was -0.11 mmol/l

(95% CI: -0.182, -0.046) for aripiprazole and -0.07 mmol/l (95% CI: -0.148, 0.007) for placebo.

-HDL: incidence of changes in levels from normal (\geq 1.04 mmol/l) to low (<1.04 mmol/l) was 11.4% for aripiprazole and 12.5% for placebo and mean change from baseline was -0.03 mmol/l

(95% CI: -0.046, -0.017) for aripiprazole and -0.04 mmol/l (95% CI: -0.056, -0.022) for placebo.

-Fasting LDL: incidence of changes in levels from normal (<2.59 mmol/l) to high (\geq 4.14 mmol/l) was 0.6% for aripiprazole and 0.7% for placebo and mean change from baseline was -0.09 mmol/l (95% CI: -0.139, -0.047) for aripiprazole and -0.06 mmol/l (95% CI: -0.116, -0.012) for placebo.

Manic episodes in Bipolar I Disorder with oral aripiprazole:

In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at

week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomization, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores ≤ 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania).

In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer.

Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate.

The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16% in aripiprazole + lithium and 18% in aripiprazole + valproate compared to 45% in placebo + lithium and 19% in placebo + valproate.

5.2 Pharmacokinetic properties

Absorption:

Aripiprazole solution for injection administered intramuscularly as a single-dose to healthy subjects is well absorbed and has an absolute bioavailability of 100%. The aripiprazole AUC in the first 2 hours after an intramuscular injection was 90% greater than the AUC after the same dose as a tablet; systemic exposure was generally similar between the 2 formulations. In 2 studies in healthy subjects the median times to the peak plasma concentrations were 1 and 3 hours after dosing.

Distribution:

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.

Metabolism:

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. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination:

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

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

Paediatric population:

The pharmacokinetics of oral aripiprazole and dehydro-aripiprazole in paediatric patients 13 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Elderly:

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender:

There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race:

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal Disease:

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic Disease:

A single-dose study in 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

Administration of aripiprazole solution for injection was well tolerated and produced no direct target organ toxicity in rats or monkeys after repeated dosing at systemic exposures (AUC) that were 15 and 5 times, respectively, human exposure at the maximum recommended human dose of 30 mg intramuscular. In intravenous reproductive toxicity studies, no new safety concerns were observed at maternal exposures up to 15 (rat) and 29 (rabbit) times human exposure at 30 mg.

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

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 (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (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 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The

highest nontumorigenic exposure in female rats was 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 (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 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 effects 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 subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 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

Sulfobutylether β -cyclodextrin (SBECD)
Tartaric acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months
After opening: use product immediately.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Each carton contains one single-use type I glass vial with a rubber butyl stopper and a "flip-off" aluminium seal.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4 June 2004
Date of latest renewal: 4 June 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

ANNEX II

- A MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR BATCH RELEASE**
- B CONDITIONS OF THE MARKETING AUTHORISATION**

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bristol-Myers Squibb Srl
Contrada Fontana Del Ceraso
I-03012 Anagni-Frosinone
Italy

B CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

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

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 6.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs

Otsuka Pharmaceutical Europe Ltd commits to provide a PSUR at 6 monthly intervals unless otherwise decided by the CHMP.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 5 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 5 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 tablets
28 x 1 tablets
49 x 1 tablets
56 x 1 tablets
98 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/001 14 x 1 tablets
EU/1/04/276/002 28 x 1 tablets
EU/1/04/276/003 49 x 1 tablets
EU/1/04/276/004 56 x 1 tablets
EU/1/04/276/005 98 x 1 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ABILIFY 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 5 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 10 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 tablets
28 x 1 tablets
49 x 1 tablets
56 x 1 tablets
98 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/006 14 x 1 tablets
EU/1/04/276/007 28 x 1 tablets
EU/1/04/276/008 49 x 1 tablets
EU/1/04/276/009 56 x 1 tablets
EU/1/04/276/010 98 x 1 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ABILIFY 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 15 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 15 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 tablets
28 x 1 tablets
49 x 1 tablets
56 x 1 tablets
98 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/011 14 x 1 tablets
EU/1/04/276/012 28 x 1 tablets
EU/1/04/276/013 49 x 1 tablets
EU/1/04/276/014 56 x 1 tablets
EU/1/04/276/015 98 x 1 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ABILIFY 15 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 15 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 30 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 30 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 tablets
28 x 1 tablets
49 x 1 tablets
56 x 1 tablets
98 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/016 14 x 1 tablets
EU/1/04/276/017 28 x 1 tablets
EU/1/04/276/018 49 x 1 tablets
EU/1/04/276/019 56 x 1 tablets
EU/1/04/276/020 98 x 1 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ABILIFY 30 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 30 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg orodispersible tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 10 mg of aripiprazole.

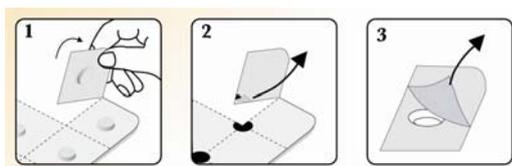
3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 orodispersible tablets
28 x 1 orodispersible tablets
49 x 1 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.



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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains aspartame. See leaflet for further information.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/024 14 x 1 orodispersible tablets
EU/1/04/276/025 28 x 1 orodispersible tablets
EU/1/04/276/026 49 x 1 orodispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

ABILIFY 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg orodispersible tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 15 mg orodispersible tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 15 mg of aripiprazole.

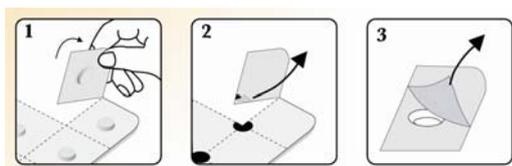
3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 orodispersible tablets
28 x 1 orodispersible tablets
49 x 1 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.



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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains aspartame. See leaflet for further information.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/027 14 x 1 orodispersible tablets
EU/1/04/276/028 28 x 1 orodispersible tablets
EU/1/04/276/029 49 x 1 orodispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ABILIFY 15 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 15 mg orodispersible tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 30 mg orodispersible tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 30 mg of aripiprazole.

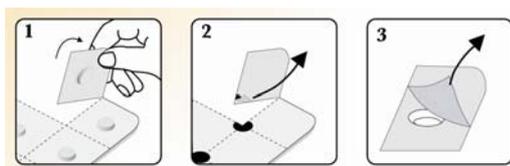
3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 orodispersible tablets
28 x 1 orodispersible tablets
49 x 1 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.



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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Contains aspartame. See leaflet for further information.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/030 14 x 1 orodispersible tablets
EU/1/04/276/031 28 x 1 orodispersible tablets
EU/1/04/276/032 49 x 1 orodispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

ABILIFY 30 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 30 mg orodispersible tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 1 mg/ml oral solution
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE

Each ml contains 1 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains fructose, sucrose, E218, and E216.

4. PHARMACEUTICAL FORM AND CONTENTS

50 ml oral solution
150 ml oral solution
480 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 6 months after first opening.

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Outer carton:

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/033 - 50 ml bottle
EU/1/04/276/034 - 150 ml bottle
EU/1/04/276/035 - 480 ml bottle

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: ABILIFY 1 mg/ml

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 7.5 mg/ml solution for injection
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 7.5 mg of aripiprazole. A vial provides 9.75 mg in 1.3 ml

3. LIST OF EXCIPIENTS

Also contains sulfobutylether b-cyclodextrin, tartaric acid, sodium hydroxide, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial
9.75 mg / 1.3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/036

13. MANUFACTURER'S 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 LABEL

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

ABILIFY 7.5 mg/ml solution for injection
aripiprazole
IM use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

9.75 mg / 1.3ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

ABILIFY 5 mg tablets aripiprazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What ABILIFY is and what it is used for
2. Before you take ABILIFY
3. How to take ABILIFY
4. Possible side effects
5. How to store ABILIFY
6. Further information

1. WHAT ABILIFY IS AND WHAT IT IS USED FOR

ABILIFY is one of a group of medicines called antipsychotics.

It is used to treat adults and adolescents 15 years and older who suffer from a disease characterised by 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 is used to treat adults who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. BEFORE YOU TAKE ABILIFY

Do not take ABILIFY

- if you are allergic (hypersensitive) to aripiprazole or any of the other ingredients of ABILIFY.

Take special care with ABILIFY

Before treatment with ABILIFY, 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
- Seizure
- Involuntary, irregular muscle movements, especially in the face
- Cardiovascular diseases, 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

If you notice you are gaining weight, experience any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat.

Children and adolescents

ABILIFY is not for use in children and adolescents under 15 years. Ask your doctor or pharmacist for advice before taking ABILIFY.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY 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.

Taking ABILIFY with some medicines may need to change your dose of ABILIFY. It is especially important to mention the following to your doctor:

- Medicines to correct heart rhythm
- Antidepressants or herbal remedy used to treat depression and anxiety
- Antifungal agents
- Certain medicines to treat HIV infection
- Anticonvulsants used to treat epilepsy

Taking ABILIFY with food and drink

ABILIFY can be taken regardless of meals.

Alcohol should be avoided when taking ABILIFY.

Pregnancy and breast-feeding

You should not take ABILIFY 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.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY, you should not breast-feed.

Driving and using machines

Do not drive or use any tools or machines, until you know how ABILIFY affects you.

Important information about some of the ingredients of ABILIFY

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE ABILIFY

Always take ABILIFY exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults:

- **The usual dose for adults is 15 mg once a day.** However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children:

- For **adolescents 15 years and older**, ABILIFY may be started at a low dose with the oral solution (liquid) form. The dose may be gradually increased to the usual dose for adolescents of 10 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take the ABILIFY tablet at the same time each day. It does not matter whether you take it with or without food. Always take the tablet with water and swallow it whole.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should

If you realise you have taken more ABILIFY tablets than your doctor has recommended (or if someone else has taken some of your ABILIFY tablets), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

If you forget to take ABILIFY

If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

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

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:

very common:	affects more than 1 user in 10
common:	affects 1 to 10 users in 100
uncommon:	affects 1 to 10 users in 1,000
rare:	affects 1 to 10 users in 10,000
very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Common side effects: uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects: some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate. Some people may feel depressed.

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

Changes in the levels of some blood cells; unusual heart beat, sudden unexplained death, heart attack; allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious; thoughts of suicide, suicide attempt and suicide; speech disorder, seizure, combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and

heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately); spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values, abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness; involuntary loss of urine, 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.

Adolescents 15 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness and uncontrollable twitching or jerking movements were very common (greater than 1 in 10 patients) and dry mouth, increased appetite, and feeling dizzy, especially when getting up from a lying or sitting position, were common.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, **please tell your doctor or pharmacist.**

5. HOW TO STORE ABILIFY

Keep out of the reach and sight of children.

Do not use ABILIFY after the expiry date which is stated on the blister and on the carton.

Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ABILIFY contains

- The active substance is aripiprazole. Each tablet contains 5 mg of aripiprazole.
- The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, indigo carmine aluminium lake (E132).

What ABILIFY looks like and contents of the pack

ABILIFY 5 mg tablets are rectangular and blue, marked with 'A-007' and '5' on one side. They are supplied in perforated unit dose blisters packed in cartons containing 14, 28, 49, 56, or 98 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

Manufacturer

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
I-03012 Anagni-Frosinone - Italy

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

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This leaflet was last approved in

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

<http://www.ema.europa.eu/>

PACKAGE LEAFLET: INFORMATION FOR THE USER

ABILIFY 10 mg tablets aripiprazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What ABILIFY is and what it is used for
2. Before you take ABILIFY
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1. WHAT ABILIFY IS AND WHAT IT IS USED FOR

ABILIFY is one of a group of medicines called antipsychotics.

It is used to treat adults and adolescents 15 years and older who suffer from a disease characterised by 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 is used to treat adults who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. BEFORE YOU TAKE ABILIFY

Do not take ABILIFY

- if you are allergic (hypersensitive) to aripiprazole or any of the other ingredients of ABILIFY.

Take special care with ABILIFY

Before treatment with ABILIFY, 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
- Seizure
- Involuntary, irregular muscle movements, especially in the face
- Cardiovascular diseases, 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

If you notice you are gaining weight, experience any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat.

Children and adolescents

ABILIFY is not for use in children and adolescents under 15 years. Ask your doctor or pharmacist for advice before taking ABILIFY.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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- Medicines to correct heart rhythm
- Antidepressants or herbal remedy used to treat depression and anxiety
- Antifungal agents
- Certain medicines to treat HIV infection
- Anticonvulsants used to treat epilepsy

Taking ABILIFY with food and drink

ABILIFY can be taken regardless of meals.

Alcohol should be avoided when taking ABILIFY.

Pregnancy and breast-feeding

You should not take ABILIFY 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.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY, you should not breast-feed.

Driving and using machines

Do not drive or use any tools or machines, until you know how ABILIFY affects you.

Important information about some of the ingredients of ABILIFY

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE ABILIFY

Always take ABILIFY exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults:

- **The usual dose for adults is 15 mg once a day.** However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children:

- For **adolescents 15 years and older**, ABILIFY may be started at a low dose with the oral solution (liquid) form. The dose may be gradually increased to the usual dose for adolescents of 10 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take the ABILIFY tablet at the same time each day. It does not matter whether you take it with or without food. Always take the tablet with water and swallow it whole.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should

If you realise you have taken more ABILIFY tablets than your doctor has recommended (or if someone else has taken some of your ABILIFY tablets), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

If you forget to take ABILIFY

If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

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

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:

very common:	affects more than 1 user in 10
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uncommon:	affects 1 to 10 users in 1,000
rare:	affects 1 to 10 users in 10,000
very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Common side effects: uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects: some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate. Some people may feel depressed.

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

Changes in the levels of some blood cells; unusual heart beat, sudden unexplained death, heart attack; allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious; thoughts of suicide, suicide attempt and suicide; speech disorder, seizure, combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and

heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately); spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values, abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness; involuntary loss of urine, 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.

Adolescents 15 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness and uncontrollable twitching or jerking movements were very common (greater than 1 in 10 patients) and dry mouth, increased appetite, and feeling dizzy, especially when getting up from a lying or sitting position, were common.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, **please tell your doctor or pharmacist.**

5. HOW TO STORE ABILIFY

Keep out of the reach and sight of children.

Do not use ABILIFY after the expiry date which is stated on the blister and on the carton.

Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ABILIFY contains

- The active substance is aripiprazole. Each tablet contains 10 mg of aripiprazole.
- The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, red iron oxide (E172).

What ABILIFY looks like and contents of the pack

ABILIFY 10 mg tablets are rectangular and pink, marked with 'A-008' and '10' on one side. They are supplied in perforated unit dose blisters packed in cartons containing 14, 28, 49, 56, or 98 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

Manufacturer

Bristol-Myers Squibb S.r.l.
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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 approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
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PACKAGE LEAFLET: INFORMATION FOR THE USER

ABILIFY 15 mg tablets aripiprazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What ABILIFY is and what it is used for
2. Before you take ABILIFY
3. How to take ABILIFY
4. Possible side effects
5. How to store ABILIFY
6. Further information

1. WHAT ABILIFY IS AND WHAT IT IS USED FOR

ABILIFY is one of a group of medicines called antipsychotics.

It is used to treat adults and adolescents 15 years and older who suffer from a disease characterised by 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 is used to treat adults who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. BEFORE YOU TAKE ABILIFY

Do not take ABILIFY

- if you are allergic (hypersensitive) to aripiprazole or any of the other ingredients of ABILIFY.

Take special care with ABILIFY

Before treatment with ABILIFY, 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
- Seizure
- Involuntary, irregular muscle movements, especially in the face
- Cardiovascular diseases, 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

If you notice you are gaining weight, experience any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat.

Children and adolescents

ABILIFY is not for use in children and adolescents under 15 years. Ask your doctor or pharmacist for advice before taking ABILIFY.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY 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.

Taking ABILIFY with some medicines may need to change your dose of ABILIFY. It is especially important to mention the following to your doctor:

- Medicines to correct heart rhythm
- Antidepressants or herbal remedy used to treat depression and anxiety
- Antifungal agents
- Certain medicines to treat HIV infection
- Anticonvulsants used to treat epilepsy

Taking ABILIFY with food and drink

ABILIFY can be taken regardless of meals.
Alcohol should be avoided when taking ABILIFY.

Pregnancy and breast-feeding

You should not take ABILIFY 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.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY, you should not breast-feed.

Driving and using machines

Do not drive or use any tools or machines, until you know how ABILIFY affects you.

Important information about some of the ingredients of ABILIFY

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE ABILIFY

Always take ABILIFY exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults:

- **The usual dose for adults is 15 mg once a day.** However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children:

- For **adolescents 15 years and older**, ABILIFY may be started at a low dose with the oral solution (liquid) form. The dose may be gradually increased to the usual dose for adolescents of 10 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take the ABILIFY tablet at the same time each day. It does not matter whether you take it with or without food. Always take the tablet with water and swallow it whole.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should

If you realise you have taken more ABILIFY tablets than your doctor has recommended (or if someone else has taken some of your ABILIFY tablets), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

If you forget to take ABILIFY

If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

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

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:

very common:	affects more than 1 user in 10
common:	affects 1 to 10 users in 100
uncommon:	affects 1 to 10 users in 1,000
rare:	affects 1 to 10 users in 10,000
very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Common side effects: uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects: some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate. Some people may feel depressed.

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

Changes in the levels of some blood cells; unusual heart beat, sudden unexplained death, heart attack; allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious; thoughts of suicide, suicide attempt and suicide; speech disorder, seizure, combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and

heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately); spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values, abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness; involuntary loss of urine, 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.

Adolescents 15 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness and uncontrollable twitching or jerking movements were very common (greater than 1 in 10 patients) and dry mouth, increased appetite, and feeling dizzy, especially when getting up from a lying or sitting position, were common.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, **please tell your doctor or pharmacist.**

5. HOW TO STORE ABILIFY

Keep out of the reach and sight of children.

Do not use ABILIFY after the expiry date which is stated on the blister and on the carton.

Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ABILIFY contains

- The active substance is aripiprazole. Each tablet contains 15 mg of aripiprazole.
- The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, yellow iron oxide (E172).

What ABILIFY looks like and contents of the pack

ABILIFY 15 mg tablets are round and yellow, marked with 'A-009' and '15' on one side. They are supplied in perforated unit dose blisters packed in cartons containing 14, 28, 49, 56, or 98 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

Manufacturer

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
I-03012 Anagni-Frosinone - Italy

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

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This leaflet was last approved in

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

<http://www.ema.europa.eu/>

PACKAGE LEAFLET: INFORMATION FOR THE USER

ABILIFY 30 mg tablets aripiprazole

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1. WHAT ABILIFY IS AND WHAT IT IS USED FOR

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It is used to treat adults and adolescents 15 years and older who suffer from a disease characterised by 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 is used to treat adults who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. BEFORE YOU TAKE ABILIFY

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Take special care with ABILIFY

Before treatment with ABILIFY, 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
- Seizure
- Involuntary, irregular muscle movements, especially in the face
- Cardiovascular diseases, 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

If you notice you are gaining weight, experience any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat.

Children and adolescents

ABILIFY is not for use in children and adolescents under 15 years. Ask your doctor or pharmacist for advice before taking ABILIFY.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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- Certain medicines to treat HIV infection
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ABILIFY can be taken regardless of meals.
Alcohol should be avoided when taking ABILIFY.

Pregnancy and breast-feeding

You should not take ABILIFY 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.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY, you should not breast-feed.

Driving and using machines

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Important information about some of the ingredients of ABILIFY

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3. HOW TO TAKE ABILIFY

Always take ABILIFY exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults:

- **The usual dose for adults is 15 mg once a day.** However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children:

- For **adolescents 15 years and older**, ABILIFY may be started at a low dose with the oral solution (liquid) form. The dose may be gradually increased to the usual dose for adolescents of 10 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take the ABILIFY tablet at the same time each day. It does not matter whether you take it with or without food. Always take the tablet with water and swallow it whole.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should

If you realise you have taken more ABILIFY tablets than your doctor has recommended (or if someone else has taken some of your ABILIFY tablets), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

If you forget to take ABILIFY

If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

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

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:

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Common side effects: uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects: some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate. Some people may feel depressed.

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

Changes in the levels of some blood cells; unusual heart beat, sudden unexplained death, heart attack; allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious; thoughts of suicide, suicide attempt and suicide; speech disorder, seizure, combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and

heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately); spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values, abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness; involuntary loss of urine, 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.

Adolescents 15 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness and uncontrollable twitching or jerking movements were very common (greater than 1 in 10 patients) and dry mouth, increased appetite, and feeling dizzy, especially when getting up from a lying or sitting position, were common.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, **please tell your doctor or pharmacist.**

5. HOW TO STORE ABILIFY

Keep out of the reach and sight of children.

Do not use ABILIFY after the expiry date which is stated on the blister and on the carton.

Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ABILIFY contains

- The active substance is aripiprazole. Each tablet contains 30 mg of aripiprazole.
- The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, red iron oxide (E172).

What ABILIFY looks like and contents of the pack

ABILIFY 30 mg tablets are round and pink, marked with 'A-011' and '30' on one side. They are supplied in perforated unit dose blisters packed in cartons containing 14, 28, 49, 56, or 98 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
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Manufacturer

Bristol-Myers Squibb S.r.l.
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I-03012 Anagni-Frosinone - Italy

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

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This leaflet was last approved in

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

ABILIFY 10 mg orodispersible tablets aripiprazole

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- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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ABILIFY is one of a group of medicines called antipsychotics.

It is used to treat adults and adolescents 15 years and older who suffer from a disease characterised by 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 is used to treat adults who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. BEFORE YOU TAKE ABILIFY

Do not take ABILIFY

- if you are allergic (hypersensitive) to aripiprazole or any of the other ingredients of ABILIFY.

Take special care with ABILIFY

Before treatment with ABILIFY, 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
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Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat.

Children and adolescents

ABILIFY is not for use in children and adolescents under 15 years. Ask your doctor or pharmacist for advice before taking ABILIFY.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY 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.

Taking ABILIFY with some medicines may need to change your dose of ABILIFY. It is especially important to mention the following to your doctor:

- Medicines to correct heart rhythm
- Antidepressants or herbal remedy used to treat depression and anxiety
- Antifungal agents
- Certain medicines to treat HIV infection
- Anticonvulsants used to treat epilepsy

Taking ABILIFY with food and drink

ABILIFY can be taken regardless of meals.
Alcohol should be avoided when taking ABILIFY.

Pregnancy and breast-feeding

You should not take ABILIFY 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.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY, you should not breast-feed.

Driving and using machines

Do not drive or use any tools or machines, until you know how ABILIFY affects you.

Important information about some of the ingredients of ABILIFY

Patients who cannot take phenylalanine should note that ABILIFY orodispersible tablets contain aspartame, which is a source of phenylalanine. **May be harmful for people with phenylketonuria.**

3. HOW TO TAKE ABILIFY

Always take ABILIFY exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults:

- **The usual dose for adults is 15 mg once a day.** However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children:

- For **adolescents 15 years and older**, ABILIFY may be started at a low dose with the oral solution (liquid) form. The dose may be gradually increased to the usual dose for adolescents of 10 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take the ABILIFY orodispersible tablet at the same time each day. It does not matter whether you take it with or without food.

Do not open the blister until ready to administer. For single tablet removal, open the package and peel back the foil on the blister to expose the tablet. Do not push the tablet through the foil because this could damage the tablet. Immediately upon opening the blister, using dry hands, remove the tablet and place the entire orodispersible tablet on the tongue. Tablet disintegration occurs rapidly in saliva. The orodispersible tablet can be taken with or without liquid.

Alternatively, disperse the tablet in water and drink the resulting suspension.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should

If you realise you have taken more ABILIFY orodispersible tablets than your doctor has recommended (or if someone else has taken some of your ABILIFY orodispersible tablets), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

If you forget to take ABILIFY

If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

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

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:

very common:	affects more than 1 user in 10
common:	affects 1 to 10 users in 100
uncommon:	affects 1 to 10 users in 1,000
rare:	affects 1 to 10 users in 10,000
very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Common side effects: uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects: some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate.

Some people may feel depressed.

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

Changes in the levels of some blood cells; unusual heart beat, sudden unexplained death, heart attack; allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious; thoughts of suicide, suicide attempt and suicide; speech disorder, seizure, combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately); spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values, abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness; involuntary loss of urine, 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.

Adolescents 15 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness and uncontrollable twitching or jerking movements were very common (greater than 1 in 10 patients) and dry mouth, increased appetite, and feeling dizzy, especially when getting up from a lying or sitting position, were common.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, **please tell your doctor or pharmacist.**

5. HOW TO STORE ABILIFY

Keep out of the reach and sight of children.

Do not use ABILIFY after the expiry date which is stated on the blister and on the carton.

Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ABILIFY contains

- The active substance is aripiprazole. Each orodispersible tablet contains 10 mg of aripiprazole.
- The other ingredients are calcium silicate, croscarmellose sodium, crospovidone, silicon dioxide, xylitol, microcrystalline cellulose, aspartame, acesulfame potassium, vanilla flavour, tartaric acid, magnesium stearate, red iron oxide (E172).

What ABILIFY looks like and contents of the pack

ABILIFY 10 mg orodispersible tablets are round and pink, marked with "A" over "640" on one side and '10' on the other. They are supplied in perforated unit dose blisters packed in cartons containing 14, 28, or 49 orodispersible tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

Manufacturer

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
I-03012 Anagni-Frosinone - Italy

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

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This leaflet was last approved in

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

ABILIFY 15 mg orodispersible tablets aripiprazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What ABILIFY is and what it is used for
2. Before you take ABILIFY
3. How to take ABILIFY
4. Possible side effects
5. How to store ABILIFY
6. Further information

1. WHAT ABILIFY IS AND WHAT IT IS USED FOR

ABILIFY is one of a group of medicines called antipsychotics.

It is used to treat adults and adolescents 15 years and older who suffer from a disease characterised by 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 is used to treat adults who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. BEFORE YOU TAKE ABILIFY

Do not take ABILIFY

- if you are allergic (hypersensitive) to aripiprazole or any of the other ingredients of ABILIFY.

Take special care with ABILIFY

Before treatment with ABILIFY, 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
- Seizure
- Involuntary, irregular muscle movements, especially in the face
- Cardiovascular diseases, 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

If you notice you are gaining weight, experience any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat.

Children and adolescents

ABILIFY is not for use in children and adolescents under 15 years. Ask your doctor or pharmacist for advice before taking ABILIFY.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY 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.

Taking ABILIFY with some medicines may need to change your dose of ABILIFY. It is especially important to mention the following to your doctor:

- Medicines to correct heart rhythm
- Antidepressants or herbal remedy used to treat depression and anxiety
- Antifungal agents
- Certain medicines to treat HIV infection
- Anticonvulsants used to treat epilepsy

Taking ABILIFY with food and drink

ABILIFY can be taken regardless of meals.

Alcohol should be avoided when taking ABILIFY.

Pregnancy and breast-feeding

You should not take ABILIFY 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.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY, you should not breast-feed.

Driving and using machines

Do not drive or use any tools or machines, until you know how ABILIFY affects you.

Important information about some of the ingredients of ABILIFY

Patients who cannot take phenylalanine should note that ABILIFY orodispersible tablets contain aspartame, which is a source of phenylalanine. **May be harmful for people with phenylketonuria.**

3. HOW TO TAKE ABILIFY

Always take ABILIFY exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults:

- **The usual dose for adults is 15 mg once a day.** However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children:

- For **adolescents 15 years and older**, ABILIFY may be started at a low dose with the oral solution (liquid) form. The dose may be gradually increased to the usual dose for adolescents of 10 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take the ABILIFY orodispersible tablet at the same time each day. It does not matter whether you take it with or without food.

Do not open the blister until ready to administer. For single tablet removal, open the package and peel back the foil on the blister to expose the tablet. Do not push the tablet through the foil because this could damage the tablet. Immediately upon opening the blister, using dry hands, remove the tablet and place the entire orodispersible tablet on the tongue. Tablet disintegration occurs rapidly in saliva. The orodispersible tablet can be taken with or without liquid.

Alternatively, disperse the tablet in water and drink the resulting suspension.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should

If you realise you have taken more ABILIFY orodispersible tablets than your doctor has recommended (or if someone else has taken some of your ABILIFY orodispersible tablets), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

If you forget to take ABILIFY

If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

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

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:

very common:	affects more than 1 user in 10
common:	affects 1 to 10 users in 100
uncommon:	affects 1 to 10 users in 1,000
rare:	affects 1 to 10 users in 10,000
very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Common side effects: uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects: some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate.

Some people may feel depressed.

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

Changes in the levels of some blood cells; unusual heart beat, sudden unexplained death, heart attack; allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious; thoughts of suicide, suicide attempt and suicide; speech disorder, seizure, combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately); spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values, abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness; involuntary loss of urine, 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.

Adolescents 15 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness and uncontrollable twitching or jerking movements were very common (greater than 1 in 10 patients) and dry mouth, increased appetite, and feeling dizzy, especially when getting up from a lying or sitting position, were common.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, **please tell your doctor or pharmacist.**

5. HOW TO STORE ABILIFY

Keep out of the reach and sight of children.

Do not use ABILIFY after the expiry date which is stated on the blister and on the carton.

Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ABILIFY contains

- The active substance is aripiprazole. Each orodispersible tablet contains 15 mg of aripiprazole.
- The other ingredients are calcium silicate, croscarmellose sodium, crospovidone, silicon dioxide, xylitol, microcrystalline cellulose, aspartame, acesulfame potassium, vanilla flavour, tartaric acid, magnesium stearate, yellow iron oxide (E172).

What ABILIFY looks like and contents of the pack

ABILIFY 15 mg orodispersible tablets are round and yellow, marked with "A" over "641" on one side and '15' on the other. They are supplied in perforated unit dose blisters packed in cartons containing 14, 28, or 49 orodispersible tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

Manufacturer

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
I-03012 Anagni-Frosinone - Italy

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

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This leaflet was last approved in

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

ABILIFY 30 mg orodispersible tablets aripiprazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What ABILIFY is and what it is used for
2. Before you take ABILIFY
3. How to take ABILIFY
4. Possible side effects
5. How to store ABILIFY
6. Further information

1. WHAT ABILIFY IS AND WHAT IT IS USED FOR

ABILIFY is one of a group of medicines called antipsychotics.

It is used to treat adults and adolescents 15 years and older who suffer from a disease characterised by 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 is used to treat adults who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. BEFORE YOU TAKE ABILIFY

Do not take ABILIFY

- if you are allergic (hypersensitive) to aripiprazole or any of the other ingredients of ABILIFY.

Take special care with ABILIFY

Before treatment with ABILIFY, 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
- Seizure
- Involuntary, irregular muscle movements, especially in the face
- Cardiovascular diseases, 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

If you notice you are gaining weight, experience any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat.

Children and adolescents

ABILIFY is not for use in children and adolescents under 15 years. Ask your doctor or pharmacist for advice before taking ABILIFY.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY 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.

Taking ABILIFY with some medicines may need to change your dose of ABILIFY. It is especially important to mention the following to your doctor:

- Medicines to correct heart rhythm
- Antidepressants or herbal remedy used to treat depression and anxiety
- Antifungal agents
- Certain medicines to treat HIV infection
- Anticonvulsants used to treat epilepsy

Taking ABILIFY with food and drink

ABILIFY can be taken regardless of meals.
Alcohol should be avoided when taking ABILIFY.

Pregnancy and breast-feeding

You should not take ABILIFY 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.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY, you should not breast-feed.

Driving and using machines

Do not drive or use any tools or machines, until you know how ABILIFY affects you.

Important information about some of the ingredients of ABILIFY

Patients who cannot take phenylalanine should note that ABILIFY orodispersible tablets contain aspartame, which is a source of phenylalanine. **May be harmful for people with phenylketonuria.**

3. HOW TO TAKE ABILIFY

Always take ABILIFY exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults:

- **The usual dose for adults is 15 mg once a day.** However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children:

- For **adolescents 15 years and older**, ABILIFY may be started at a low dose with the oral solution (liquid) form. The dose may be gradually increased to the usual dose for adolescents of 10 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take the ABILIFY orodispersible tablet at the same time each day. It does not matter whether you take it with or without food.

Do not open the blister until ready to administer. For single tablet removal, open the package and peel back the foil on the blister to expose the tablet. Do not push the tablet through the foil because this could damage the tablet. Immediately upon opening the blister, using dry hands, remove the tablet and place the entire orodispersible tablet on the tongue. Tablet disintegration occurs rapidly in saliva. The orodispersible tablet can be taken with or without liquid.

Alternatively, disperse the tablet in water and drink the resulting suspension.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should

If you realise you have taken more ABILIFY orodispersible tablets than your doctor has recommended (or if someone else has taken some of your ABILIFY orodispersible tablets), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

If you forget to take ABILIFY

If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

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

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:

very common:	affects more than 1 user in 10
common:	affects 1 to 10 users in 100
uncommon:	affects 1 to 10 users in 1,000
rare:	affects 1 to 10 users in 10,000
very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Common side effects: uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects: some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate.

Some people may feel depressed.

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

Changes in the levels of some blood cells; unusual heart beat, sudden unexplained death, heart attack; allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious; thoughts of suicide, suicide attempt and suicide; speech disorder, seizure, combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately); spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values, abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness; involuntary loss of urine, 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.

Adolescents 15 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness and uncontrollable twitching or jerking movements were very common (greater than 1 in 10 patients) and dry mouth, increased appetite, and feeling dizzy, especially when getting up from a lying or sitting position, were common.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, **please tell your doctor or pharmacist.**

5. HOW TO STORE ABILIFY

Keep out of the reach and sight of children.

Do not use ABILIFY after the expiry date which is stated on the blister and on the carton.

Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ABILIFY contains

- The active substance is aripiprazole. Each orodispersible tablet contains 30 mg of aripiprazole.
- The other ingredients are calcium silicate, croscarmellose sodium, crospovidone, silicon dioxide, xylitol, microcrystalline cellulose, aspartame, acesulfame potassium, vanilla flavour, tartaric acid, magnesium stearate, red iron oxide (E172).

What ABILIFY looks like and contents of the pack

ABILIFY 30 mg orodispersible tablets are round and pink, marked with "A" over "643" on one side and '30' on the other. They are supplied in perforated unit dose blisters packed in cartons containing 14, 28, or 49 orodispersible tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
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Manufacturer

Bristol-Myers Squibb S.r.l.
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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 approved in

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

ABILIFY 1 mg/ml oral solution aripiprazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What ABILIFY is and what it is used for
2. Before you take ABILIFY
3. How to take ABILIFY
4. Possible side effects
5. How to store ABILIFY
6. Further information

1. WHAT ABILIFY IS AND WHAT IT IS USED FOR

ABILIFY is one of a group of medicines called antipsychotics.

It is used to treat adults and adolescents 15 years and older who suffer from a disease characterised by 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 is used to treat adults who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. BEFORE YOU TAKE ABILIFY

Do not take ABILIFY

- if you are allergic (hypersensitive) to aripiprazole or any of the other ingredients of ABILIFY.

Take special care with ABILIFY

Before treatment with ABILIFY, 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
- Seizure
- Involuntary, irregular muscle movements, especially in the face
- Cardiovascular diseases, 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

If you notice you are gaining weight, experience any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat.

Children and adolescents

ABILIFY is not for use in children and adolescents under 15 years. Ask your doctor or pharmacist for advice before taking ABILIFY.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY 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.

Taking ABILIFY with some medicines may need to change your dose of ABILIFY. It is especially important to mention the following to your doctor:

- Medicines to correct heart rhythm
- Antidepressants or herbal remedy used to treat depression and anxiety
- Antifungal agents
- Certain medicines to treat HIV infection
- Anticonvulsants used to treat epilepsy

Taking ABILIFY with food and drink

ABILIFY can be taken regardless of meals. However, the oral solution should not be diluted with other liquids or mixed with any food prior to administration.

Alcohol should be avoided when taking ABILIFY.

Pregnancy and breast-feeding

You should not take ABILIFY 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.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY, you should not breast-feed.

Driving and using machines

Do not drive or use any tools or machines until you know how ABILIFY affects you.

Important information about some of the ingredients of ABILIFY

Each ml of ABILIFY oral solution contains 200 mg of fructose and 400 mg of sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine. Parahydroxybenzoates may cause allergic reactions (possibly delayed).

3. HOW TO TAKE ABILIFY

Always take ABILIFY exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults:

- **The usual dose for adults is 15 ml solution (corresponding to 15 mg aripiprazole) once a day.** However your doctor may prescribe a lower or higher dose to a maximum of 30 mg (i.e. 30 ml) once a day.

Use in children:

- For **adolescents 15 years and older**, ABILIFY may be started at a low dose with the oral solution (liquid) form. The dose may be gradually increased to the usual dose for adolescents of 10 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

The dose of ABILIFY oral solution must be measured using the calibrated cup or the 2 ml calibrated dropper supplied in the carton.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take the ABILIFY oral solution at the same time each day. It does not matter whether you take it with or without food. However, you should not dilute with other liquids or mix with other food prior to taking ABILIFY oral solution.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should

If you realise you have taken more ABILIFY oral solution than your doctor has recommended (or if someone else has taken some of your ABILIFY oral solution), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

If you forget to take ABILIFY

If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

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

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:

very common:	affects more than 1 user in 10
common:	affects 1 to 10 users in 100
uncommon:	affects 1 to 10 users in 1,000
rare:	affects 1 to 10 users in 10,000
very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Common side effects: uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects: some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate. Some people may feel depressed.

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

Changes in the levels of some blood cells; unusual heart beat, sudden unexplained death, heart attack; allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious; thoughts of suicide, suicide attempt and suicide; speech disorder, seizure, combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately); spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values, abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness; involuntary loss of urine, 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.

Adolescents 15 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness and uncontrollable twitching or jerking movements were very common (greater than 1 in 10 patients) and dry mouth, increased appetite, and feeling dizzy, especially when getting up from a lying or sitting position, were common.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, **please tell your doctor or pharmacist.**

5. HOW TO STORE ABILIFY

Keep out of the reach and sight of children.

Do not use ABILIFY after the expiry date which is stated on the bottle and on the carton.

This medicinal product does not require any special storage conditions.
Use within 6 months after first opening.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ABILIFY contains

- The active substance is aripiprazole. Each ml contains 1 mg of aripiprazole.
- The other ingredients are disodium edetate, fructose, glycerin, lactic acid, methyl parahydroxybenzoate (E218), propylene glycol, propyl parahydroxybenzoate (E216), sodium hydroxide, sucrose, purified water, and natural orange cream with other natural flavours.

What ABILIFY looks like and contents of the pack

ABILIFY 1 mg/ml oral solution is a clear, colourless to light yellow liquid supplied in bottles with polypropylene child-resistant closure containing 50 ml, 150 ml or 480 ml per bottle. Each carton

contains one bottle and both a calibrated polypropylene measuring cup and a calibrated polypropylene low-density polyethylene dropper.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Europe Ltd.
Hunton House, Highbridge Business Park, Oxford Road
Uxbridge - Middlesex UB8 1HU - United Kingdom

Manufacturer

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
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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 approved in

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

ABILIFY 7.5 mg/ml solution for injection aripiprazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What ABILIFY is and what it is used for
2. Before you use ABILIFY
3. How to use ABILIFY
4. Possible side effects
5. How to store ABILIFY
6. Further information

1. WHAT ABILIFY IS AND WHAT IT IS USED FOR

ABILIFY is one of a group of medicines called antipsychotics.

ABILIFY solution for injection is used to treat quickly symptoms of agitation and distressing behaviour that may occur in a disease characterised by 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.
- feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability.

ABILIFY solution for injection is given when treatment with oral formulations of ABILIFY is not appropriate. Your doctor will change your treatment to ABILIFY tablets, ABILIFY orodispersible tablets or ABILIFY oral solution as soon as appropriate.

2. BEFORE YOU USE ABILIFY

Do not use ABILIFY

- if you are allergic (hypersensitive) to aripiprazole or any of the other ingredients of ABILIFY.

Take special care with ABILIFY

Before treatment with ABILIFY, 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
- Seizure
- Involuntary, irregular muscle movements, especially in the face
- Cardiovascular diseases, 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

If you notice you are gaining weight, experience any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell the doctor or nurse if you feel dizzy or faint after the injection. You will probably need to lie down until you feel better. The doctor may also want to measure your blood pressure and pulse.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat.

Children and adolescents

ABILIFY solution for injection is not for use in children and adolescents under 18 years. Ask your doctor or pharmacist for advice before taking ABILIFY.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY 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.

Taking ABILIFY with some medicines may need to change your dose of ABILIFY. It is especially important to mention the following to your doctor:

- Medicines to correct heart rhythm
- Antidepressants or herbal remedy used to treat depression and anxiety
- Antifungal agents
- Certain medicines to treat HIV infection
- Anticonvulsants used to treat epilepsy

A combination of ABILIFY solution for injection with medicines taken for anxiety might make you feel drowsy or dizzy. Only take other medicines while you are on ABILIFY if your doctor tells you that you can.

Using ABILIFY with food and drink

ABILIFY can be administered regardless of meals.
Alcohol should be avoided when taking ABILIFY.

Pregnancy and breast-feeding

You should not use ABILIFY 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.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY, you should not breast-feed.

Driving and using machines

Do not drive or use any tools or machines if you feel drowsy after receiving ABILIFY solution for injection.

3. HOW TO USE ABILIFY

Your doctor will decide how much ABILIFY solution for injection you need and how long you need it for. The usual dose is 9.75 mg (1.3 ml) for the first injection. Up to three injections in 24 hours may be given. The total dose of ABILIFY (all formulations) should not exceed 30 mg per day.

ABILIFY solution for injection is ready to use. The correct amount of solution will be injected into your muscle by your doctor or nurse.

If you are concerned that you are given more ABILIFY solution for injection than you feel necessary, tell your doctor or nurse of your concern. Only a few doses of ABILIFY solution for injection may be needed. Your doctor will decide when you need another dose of ABILIFY solution for injection.

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

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:

very common:	affects more than 1 user in 10
common:	affects 1 to 10 users in 100
uncommon:	affects 1 to 10 users in 1,000
rare:	affects 1 to 10 users in 10,000
very rare:	affects less than 1 user in 10,000
not known:	frequency cannot be estimated from the available data

Common side effects of ABILIFY solution for injection include sleepiness, dizziness, headache, restlessness, nausea and vomiting.

Uncommon side effects: some people may have changes in blood pressure, may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate, dry mouth or fatigue.

In addition, the following side effects have been seen in patients treated with oral formulations of ABILIFY:

Common side effects: uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects: some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate.
Some people may feel depressed.

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

Changes in the levels of some blood cells; unusual heart beat, sudden unexplained death, heart attack; allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious; thoughts of suicide, suicide attempt and suicide; speech disorder, seizure, combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms

include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately); spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values, abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness; involuntary loss of urine, 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.

Adolescents 15 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness and uncontrollable twitching or jerking movements were very common (greater than 1 in 10 patients) and dry mouth, increased appetite, and feeling dizzy, especially when getting up from a lying or sitting position, were common.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, **please tell your doctor or pharmacist.**

5. HOW TO STORE ABILIFY

Keep out of the reach and sight of children.

Do not use ABILIFY after the expiry date which is stated on the carton and on the vial.

Keep the vial in the outer carton in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ABILIFY contains

- The active substance is aripiprazole. Each ml contains 7.5 mg aripiprazole. A vial contains 9.75 mg (1.3 ml) aripiprazole.
- The other ingredients are sulfobutylether β -cyclodextrin (SBECD), tartaric acid, sodium hydroxide, and water for injections.

What ABILIFY looks like and contents of the pack

The ABILIFY solution for injection is a clear, colourless, aqueous solution.

Each carton contains one single-use type I glass vial with a rubber butyl stopper and a "flip-off" aluminium seal.

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

<http://www.ema.europa.eu/>