

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 5 mg tablets  
ABILIFY 10 mg tablets  
ABILIFY 15 mg tablets  
ABILIFY 30 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### *ABILIFY 5 mg tablets*

Each tablet contains 5 mg of aripiprazole.

Excipient with known effect

67 mg lactose per tablet

### *ABILIFY 10 mg tablets*

Each tablet contains 10 mg of aripiprazole.

Excipient with known effect

62.18 mg lactose per tablet

### *ABILIFY 15 mg tablets*

Each tablet contains 15 mg of aripiprazole.

Excipient with known effect

57 mg lactose per tablet

### *ABILIFY 30 mg tablets*

Each tablet contains 30 mg of aripiprazole.

Excipient with known effect

186.54 mg lactose per tablet

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

### *ABILIFY 5 mg tablets*

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

### *ABILIFY 10 mg tablets*

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

### *ABILIFY 15 mg tablets*

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

### *ABILIFY 30 mg tablets*

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 aged 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 adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older (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 in Bipolar I Disorder:* 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.

### Special populations

#### *Paediatric population*

*Schizophrenia in adolescents aged 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 although individual patients may benefit from a higher dose.

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

*Manic episodes in Bipolar I Disorder in adolescents aged 13 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. The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant undesirable effects including EPS related events, somnolence, fatigue and weight gain (see section 4.8). Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring (see sections 4.4, 4.8 and 5.1). Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, ABILIFY is not recommended for use in patients below 13 years of age (see sections 4.8 and 5.1).

*Irritability associated with autistic disorder:* the safety and efficacy of ABILIFY in children and adolescents aged below 18 years have not yet been established. Currently available data are described

in section 5.1 but no recommendation on a posology can be made.

*Tics associated with Tourette's disorder:* the safety and efficacy of ABILIFY in children and adolescents 6 to 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.

#### *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).

#### *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 aged 65 years and 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 is for oral use.

Orodispersible tablets or 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 listed in section 6.1.

### **4.4 Special warnings and precautions for use**

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

#### Suicidality

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

Results of an epidemiological study suggested that there was no increased risk of suicidality with

aripiprazole compared to other antipsychotics among adult patients with schizophrenia or bipolar disorder. There are insufficient paediatric data to evaluate this risk in younger patients (below 18 years of age), but there is evidence that the risk of suicide persists beyond the first 4 weeks of treatment for atypical antipsychotics, including aripiprazole.

#### Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant. Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with aripiprazole and preventive measures undertaken.

#### QT prolongation

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 (see section 4.8).

#### Tardive dyskinesia

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

#### Other extrapyramidal symptoms

In paediatric clinical trials of aripiprazole akathisia and parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

#### 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 active substances, including aripiprazole, 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 (see section 4.8).

#### 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 (see section 4.8).

### *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 (see section 4.8).

Aripiprazole 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 medicinal products, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotic medicinal products are not available to allow direct comparisons. Patients treated with any antipsychotic medicinal products, including aripiprazole, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control (see section 4.8).

### Hypersensitivity

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 aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

### Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic medicinal product use, including aripiprazole. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

### Pathological gambling

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

### 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.

### Patients with ADHD comorbidity

Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are

available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these medicinal products are co-administered.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Due to its  $\alpha_1$ -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 aripiprazole

A gastric acid blocker, the H<sub>2</sub> 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.

##### *Quinidine and other CYP2D6 inhibitors*

In a clinical trial in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while C<sub>max</sub> was unchanged. The AUC and C<sub>max</sub> of dehydro-aripiprazole, the active metabolite, decreased by 32 % and 47 %, respectively. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole 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.

##### *Ketoconazole and other CYP3A4 inhibitors*

In a clinical trial in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C<sub>max</sub> by 63 % and 37 %, respectively. The AUC and C<sub>max</sub> 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 aripiprazole, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole 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 CYP3A4 inhibitor, the dosage of aripiprazole 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 aripiprazole, modest increases in aripiprazole concentrations might be expected.

##### *Carbamazepine and other CYP3A4 inducers*

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C<sub>max</sub> 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<sub>max</sub> and AUC after carbamazepine co-administration were 69 % and 71 % lower, respectively, than those following treatment with aripiprazole alone.

Aripiprazole dose should be doubled when concomitant administration of aripiprazole 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 aripiprazole should be reduced to the recommended dose.

#### *Valproate and lithium*

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

#### *Serotonin syndrome*

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

#### Potential for aripiprazole 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), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (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**

### Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients 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.

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

### Breast-feeding

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. Some paediatric patients with Bipolar I Disorder have an increased incidence of somnolence and fatigue (see section 4.8).

## **4.8 Undesirable effects**

### Summary of the safety profile



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.

Tabulated list of adverse reactions

All ADRs are listed by system organ class and frequency; very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known"

	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<b>Blood and lymphatic system disorders</b>			Leukopenia Neutropenia Thrombocytopenia
<b>Immune system disorders</b>			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
<b>Endocrine disorders</b>		Hyperprolactinaemia	Diabetic hyperosmolar coma Diabetic ketoacidosis Hyperglycaemia
<b>Metabolism and nutrition disorders</b>	Diabetes mellitus	Hyperglycaemia	Hyponatremia Anorexia Weight decreased Weight gain
<b>Psychiatric disorders</b>	Insomnia Anxiety Restlessness	Depression, Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) Pathological gambling Aggression Agitation Nervousness
<b>Nervous system disorders</b>	Akathisia Extrapyramidal disorder Tremor Headache Sedation Somnolence Dizziness	Tardive dyskinesia Dystonia	Neuroleptic Malignant Syndrome (NMS) Grand mal convulsion Serotonin syndrome Speech disorder
<b>Eye disorders</b>	Vision blurred	Diplopia	
<b>Cardiac disorders</b>		Tachycardia	Sudden unexplained death Torsades de pointes QT prolongation Ventricular arrhythmias Cardiac arrest Bradycardia
<b>Vascular disorders</b>		Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Hypertension Syncope
<b>Respiratory,</b>		Hiccups	Aspiration pneumonia

	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<b>thoracic and mediastinal disorders</b>			Laryngospasm Oropharyngeal spasm
<b>Gastrointestinal disorders</b>	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting		Pancreatitis Dysphagia Diarrhoea Abdominal discomfort Stomach discomfort
<b>Hepatobiliary disorders</b>			Hepatic failure Hepatitis Jaundice Increased Alanine Aminotransferase (ALT) Increased Aspartate Aminotransferase (AST) Increased Gamma Glutamyl Transferase (GGT) Increased alkaline phosphatase
<b>Skin and subcutaneous tissue disorders</b>			Rash Photosensitivity reaction Alopecia Hyperhidrosis
<b>Musculoskeletal and connective tissue disorders</b>			Rhabdomyolysis Myalgia Stiffness
<b>Renal and urinary disorders</b>			Urinary incontinence Urinary retention
<b>Pregnancy, puerperium and perinatal conditions</b>			Drug withdrawal syndrome neonatal (see section 4.6)
<b>Reproductive system and breast disorders</b>			Priapism
<b>General disorders and administration site conditions</b>	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
<b>Investigations</b>			Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Increased creatine phosphokinase

#### Description of selected adverse reactions

##### *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.

#### *Akathisia*

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 medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

#### *Prolactin*

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

#### *Laboratory parameters*

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.

#### Paediatric population

##### *Schizophrenia in adolescents aged 15 years and older*

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 reactions 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.

The safety profile of a long-term, double-blind placebo controlled trial was also similar except for the following reactions that were reported more frequently than paediatric patients taking placebo: weight decreased, blood insulin increased, arrhythmia, and leukopenia were reported commonly ( $\geq 1/100$ ,  $< 1/10$ ).

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. In the adolescent (13-17 years) schizophrenia population with aripiprazole exposure of 5 to 30 mg up to 72 months, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 25.6 % and 45.0 %, respectively.

In two long term trials with adolescent (13-17 years) schizophrenia and bipolar patients treated with aripiprazole, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 37.0 % and 59.4 %, respectively.

##### *Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older*

The frequency and type of undesirable effects in adolescents with Bipolar I Disorder were similar to

those in adults except for the following reactions: very commonly ( $\geq 1/10$ ) somnolence (23.0 %), extrapyramidal disorder (18.4 %), akathisia (16.0 %), and fatigue (11.8 %); and commonly ( $\geq 1/100$ ,  $< 1/10$ ) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.

The following undesirable effects had a possible dose response relationship; extrapyramidal disorder (incidences were 10 mg, 9.1 %, 30 mg, 28.8 %, placebo, 1.7 %); and akathisia (incidences were 10 mg, 12.1 %, 30 mg, 20.3 %, placebo, 1.7 %).

Mean changes in body weight in adolescents with Bipolar I Disorder at 12 and 30 weeks for aripiprazole were 2.4 kg and 5.8 kg, and for placebo 0.2 kg and 2.3 kg, respectively.

In the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.

In the paediatric bipolar population (10-17 years) with exposure up to 30 weeks, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 28.0 % and 53.3 %, respectively.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **via the national reporting system listed in [Appendix V](#)**.

## **4.9 Overdose**

### Signs and symptoms

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

### Management of overdose

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

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.

### Haemodialysis

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: other antipsychotics, ATC code: N05AX12

### Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D<sub>2</sub> and serotonin HT<sub>1A</sub> receptors and antagonism of serotonin 5-HT<sub>2A</sub> 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 D<sub>2</sub> and D<sub>3</sub>, serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors and moderate affinity for dopamine D<sub>4</sub>, serotonin 5-HT<sub>2C</sub> and 5-HT<sub>7</sub>, alpha-1 adrenergic and histamine H<sub>1</sub> 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 <sup>11</sup>C-raclopride, a D<sub>2</sub>/D<sub>3</sub> receptor ligand, to the caudate and putamen detected by positron emission tomography.

### Clinical efficacy and safety

#### *Schizophrenia*

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.

Aripiprazole 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 adult stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34 % in aripiprazole group and 57 % in placebo.

#### *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 adult 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 ( $\geq 1.04$  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.

### *Prolactin*

Prolactin levels were evaluated in all trials of all doses of aripiprazole ( $n = 28,242$ ). The incidence of hyperprolactinaemia or increased serum prolactin in patients treated with aripiprazole (0.3 %) was similar to that of placebo (0.2 %). For patients receiving aripiprazole, the median time to onset was 42 days and median duration was 34 days.

The incidence of hypoprolactinaemia or decreased serum prolactin in patients treated with aripiprazole was 0.4 %, compared with 0.02 % for patients treated with placebo. For patients receiving aripiprazole, the median time to onset was 30 days and median duration was 194 days.

### *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.

### 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.

In a 60- to 89-week, randomised, double-blind, placebo-controlled trial in adolescent subjects (n = 146; ages 13-17 years) with schizophrenia, there was a statistically significant difference in the rate of relapse of psychotic symptoms between the aripiprazole (19.39 %) and placebo (37.50 %) groups. The point estimate of the hazard ratio (HR) was 0.461 (95% confidence interval, 0.242-0.879) in the full population. In subgroup analyses the point estimate of the HR was 0.495 for subjects 13 to 14 years of age compared to 0.454 for subjects 15 to 17 years of age. However, the estimation of the HR for the younger (13-14 years) group was not precise, reflecting the smaller number of subjects in that group (aripiprazole, n = 29; placebo, n = 12), and the confidence interval for this estimation (ranging from 0.151 to 1.628) did not allow conclusions to be drawn on the presence of a treatment effect. In contrast the 95 % confidence interval for the HR in the older subgroup (aripiprazole, n = 69; placebo, n = 36) was 0.242 to 0.879 and hence a treatment effect could be concluded in the older patients.

#### *Manic episodes in Bipolar I Disorder in children and adolescents*

Aripiprazole was studied in a 30-week placebo-controlled trial involving 296 children and adolescents (10-17 years), who met DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes with or without psychotic features and had a Y-MRS score  $\geq$  20 at baseline. Among the patients included in the primary efficacy analysis, 139 patients had a current co-morbid diagnosis of ADHD.

Aripiprazole was superior to placebo in change from baseline at week 4 and at week 12 on the Y-MRS total score. In a post-hoc analysis, the improvement over placebo was more pronounced in the patients with associated co-morbidity of ADHD compared to the group without ADHD, where there was no difference from placebo. Recurrence prevention was not established.

**Table 1: Mean improvement from baseline YMRS score by psychiatric comorbidity**

<b>Psychiatric comorbidities</b>	<b>Week 4</b>	<b>Week 12</b>	<b>ADHD</b>	<b>Week 4</b>	<b>Week 12</b>
ABILIFY 10 mg (n = 48)	14.9	15.1	ABILIFY 10 mg (n = 44)	15.2	15.6
ABILIFY 30 mg (n = 51)	16.7	16.9	ABILIFY 30 mg (n = 48)	15.9	16.7
Placebo (n = 52) <sup>a</sup>	7.0	8.2	Placebo (n = 47) <sup>b</sup>	6.3	7.0
<b>No psychiatric comorbidities</b>	<b>Week 4</b>	<b>Week 12</b>	<b>No ADHD</b>	<b>Week 4</b>	<b>Week 12</b>
ABILIFY 10 mg (n = 27)	12.8	15.9	ABILIFY 10 mg (n = 37)	12.7	15.7
ABILIFY 30 mg (n = 25)	15.3	14.7	ABILIFY 30 mg (n = 30)	14.6	13.4
Placebo (n = 18)	9.4	9.7	Placebo (n = 25)	9.9	10.0

<sup>a</sup> n = 51 at Week 4

<sup>b</sup> n = 46 at Week 4

The most common treatment-emergent adverse events among patients receiving 30 mg were extrapyramidal disorder (28.3 %), somnolence (27.3 %), headache (23.2 %), and nausea (14.1 %). Mean weight gain in the 30 weeks treatment-interval was 2.9 kg as compared to 0.98 kg in patients treated with placebo.

*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.

Aripiprazole was also studied in a placebo-controlled, long-term maintenance trial. After a 13-26 week stabilisation on aripiprazole (2-15 mg/day) patients with a stable response were either maintained on aripiprazole or substituted to placebo for further 16 weeks. Kaplan-Meier relapse rates at week 16 were 35 % for aripiprazole and 52 % for placebo; the hazard ratio for relapse within 16 weeks (aripiprazole/placebo) was 0.57 (non-statistically significant difference). The mean weight gain over the stabilisation phase (up to 26 weeks) on aripiprazole was 3.2 kg, and a further mean increase of 2.2 kg for aripiprazole as compared to 0.6 kg for placebo was observed in the second phase (16 weeks) of the trial. Extrapyramidal symptoms were mainly reported during the stabilisation phase in 17 % of patients, with tremor accounting for 6.5 %.

*Tics associated with Tourette's disorder in paediatric patients (see section 4.2)*

The efficacy of aripiprazole was studied in paediatric subjects with Tourette's disorder (aripiprazole: n = 99, placebo: n = 44) in a randomised, double-blind, placebo controlled, 8 week study using a fixed dose weight-based treatment group design over the dose range of 5 mg/day to 20 mg/day and a starting dose of 2 mg. Patients were 7 - 17 years of age and presented an average score of 30 on Total Tic Score on the Yale Global Tic Severity Scale (TTS-YGTSS) at baseline. Aripiprazole showed an improvement on TTS-YGTSS change from baseline to week 8 of 13.35, for the low dose group (5 mg or 10 mg) and 16.94 for the high dose group (10 mg or 20 mg) as compared with an improvement of 7.09 in the placebo group.

The efficacy of aripiprazole in paediatric subjects with Tourette's syndrome (aripiprazole: n = 32, placebo: n = 29) was also evaluated over a flexible dose range of 2 mg/day to 20 mg/day and a starting dose of 2 mg, in a 10 week, randomised, double blind, placebo-controlled study conducted in South-Korea. Patients were 6 - 18 years and presented an average score of 29 on TTS-YGTSS at baseline. Aripiprazole group showed an improvement of 14.97 on TTS-YGTSS change from baseline to week 10 as compared with an improvement of 9.62 in the placebo group.

In both of these short term trials, the clinical relevance of the efficacy findings has not been established, considering the magnitude of treatment effect compared to the large placebo effect and the unclear effects regarding psycho-social functioning. No long term data are available with regard to the efficacy and the safety of aripiprazole in this fluctuating disorder.

The European Medicines Agency has deferred the obligation to submit the results of studies with ABILIFY in one or more subsets of the paediatric population in the treatment of schizophrenia and in the treatment of bipolar affective disorder (see section 4.2 for information on paediatric use).

## **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.

### Biotransformation

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. 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 [<sup>14</sup>C]-labelled aripiprazole, approximately 27 % of the administered radioactivity was recovered in the urine and approximately 60 % in the faeces. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged in the faeces.

### Pharmacokinetics in special patient groups

#### *Paediatric population*

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 10 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*

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

#### *Race*

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

#### *Renal impairment*

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 impairment*

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 data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, 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/m<sup>2</sup>). 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 reactions 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**

#### Tablet core

Lactose monohydrate  
Maize starch  
Microcrystalline cellulose  
Hydroxypropyl cellulose  
Magnesium stearate

#### Tablet coat

*ABILIFY 5 mg tablets*  
Indigo carmine aluminium lake (E 132)

*ABILIFY 10 mg tablets*  
Red iron oxide (E 172)

*ABILIFY 15 mg tablets*  
Yellow iron oxide (E 172)

*ABILIFY 30 mg tablets*  
Red iron oxide (E 172)

## **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 medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

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

## **8. MARKETING AUTHORISATION NUMBER(S)**

*ABILIFY 5 mg tablets*  
EU/1/04/276/001 (5 mg, 14 x 1 tablets)  
EU/1/04/276/002 (5 mg, 28 x 1 tablets)  
EU/1/04/276/003 (5 mg, 49 x 1 tablets)  
EU/1/04/276/004 (5 mg, 56 x 1 tablets)  
EU/1/04/276/005 (5 mg, 98 x 1 tablets)

*ABILIFY 10 mg tablets*  
EU/1/04/276/006 (10 mg, 14 x 1 tablets)  
EU/1/04/276/007 (10 mg, 28 x 1 tablets)  
EU/1/04/276/008 (10 mg, 49 x 1 tablets)  
EU/1/04/276/009 (10 mg, 56 x 1 tablets)

EU/1/04/276/010 (10 mg, 98 x 1 tablets)

*ABILIFY 15 mg tablets*

EU/1/04/276/011 (15 mg, 14 x 1 tablets)

EU/1/04/276/012 (15 mg, 28 x 1 tablets)

EU/1/04/276/013 (15 mg, 49 x 1 tablets)

EU/1/04/276/014 (15 mg, 56 x 1 tablets)

EU/1/04/276/015 (15 mg, 98 x 1 tablets)

*ABILIFY 30 mg tablets*

EU/1/04/276/016 (30 mg, 14 x 1 tablets)

EU/1/04/276/017 (30 mg, 28 x 1 tablets)

EU/1/04/276/018 (30 mg, 49 x 1 tablets)

EU/1/04/276/019 (30 mg, 56 x 1 tablets)

EU/1/04/276/020 (30 mg, 98 x 1 tablets)

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 04 June 2004

Date of latest renewal: 04 June 2009

**10. DATE OF REVISION OF THE TEXT**

{MM/YYYY}

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

## 1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg orodispersible tablets  
ABILIFY 15 mg orodispersible tablets  
ABILIFY 30 mg orodispersible tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### *ABILIFY 10 mg orodispersible tablets*

Each orodispersible tablet contains 10 mg of aripiprazole.

#### Excipient with known effect

2 mg aspartame (E 951) and 0.075 mg lactose per orodispersible tablet

### *ABILIFY 15 mg orodispersible tablets*

Each orodispersible tablet contains 15 mg of aripiprazole.

#### Excipient with known effect

3 mg aspartame (E 951) and 0.1125 mg lactose per orodispersible tablet

### *ABILIFY 30 mg orodispersible tablets*

Each orodispersible tablet contains 30 mg of aripiprazole.

#### Excipient with known effect

6 mg aspartame (E 951) and 0.225 mg lactose per orodispersible tablet

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Orodispersible tablet

### *ABILIFY 10 mg orodispersible tablets*

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

### *ABILIFY 15 mg orodispersible tablets*

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

### *ABILIFY 30 mg orodispersible tablets*

30 mg: 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 aged 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 adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older (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 in Bipolar I Disorder:* 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.

### Special populations

#### *Paediatric population*

*Schizophrenia in adolescents aged 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 although individual patients may benefit from a higher dose.

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

*Manic episodes in Bipolar I Disorder in adolescents aged 13 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. The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant undesirable effects including EPS related events, somnolence, fatigue and weight gain (see section 4.8). Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring (see sections 4.4, 4.8 and 5.1). Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, ABILIFY is not recommended for use in patients below 13 years of age (see sections 4.8 and 5.1).

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

*Tics associated with Tourette's disorder:* the safety and efficacy of ABILIFY in children and adolescents 6 to 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.

#### *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).

#### *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 aged 65 years and 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 is 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.

Orodispersible tablets or 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 listed in section 6.1.

### **4.4 Special warnings and precautions for use**

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

#### Suicidality

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

Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among adult patients with schizophrenia or bipolar disorder. There are insufficient paediatric data to evaluate this risk in younger patients (below 18 years of age), but there is evidence that the risk of suicide persists beyond the first 4 weeks of treatment for atypical antipsychotics, including aripiprazole.

### Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant. Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with aripiprazole and preventive measures undertaken.

### QT prolongation

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 (see section 4.8).

### Tardive dyskinesia

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

### Other extrapyramidal symptoms

In paediatric clinical trials of aripiprazole akathisia and parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

### 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 active substances, including aripiprazole, 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 (see section 4.8).

### 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 (see section 4.8).

#### *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 (see section 4.8).

Aripiprazole 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 medicinal products, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotic medicinal products are not available to allow direct comparisons. Patients treated with any antipsychotic medicinal products, including aripiprazole, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control (see section 4.8).

#### Hypersensitivity

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 aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

#### Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic medicinal product use, including aripiprazole. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

#### Pathological gambling

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

#### Phenylketonurics

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

#### Lactose

ABILIFY orodispersible 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.

#### Patients with ADHD comorbidity

Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these medicinal products are co-administered.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Due to its  $\alpha_1$ -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 aripiprazole

A gastric acid blocker, the  $H_2$  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.

##### *Quinidine and other CYP2D6 inhibitors*

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 %, respectively. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole 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.

##### *Ketoconazole and other CYP3A4 inhibitors*

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 aripiprazole, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole 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 CYP3A4 inhibitor, the dosage of aripiprazole 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 aripiprazole, modest increases in aripiprazole concentrations might be expected.

##### *Carbamazepine and other CYP3A4 inducers*

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.

Aripiprazole dose should be doubled when concomitant administration of aripiprazole 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 aripiprazole should be reduced to the recommended dose.

#### *Valproate and lithium*

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

#### *Serotonin syndrome*

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

#### Potential for aripiprazole 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), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (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**

### Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients 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.

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

### Breast-feeding

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. Some paediatric patients with Bipolar I Disorder have an increased incidence of somnolence and fatigue (see section 4.8).

## **4.8 Undesirable effects**

### Summary of the safety profile

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.

Tabulated list of adverse reactions

All ADRs are listed by system organ class and frequency; very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known"

	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<b>Blood and lymphatic system disorders</b>			Leukopenia Neutropenia Thrombocytopenia
<b>Immune system disorders</b>			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
<b>Endocrine disorders</b>		Hyperprolactinaemia	Diabetic hyperosmolar coma Diabetic ketoacidosis Hyperglycaemia
<b>Metabolism and nutrition disorders</b>	Diabetes mellitus	Hyperglycaemia	Hyponatremia Anorexia Weight decreased Weight gain
<b>Psychiatric disorders</b>	Insomnia Anxiety Restlessness	Depression, Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) Pathological gambling Aggression Agitation Nervousness
<b>Nervous system disorders</b>	Akathisia Extrapyramidal disorder Tremor Headache Sedation Somnolence Dizziness	Tardive dyskinesia Dystonia	Neuroleptic Malignant Syndrome (NMS) Grand mal convulsion Serotonin syndrome Speech disorder
<b>Eye disorders</b>	Vision blurred	Diplopia	
<b>Cardiac disorders</b>		Tachycardia	Sudden unexplained death Torsades de pointes QT prolongation Ventricular arrhythmias Cardiac arrest Bradycardia
<b>Vascular disorders</b>		Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Hypertension Syncope

	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<b>Respiratory, thoracic and mediastinal disorders</b>		Hiccups	Aspiration pneumonia Laryngospasm Oropharyngeal spasm
<b>Gastrointestinal disorders</b>	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting		Pancreatitis Dysphagia Diarrhoea Abdominal discomfort Stomach discomfort
<b>Hepatobiliary disorders</b>			Hepatic failure Hepatitis Jaundice Increased Alanine Aminotransferase (ALT) Increased Aspartate Aminotransferase (AST) Increased Gamma Glutamyl Transferase (GGT) Increased alkaline phosphatase
<b>Skin and subcutaneous tissue disorders</b>			Rash Photosensitivity reaction Alopecia Hyperhidrosis
<b>Musculoskeletal and connective tissue disorders</b>			Rhabdomyolysis Myalgia Stiffness
<b>Renal and urinary disorders</b>			Urinary incontinence Urinary retention
<b>Pregnancy, puerperium and perinatal conditions</b>			Drug withdrawal syndrome neonatal (see section 4.6)
<b>Reproductive system and breast disorders</b>			Priapism
<b>General disorders and administration site conditions</b>	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
<b>Investigations</b>			Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Increased creatine phosphokinase

#### Description of selected adverse reactions

##### *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.

#### *Akathisia*

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 medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

#### *Prolactin*

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

#### *Laboratory parameters*

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.

#### Paediatric population

##### *Schizophrenia in adolescents aged 15 years and older*

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 reactions 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.

The safety profile of a long-term, double-blind placebo controlled trial was also similar except for the following reactions that were reported more frequently than paediatric patients taking placebo: weight decreased, blood insulin increased, arrhythmia, and leukopenia were reported commonly ( $\geq 1/100$ ,  $< 1/10$ ).

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. In the adolescent (13-17 years) schizophrenia population with aripiprazole exposure of 5 to 30 mg up to 72 months, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 25.6 % and 45.0 %, respectively.

In two long term trials with adolescent (13-17 years) schizophrenia and bipolar patients treated with aripiprazole, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 37.0 % and 59.4 %, respectively.

##### *Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older*

The frequency and type of undesirable effects in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly ( $\geq 1/10$ ) somnolence (23.0 %), extrapyramidal disorder (18.4 %), akathisia (16.0 %), and fatigue (11.8 %); and commonly ( $\geq 1/100$ ,  $< 1/10$ ) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.

The following undesirable effects had a possible dose response relationship; extrapyramidal disorder (incidences were 10 mg, 9.1 %, 30 mg, 28.8 %, placebo, 1.7 %); and akathisia (incidences were 10 mg, 12.1 %, 30 mg, 20.3 %, placebo, 1.7 %).

Mean changes in body weight in adolescents with Bipolar I Disorder at 12 and 30 weeks for aripiprazole were 2.4 kg and 5.8 kg, and for placebo 0.2 kg and 2.3 kg, respectively.

In the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.

In the paediatric bipolar population (10-17 years) with exposure up to 30 weeks, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 28.0 % and 53.3 %, respectively.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **via the national reporting system listed in [Appendix V](#)**.

## **4.9 Overdose**

### Signs and symptoms

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

### Management of overdose

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

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.

### Haemodialysis

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

## **5. PHARMACOLOGICAL PROPERTIES**

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antipsychotics, ATC code: N05AX12

### Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D<sub>2</sub> and serotonin 5-HT<sub>1A</sub> receptors and antagonism of serotonin 5-HT<sub>2A</sub> 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 D<sub>2</sub> and D<sub>3</sub>, serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors and moderate affinity for dopamine D<sub>4</sub>, serotonin 5-HT<sub>2C</sub> and 5-HT<sub>7</sub>, alpha-1 adrenergic and histamine H<sub>1</sub> 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 <sup>11</sup>C-raclopride, a D<sub>2</sub>/D<sub>3</sub> receptor ligand, to the caudate and putamen detected by positron emission tomography.

### Clinical efficacy and safety

#### *Schizophrenia*

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.

Aripiprazole 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 adult stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34 % in aripiprazole group and 57 % in placebo.

#### *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 adult 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 ( $\geq 1.04$  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.

### *Prolactin*

Prolactin levels were evaluated in all trials of all doses of aripiprazole ( $n = 28,242$ ). The incidence of hyperprolactinaemia or increased serum prolactin in patients treated with aripiprazole (0.3 %) was similar to that of placebo (0.2 %). For patients receiving aripiprazole, the median time to onset was 42 days and median duration was 34 days.

The incidence of hypoprolactinaemia or decreased serum prolactin in patients treated with aripiprazole was 0.4 %, compared with 0.02 % for patients treated with placebo. For patients receiving aripiprazole, the median time to onset was 30 days and median duration was 194 days.

### *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.

### 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.

In a 60- to 89-week, randomised, double-blind, placebo-controlled trial in adolescent subjects (n = 146; ages 13-17 years) with schizophrenia, there was a statistically significant difference in the rate of relapse of psychotic symptoms between the aripiprazole (19.39 %) and placebo (37.50 %) groups. The point estimate of the hazard ratio (HR) was 0.461 (95% confidence interval, 0.242-0.879) in the full population. In subgroup analyses the point estimate of the HR was 0.495 for subjects 13 to 14 years of age compared to 0.454 for subjects 15 to 17 years of age. However, the estimation of the HR for the younger (13-14 years) group was not precise, reflecting the smaller number of subjects in that group (aripiprazole, n = 29; placebo, n = 12), and the confidence interval for this estimation (ranging from 0.151 to 1.628) did not allow conclusions to be drawn on the presence of a treatment effect. In contrast the 95 % confidence interval for the HR in the older subgroup (aripiprazole, n = 69; placebo, n = 36) was 0.242 to 0.879 and hence a treatment effect could be concluded in the older patients.

#### *Manic episodes in Bipolar I Disorder in children and adolescents*

Aripiprazole was studied in a 30-week placebo-controlled trial involving 296 children and adolescents (10-17 years), who met DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes with or without psychotic features and had a Y-MRS score  $\geq$  20 at baseline. Among the patients included in the primary efficacy analysis, 139 patients had a current co-morbid diagnosis of ADHD.

Aripiprazole was superior to placebo in change from baseline at week 4 and at week 12 on the Y-MRS total score. In a post-hoc analysis, the improvement over placebo was more pronounced in the patients with associated co-morbidity of ADHD compared to the group without ADHD, where there was no difference from placebo. Recurrence prevention was not established.

**Table 1: Mean improvement from baseline YMRS score by psychiatric comorbidity**

<b>Psychiatric comorbidities</b>	Week 4	Week 12	<b>ADHD</b>	Week 4	Week 12
ABILIFY 10 mg (n = 48)	14.9	15.1	ABILIFY 10 mg (n = 44)	15.2	15.6
ABILIFY 30 mg (n = 51)	16.7	16.9	ABILIFY 30 mg (n = 48)	15.9	16.7
Placebo (n = 52) <sup>a</sup>	7.0	8.2	Placebo (n = 47) <sup>b</sup>	6.3	7.0
<b>No psychiatric comorbidities</b>	Week 4	Week 12	<b>No ADHD</b>	Week 4	Week 12
ABILIFY 10 mg (n = 27)	12.8	15.9	ABILIFY 10 mg (n = 37)	12.7	15.7
ABILIFY 30 mg (n = 25)	15.3	14.7	ABILIFY 30 mg (n = 30)	14.6	13.4
Placebo (n = 18)	9.4	9.7	Placebo (n = 25)	9.9	10.0

<sup>a</sup> n = 51 at Week 4

<sup>b</sup> n = 46 at Week 4

The most common treatment-emergent adverse events among patients receiving 30 mg were extrapyramidal disorder (28.3 %), somnolence (27.3 %), headache (23.2 %), and nausea (14.1 %). Mean weight gain in the 30 weeks treatment-interval was 2.9 kg as compared to 0.98 kg in patients treated with placebo.

*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.

Aripiprazole was also studied in a placebo-controlled, long-term maintenance trial. After a 13-26 week stabilisation on aripiprazole (2-15 mg/day) patients with a stable response were either maintained on aripiprazole or substituted to placebo for further 16 weeks. Kaplan-Meier relapse rates at week 16 were 35 % for aripiprazole and 52 % for placebo; the hazard ratio for relapse within 16 weeks (aripiprazole/placebo) was 0.57 (non-statistically significant difference). The mean weight gain over the stabilisation phase (up to 26 weeks) on aripiprazole was 3.2 kg, and a further mean increase of 2.2 kg for aripiprazole as compared to 0.6 kg for placebo was observed in the second phase (16 weeks) of the trial. Extrapyramidal symptoms were mainly reported during the stabilisation phase in 17 % of patients, with tremor accounting for 6.5 %.

*Tics associated with Tourette's disorder in paediatric patients (see section 4.2)*

The efficacy of aripiprazole was studied in paediatric subjects with Tourette's disorder (aripiprazole: n = 99, placebo: n = 44) in a randomised, double-blind, placebo controlled, 8 week study using a fixed dose weight-based treatment group design over the dose range of 5 mg/day to 20 mg/day and a starting dose of 2 mg. Patients were 7 - 17 years of age and presented an average score of 30 on Total Tic Score on the Yale Global Tic Severity Scale (TTS-YGTSS) at baseline. Aripiprazole showed an improvement on TTS-YGTSS change from baseline to week 8 of 13.35, for the low dose group (5 mg or 10 mg) and 16.94 for the high dose group (10 mg or 20 mg) as compared with an improvement of 7.09 in the placebo group.

The efficacy of aripiprazole in paediatric subjects with Tourette's syndrome (aripiprazole: n = 32, placebo: n = 29) was also evaluated over a flexible dose range of 2 mg/day to 20 mg/day and a starting dose of 2 mg, in a 10 week, randomised, double blind, placebo-controlled study conducted in South-Korea. Patients were 6 - 18 years and presented an average score of 29 on TTS-YGTSS at baseline. Aripiprazole group showed an improvement of 14.97 on TTS-YGTSS change from baseline to week 10 as compared with an improvement of 9.62 in the placebo group.

In both of these short term trials, the clinical relevance of the efficacy findings has not been established, considering the magnitude of treatment effect compared to the large placebo effect and the unclear effects regarding psycho-social functioning. No long term data are available with regard to the efficacy and the safety of aripiprazole in this fluctuating disorder.

The European Medicines Agency has deferred the obligation to submit the results of studies with ABILIFY in one or more subsets of the paediatric population in the treatment of schizophrenia and in the treatment of bipolar affective disorder (see section 4.2 for information on paediatric use).

## **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.

### Biotransformation

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. 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 [<sup>14</sup>C]-labelled aripiprazole, approximately 27 % of the administered radioactivity was recovered in the urine and approximately 60 % in the faeces. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged in the faeces.

### Pharmacokinetics in special patient groups

#### *Paediatric population*

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 10 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*

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

#### *Race*

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

#### *Renal impairment*

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 impairment*

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 data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, 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/m<sup>2</sup>). 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 reactions 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**

#### Tablet core

Calcium silicate  
Croscarmellose sodium  
Crospovidone  
Silicon dioxide  
Xylitol  
Microcrystalline cellulose  
Aspartame (E 951)

Acesulfame potassium  
Vanilla flavour (including vanillin and ethyl vanillin)  
Tartaric acid  
Magnesium stearate

#### Tablet coat

*ABILIFY 10 mg orodispersible tablets*  
Red iron oxide (E 172)

*ABILIFY 15 mg orodispersible tablets*  
Yellow iron oxide (E 172)

*ABILIFY 30 mg orodispersible tablets*  
Red iron oxide (E 172)

### **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 tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

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

## **7. MARKETING AUTHORISATION HOLDER**

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

## **8. MARKETING AUTHORISATION NUMBER(S)**

*ABILIFY 10 mg orodispersible tablets*  
EU/1/04/276/024 (10 mg, 14 x 1 orodispersible tablets)  
EU/1/04/276/025 (10 mg, 28 x 1 orodispersible tablets)  
EU/1/04/276/026 (10 mg, 49 x 1 orodispersible tablets)

*ABILIFY 15 mg orodispersible tablets*  
EU/1/04/276/027 (15 mg, 14 x 1 orodispersible tablets)  
EU/1/04/276/028 (15 mg, 28 x 1 orodispersible tablets)

EU/1/04/276/029 (15 mg, 49 x 1 orodispersible tablets)

*ABILIFY 30 mg orodispersible tablets*

EU/1/04/276/030 (30 mg, 14 x 1 orodispersible tablets)

EU/1/04/276/031 (30 mg, 28 x 1 orodispersible tablets)

EU/1/04/276/032 (30 mg, 49 x 1 orodispersible tablets)

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 04 June 2004

Date of latest renewal: 04 June 2009

## **10. DATE OF REVISION OF THE TEXT**

{MM/YYYY}

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

## 1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 1 mg/ml oral solution

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml oral solution contains 1 mg of aripiprazole.

### Excipients with known effect (per ml)

200 mg fructose, 400 mg sucrose, 1.8 mg methyl parahydroxybenzoate (E218), 0.2 mg propyl parahydroxybenzoate (E 216)

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Oral solution

Clear, colourless to light yellow liquid solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents aged 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 adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older (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. 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 in Bipolar I Disorder:* 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.

*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.



## Special populations

### *Paediatric population*

*Schizophrenia in adolescents aged 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 although individual patients may benefit from a higher dose.

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

*Manic episodes in Bipolar I Disorder in adolescents aged 13 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. The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant undesirable effects including EPS related events, somnolence, fatigue and weight gain (see section 4.8). Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring (see sections 4.4, 4.8 and 5.1). Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, ABILIFY is not recommended for use in patients below 13 years of age (see sections 4.8 and 5.1).

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

*Tics associated with Tourette's disorder:* the safety and efficacy of ABILIFY in children and adolescents 6 to 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.

### *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).

### *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 aged 65 years and 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 is for oral use.

Orodispersible tablets or 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 listed in section 6.1.

### **4.4 Special warnings and precautions for use**

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

#### Suicidality

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

Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among adult patients with schizophrenia or bipolar disorder. There are insufficient paediatric data to evaluate this risk in younger patients (below 18 years of age), but there is evidence that the risk of suicide persists beyond the first 4 weeks of treatment for atypical antipsychotics, including aripiprazole.

#### Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant. Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with aripiprazole and preventive measures undertaken.

#### QT prolongation

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 (see section 4.8).

#### Tardive dyskinesia

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

#### Other extrapyramidal symptoms

In paediatric clinical trials of aripiprazole akathisia and parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

#### 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 active substances, including aripiprazole, 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 (see section 4.8).

#### 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 (see section 4.8).

##### *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 (see section 4.8).

Aripiprazole 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 medicinal products, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotic medicinal products are not available to allow direct comparisons. Patients treated with any antipsychotic medicinal products, including aripiprazole, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control (see section 4.8).

#### Hypersensitivity

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 aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

#### Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic medicinal product use, including aripiprazole. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

#### Pathological gambling

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

#### Intolerance

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

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

#### Patients with ADHD comorbidity

Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these medicinal products are co-administered.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Due to its  $\alpha_1$ -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 aripiprazole

A gastric acid blocker, the H<sub>2</sub> 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.

#### *Quinidine and other CYP2D6 inhibitors*

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 %, respectively. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole 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.

#### *Ketoconazole and other CYP3A4 inhibitors*

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 aripiprazole, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole 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 CYP3A4 inhibitor, the dosage of aripiprazole 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 aripiprazole, modest increases in aripiprazole concentrations might be expected.

#### *Carbamazepine and other CYP3A4 inducers*

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.

Aripiprazole dose should be doubled when concomitant administration of aripiprazole 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 aripiprazole should be reduced to the recommended dose.

#### *Valproate and lithium*

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

#### *Serotonin syndrome*

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

#### Potential for aripiprazole 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), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (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

##### Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients 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.

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

##### Breast-feeding

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. Some paediatric patients with Bipolar I Disorder have an increased incidence of somnolence and fatigue (see section 4.8).

#### 4.8 Undesirable effects

##### Summary of the safety profile

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.

##### Tabulated list of adverse reactions

All ADRs are listed by system organ class and frequency; very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known"

	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<b>Blood and lymphatic system disorders</b>			Leukopenia Neutropenia Thrombocytopenia
<b>Immune system disorders</b>			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)

	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<b>Endocrine disorders</b>		Hyperprolactinaemia	Diabetic hyperosmolar coma Diabetic ketoacidosis Hyperglycaemia
<b>Metabolism and nutrition disorders</b>	Diabetes mellitus	Hyperglycaemia	Hyponatremia Anorexia Weight decreased Weight gain
<b>Psychiatric disorders</b>	Insomnia Anxiety Restlessness	Depression, Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) Pathological gambling Aggression Agitation Nervousness
<b>Nervous system disorders</b>	Akathisia Extrapyramidal disorder Tremor Headache Sedation Somnolence Dizziness	Tardive dyskinesia Dystonia	Neuroleptic Malignant Syndrome (NMS) Grand mal convulsion Serotonin syndrome Speech disorder
<b>Eye disorders</b>	Vision blurred	Diplopia	
<b>Cardiac disorders</b>		Tachycardia	Sudden unexplained death Torsades de pointes QT prolongation Ventricular arrhythmias Cardiac arrest Bradycardia
<b>Vascular disorders</b>		Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Hypertension Syncope
<b>Respiratory, thoracic and mediastinal disorders</b>		Hiccups	Aspiration pneumonia Laryngospasm Oropharyngeal spasm
<b>Gastrointestinal disorders</b>	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting		Pancreatitis Dysphagia Diarrhoea Abdominal discomfort Stomach discomfort
<b>Hepatobiliary disorders</b>			Hepatic failure Hepatitis Jaundice Increased Alanine Aminotransferase (ALT) Increased Aspartate Aminotransferase (AST) Increased Gamma Glutamyl Transferase (GGT) Increased alkaline phosphatase
<b>Skin and</b>			Rash

	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<b>subcutaneous tissue disorders</b>			Photosensitivity reaction Alopecia Hyperhidrosis
<b>Musculoskeletal and connective tissue disorders</b>			Rhabdomyolysis Myalgia Stiffness
<b>Renal and urinary disorders</b>			Urinary incontinence Urinary retention
<b>Pregnancy, puerperium and perinatal conditions</b>			Drug withdrawal syndrome neonatal (see section 4.6)
<b>Reproductive system and breast disorders</b>			Priapism
<b>General disorders and administration site conditions</b>	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
<b>Investigations</b>			Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Increased creatine phosphokinase

#### Description of selected adverse reactions

##### *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.

##### *Akathisia*

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 medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

##### *Prolactin*



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

#### *Laboratory parameters*

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.

#### Paediatric population

##### *Schizophrenia in adolescents aged 15 years and older*

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 reactions 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.

The safety profile of a long-term, double-blind placebo controlled trial was also similar except for the following reactions that were reported more frequently than paediatric patients taking placebo: weight decreased, blood insulin increased, arrhythmia, and leukopenia were reported commonly ( $\geq 1/100$ ,  $< 1/10$ ).

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. In the adolescent (13-17 years) schizophrenia population with aripiprazole exposure of 5 to 30 mg up to 72 months, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 25.6 % and 45.0 %, respectively.

In two long term trials with adolescent (13-17 years) schizophrenia and bipolar patients treated with aripiprazole, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 37.0 % and 59.4 %, respectively.

##### *Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older*

The frequency and type of undesirable effects in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly ( $\geq 1/10$ ) somnolence (23.0 %), extrapyramidal disorder (18.4 %), akathisia (16.0 %), and fatigue (11.8 %); and commonly ( $\geq 1/100$ ,  $< 1/10$ ) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.

The following undesirable effects had a possible dose response relationship; extrapyramidal disorder (incidences were 10 mg, 9.1 %, 30 mg, 28.8 %, placebo, 1.7 %); and akathisia (incidences were 10 mg, 12.1 %, 30 mg, 20.3 %, placebo, 1.7 %).

Mean changes in body weight in adolescents with Bipolar I Disorder at 12 and 30 weeks for aripiprazole were 2.4 kg and 5.8 kg, and for placebo 0.2 kg and 2.3 kg, respectively.

In the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.

In the paediatric bipolar population (10-17 years) with exposure up to 30 weeks, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 28.0 % and 53.3 %, respectively.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **via the national reporting system listed in [Appendix V](#)**.

## 4.9 Overdose

### Signs and symptoms

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

### Management of overdose

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

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.

### Haemodialysis

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antipsychotics, ATC code: N05AX12

#### Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine  $D_2$  and serotonin 5-HT<sub>1A</sub> receptors and antagonism of serotonin 5-HT<sub>2A</sub> 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  $D_2$  and  $D_3$ , serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors and moderate affinity for dopamine  $D_4$ , serotonin 5-HT<sub>2C</sub> and 5-HT<sub>7</sub>, alpha-1 adrenergic and histamine H<sub>1</sub> 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 <sup>11</sup>C-raclopride, a  $D_2/D_3$  receptor ligand, to the caudate and putamen detected by positron emission tomography.

#### Clinical efficacy and safety

### *Schizophrenia*

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.

Aripiprazole 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 adult stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34 % in aripiprazole group and 57 % in placebo.

### *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 adult 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.

### *Prolactin*

Prolactin levels were evaluated in all trials of all doses of aripiprazole (n = 28,242). The incidence of hyperprolactinaemia or increased serum prolactin in patients treated with aripiprazole (0.3 %) was similar to that of placebo (0.2 %). For patients receiving aripiprazole, the median time to onset was 42 days and median duration was 34 days.

The incidence of hypoprolactinaemia or decreased serum prolactin in patients treated with aripiprazole was 0.4 %, compared with 0.02 % for patients treated with placebo. For patients receiving aripiprazole, the median time to onset was 30 days and median duration was 194 days.

### *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.

### 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.

In a 60- to 89-week, randomised, double-blind, placebo-controlled trial in adolescent subjects (n = 146; ages 13-17 years) with schizophrenia, there was a statistically significant difference in the rate of relapse of psychotic symptoms between the aripiprazole (19.39 %) and placebo (37.50 %) groups. The point estimate of the hazard ratio (HR) was 0.461 (95% confidence interval, 0.242-0.879) in the full population. In subgroup analyses the point estimate of the HR was 0.495 for subjects 13 to 14 years of age compared to 0.454 for subjects 15 to 17 years of age. However, the estimation of the HR for the younger (13-14 years) group was not precise, reflecting the smaller number of subjects in

that group (aripiprazole, n = 29; placebo, n = 12), and the confidence interval for this estimation (ranging from 0.151 to 1.628) did not allow conclusions to be drawn on the presence of a treatment effect. In contrast the 95 % confidence interval for the HR in the older subgroup (aripiprazole, n = 69; placebo, n = 36) was 0.242 to 0.879 and hence a treatment effect could be concluded in the older patients.

#### *Manic episodes in Bipolar I Disorder in children and adolescents*

Aripiprazole was studied in a 30-week placebo-controlled trial involving 296 children and adolescents (10-17 years), who met DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes with or without psychotic features and had a Y-MRS score  $\geq$  20 at baseline. Among the patients included in the primary efficacy analysis, 139 patients had a current co-morbid diagnosis of ADHD.

Aripiprazole was superior to placebo in change from baseline at week 4 and at week 12 on the Y-MRS total score. In a post-hoc analysis, the improvement over placebo was more pronounced in the patients with associated co-morbidity of ADHD compared to the group without ADHD, where there was no difference from placebo. Recurrence prevention was not established.

**Table 1: Mean improvement from baseline YMRS score by psychiatric comorbidity**

<b>Psychiatric comorbidities</b>	Week 4	Week 12	<b>ADHD</b>	Week 4	Week 12
ABILIFY 10 mg (n = 48)	14.9	15.1	ABILIFY 10 mg (n = 44)	15.2	15.6
ABILIFY 30 mg (n = 51)	16.7	16.9	ABILIFY 30 mg (n = 48)	15.9	16.7
Placebo (n = 52) <sup>a</sup>	7.0	8.2	Placebo (n = 47) <sup>b</sup>	6.3	7.0
<b>No psychiatric comorbidities</b>	Week 4	Week 12	<b>No ADHD</b>	Week 4	Week 12
ABILIFY 10 mg (n = 27)	12.8	15.9	ABILIFY 10 mg (n = 37)	12.7	15.7
ABILIFY 30 mg (n = 25)	15.3	14.7	ABILIFY 30 mg (n = 30)	14.6	13.4
Placebo (n = 18)	9.4	9.7	Placebo (n = 25)	9.9	10.0

<sup>a</sup> n = 51 at Week 4

<sup>b</sup> n = 46 at Week 4

The most common treatment-emergent adverse events among patients receiving 30 mg were extrapyramidal disorder (28.3 %), somnolence (27.3 %), headache (23.2 %), and nausea (14.1 %). Mean weight gain in the 30 weeks treatment-interval was 2.9 kg as compared to 0.98 kg in patients treated with placebo.

#### *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.

Aripiprazole was also studied in a placebo-controlled, long-term maintenance trial. After a 13-26 week

stabilisation on aripiprazole (2-15 mg/day) patients with a stable response were either maintained on aripiprazole or substituted to placebo for further 16 weeks. Kaplan-Meier relapse rates at week 16 were 35 % for aripiprazole and 52 % for placebo; the hazard ratio for relapse within 16 weeks (aripiprazole/placebo) was 0.57 (non-statistically significant difference). The mean weight gain over the stabilisation phase (up to 26 weeks) on aripiprazole was 3.2 kg, and a further mean increase of 2.2 kg for aripiprazole as compared to 0.6 kg for placebo was observed in the second phase (16 weeks) of the trial. Extrapyramidal symptoms were mainly reported during the stabilisation phase in 17 % of patients, with tremor accounting for 6.5 %.

#### *Tics associated with Tourette's disorder in paediatric patients (see section 4.2)*

The efficacy of aripiprazole was studied in paediatric subjects with Tourette's disorder (aripiprazole: n = 99, placebo: n = 44) in a randomised, double-blind, placebo controlled, 8 week study using a fixed dose weight-based treatment group design over the dose range of 5 mg/day to 20 mg/day and a starting dose of 2 mg. Patients were 7 - 17 years of age and presented an average score of 30 on Total Tic Score on the Yale Global Tic Severity Scale (TTS-YGTSS) at baseline. Aripiprazole showed an improvement on TTS-YGTSS change from baseline to week 8 of 13.35, for the low dose group (5 mg or 10 mg) and 16.94 for the high dose group (10 mg or 20 mg) as compared with an improvement of 7.09 in the placebo group.

The efficacy of aripiprazole in paediatric subjects with Tourette's syndrome (aripiprazole: n = 32, placebo: n = 29) was also evaluated over a flexible dose range of 2 mg/day to 20 mg/day and a starting dose of 2 mg, in a 10 week, randomised, double blind, placebo-controlled study conducted in South-Korea. Patients were 6 - 18 years and presented an average score of 29 on TTS-YGTSS at baseline. Aripiprazole group showed an improvement of 14.97 on TTS-YGTSS change from baseline to week 10 as compared with an improvement of 9.62 in the placebo group.

In both of these short term trials, the clinical relevance of the efficacy findings has not been established, considering the magnitude of treatment effect compared to the large placebo effect and the unclear effects regarding psycho-social functioning. No long term data are available with regard to the efficacy and the safety of aripiprazole in this fluctuating disorder.

The European Medicines Agency has deferred the obligation to submit the results of studies with ABILIFY in one or more subsets of the paediatric population in the treatment of schizophrenia and in the treatment of bipolar affective disorder (see section 4.2 for information on paediatric use).

## **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.

### Biotransformation

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. 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 [<sup>14</sup>C]-labelled aripiprazole, approximately 27 % of the administered radioactivity was recovered in the urine and approximately 60 % in the faeces. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged in the faeces.

#### *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 was linear and dose-proportional.

#### Pharmacokinetics in special patient groups

##### *Paediatric population*

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 10 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*

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

##### *Race*

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

##### *Renal impairment*

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 impairment*

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 data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, 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/m<sup>2</sup>). 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 reactions 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 (E 218)  
Propylene glycol  
Propyl parahydroxybenzoate (E 216)  
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.  
For storage conditions after first opening of the medicinal product, see section 6.3.

#### **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 medicinal product or waste material should be disposed of in accordance with local requirements.

### **7. MARKETING AUTHORISATION HOLDER**

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

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/276/033 (1 mg/ml, 50 ml per bottle)  
EU/1/04/276/034 (1 mg/ml, 150 ml per bottle)  
EU/1/04/276/035 (1 mg/ml, 480 ml per bottle)

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 04 June 2004  
Date of latest renewal: 04 June 2009

### **10. DATE OF REVISION OF THE TEXT**

{MM/YYYY}

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

## **1. NAME OF THE MEDICINAL PRODUCT**

ABILIFY 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 the 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 adult patients with schizophrenia or with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate.

Treatment with ABILIFY 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

##### *Adults*

The recommended initial dose for ABILIFY solution for injection is 9.75 mg (1.3 ml), administered as a single intramuscular injection. The effective dose range of ABILIFY 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 ABILIFY).

If continued treatment is indicated with oral aripiprazole, see the Summary of Product Characteristics for ABILIFY tablets, ABILIFY orodispersible tablets, or ABILIFY oral solution.

#### Special populations

##### *Paediatric population*

The safety and efficacy of ABILIFY solution for injection in children and adolescents aged 0-17 years have not been established. No data are available.

##### *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).

#### *Renal impairment*

No dosage adjustment is required in patients with renal impairment.

#### *Elderly*

The effectiveness of ABILIFY solution for injection in patients aged 65 years and 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 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 listed in section 6.1.

### **4.4 Special warnings and precautions for use**

The efficacy of ABILIFY 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 ABILIFY 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 ABILIFY 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.

### Suicidality

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 treatment, 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 adult patients with schizophrenia or bipolar disorder. There are insufficient paediatric data to evaluate this risk in younger patients (below 18 years of age), but there is evidence that the risk of suicide persists beyond the first 4 weeks of treatment for atypical antipsychotics, including aripiprazole.

### Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant. Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with aripiprazole and preventive measures undertaken (see section 4.8).

### QT prolongation

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

### Tardive dyskinesia

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

### Other extrapyramidal symptoms

In paediatric clinical trials of aripiprazole akathisia and parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

### 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 active substances, including aripiprazole, 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 (see section 4.8).

## 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 (see section 4.8).

### *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 (see section 4.8).

Aripiprazole 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 medicinal products, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotic medicinal products are not available to allow direct comparisons. Patients treated with any antipsychotic medicinal products, including aripiprazole, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control (see section 4.8).

## Hypersensitivity

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 oral aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

## Dysphagia

Oesophageal dysmotility and aspiration have been associated with antipsychotic medicinal product use, including aripiprazole. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

## Pathological gambling

Post-marketing reports of pathological gambling have been reported among patients prescribed oral aripiprazole, regardless of whether these patients had a prior history of gambling. Patients with a prior

history of pathological gambling may be at increased risk and should be monitored carefully (see section 4.8).

#### Patients with ADHD comorbidity

Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these medicinal products are co-administered.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

No specific interaction studies have been performed with ABILIFY solution for injection. The information below is obtained from studies with oral aripiprazole.

Due to its  $\alpha_1$ -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 solution for injection

The administration of lorazepam solution for injection had no effect on the pharmacokinetics of ABILIFY 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 H<sub>2</sub> 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.

#### *Quinidine and other CYP2D6 inhibitors*

In a clinical trial of oral aripiprazole in healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while C<sub>max</sub> was unchanged. The AUC and C<sub>max</sub> of dehydro-aripiprazole, the active metabolite, decreased by 32 % and 47 %, respectively. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole 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.

#### *Ketoconazole and other CYP3A4 inhibitors*

In a clinical trial of oral aripiprazole in healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C<sub>max</sub> by 63 % and 37 %, respectively. The AUC and C<sub>max</sub> 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 aripiprazole, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole 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 CYP3A4 inhibitor, the dosage of aripiprazole 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 aripiprazole, modest increases in aripiprazole concentrations might be expected.

#### *Carbamazepine and other CYP3A4 inducers*

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.

Aripiprazole dose should be doubled when concomitant administration of aripiprazole 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 aripiprazole should be reduced to the recommended dose.

#### *Valproate and lithium*

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

#### *Serotonin syndrome*

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

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

The administration of ABILIFY 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, oral doses of 10-30 mg/day of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, 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**

### Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients 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.

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

#### Breast-feeding

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. Some paediatric patients with Bipolar I Disorder have an increased incidence of somnolence and fatigue (see section 4.8).

#### **4.8 Undesirable effects**

##### Summary of the safety profile

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.

##### Tabulated list of adverse reactions

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 (see section 5.1).

All ADRs are listed by system organ class and frequency; very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known"

	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<b>Blood and lymphatic system disorders</b>			Leukopenia Neutropenia Thrombocytopenia
<b>Immune system disorders</b>			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
<b>Endocrine disorders</b>		Hyperprolactinaemia	Diabetic hyperosmolar coma Diabetic ketoacidosis Hyperglycaemia
<b>Metabolism and nutrition disorders</b>	Diabetes mellitus	Hyperglycaemia	Hyponatremia Anorexia Weight decreased Weight gain
<b>Psychiatric disorders</b>	Insomnia Anxiety	Depression, Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see



	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
	Restlessness		section 4.4) Pathological gambling Aggression Agitation Nervousness
<b>Nervous system disorders</b>	Akathisia Extrapyramidal disorder Tremor Headache Sedation Somnolence Dizziness	Tardive dyskinesia Dystonia	Neuroleptic Malignant Syndrome (NMS) Grand mal convulsion Serotonin syndrome Speech disorder
<b>Eye disorders</b>	Vision blurred	Diplopia	
<b>Cardiac disorders</b>		Tachycardia	Sudden unexplained death Torsades de pointes QT prolongation Ventricular arrhythmias Cardiac arrest Bradycardia
<b>Vascular disorders</b>		Increased diastolic blood pressure Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Hypertension Syncope
<b>Respiratory, thoracic and mediastinal disorders</b>		Hiccups	Aspiration pneumonia Laryngospasm Oropharyngeal spasm
<b>Gastrointestinal disorders</b>	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting	Dry mouth	Pancreatitis Dysphagia Diarrhoea Abdominal discomfort Stomach discomfort
<b>Hepatobiliary disorders</b>			Hepatic failure Hepatitis Jaundice Increased Alanine Aminotransferase (ALT) Increased Aspartate Aminotransferase (AST) Increased Gamma Glutamyl Transferase (GGT) Increased alkaline phosphatase
<b>Skin and subcutaneous tissue disorders</b>			Rash Photosensitivity reaction Alopecia Hyperhidrosis
<b>Musculoskeletal and connective tissue disorders</b>			Rhabdomyolysis Myalgia Stiffness
<b>Renal and urinary disorders</b>			Urinary incontinence Urinary retention
<b>Pregnancy,</b>			Drug withdrawal syndrome

	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<b>puerperium and perinatal conditions</b>			neonatal (see section 4.6)
<b>Reproductive system and breast disorders</b>			Priapism
<b>General disorders and administration site conditions</b>	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
<b>Investigations</b>			Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Increased creatine phosphokinase

### Description of selected adverse reactions

#### *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.

#### *Akathisia*

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 medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

#### *Prolactin*

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

#### *Laboratory parameters*

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.

## Paediatric population

### *Schizophrenia in adolescents aged 15 years and older*

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 reactions 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.

The safety profile of a long-term, double-blind placebo controlled trial was also similar except for the following reactions that were reported more frequently than paediatric patients taking placebo: weight decreased, blood insulin increased, arrhythmia, and leukopenia were reported commonly ( $\geq 1/100$ ,  $< 1/10$ ).

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. In the adolescent (13-17 years) schizophrenia population with aripiprazole exposure of 5 to 30 mg up to 72 months, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 25.6 % and 45.0 %, respectively.

In two long term trials with adolescent (13-17 years) schizophrenia and bipolar patients treated with aripiprazole, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 37.0 % and 59.4 %, respectively.

### *Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older*

The frequency and type of undesirable effects in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly ( $\geq 1/10$ ) somnolence (23.0 %), extrapyramidal disorder (18.4 %), akathisia (16.0 %), and fatigue (11.8 %); and commonly ( $\geq 1/100$ ,  $< 1/10$ ) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.

The following undesirable effects had a possible dose response relationship; extrapyramidal disorder (incidences were 10 mg, 9.1 %, 30 mg, 28.8 %, placebo, 1.7 %); and akathisia (incidences were 10 mg, 12.1 %, 30 mg, 20.3 %, placebo, 1.7 %).

Mean changes in body weight in adolescents with Bipolar I Disorder at 12 and 30 weeks for aripiprazole were 2.4 kg and 5.8 kg, and for placebo 0.2 kg and 2.3 kg, respectively.

In the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.

In the paediatric bipolar population (10-17 years) with exposure up to 30 weeks, incidence of low serum prolactin levels in females ( $< 3$  ng/ml) and males ( $< 2$  ng/ml) was 28.0 % and 53.3 %, respectively.

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **via the national reporting system listed in [Appendix V](#)**.

## **4.9 Overdose**

### Signs and symptoms

In clinical trials and post-marketing experience, accidental or intentional acute overdose of

aripiprazole alone was identified in adult patients with reported estimated doses up to 1,260 mg with no fatalities. The potentially medically important signs and symptoms observed included lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting and diarrhoea. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence, transient loss of consciousness and extrapyramidal symptoms.

#### Management of overdose

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

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.

#### Haemodialysis

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: other antipsychotics, ATC code: N05AX12

#### Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine  $D_2$  and serotonin 5-HT<sub>1A</sub> receptors and antagonism of serotonin 5-HT<sub>2A</sub> 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  $D_2$  and  $D_3$ , serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors and moderate affinity for dopamine  $D_4$ , serotonin 5-HT<sub>2C</sub> and 5-HT<sub>7</sub>, alpha-1 adrenergic and histamine H<sub>1</sub> 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 <sup>11</sup>C-raclopride, a  $D_2/D_3$  receptor ligand, to the caudate and putamen detected by positron emission tomography.

#### Clinical efficacy and safety

##### *Agitation in schizophrenia and Bipolar I Disorder with ABILIFY solution for injection*

In two short-term (24-hour) placebo-controlled trials involving 554 schizophrenic adult patients presenting with agitation and disturbed behaviours, ABILIFY 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, ABILIFY 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 ABILIFY solution for injection. 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 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.

Aripiprazole 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 adult stabilised patients with chronic schizophrenia, oral aripiprazole had significantly greater reduction in relapse rate, 34 % in oral aripiprazole group and 57 % in placebo.

#### *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 adult 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.

#### *Prolactin*

Prolactin levels were evaluated in all trials of all doses of aripiprazole (n = 28,242). The incidence of hyperprolactinaemia or increased serum prolactin in patients treated with aripiprazole (0.3 %) was similar to that of placebo (0.2 %). For patients receiving aripiprazole, the median time to onset was 42 days and median duration was 34 days.

The incidence of hypoprolactinaemia or decreased serum prolactin in patients treated with aripiprazole was 0.4 %, compared with 0.02 % for patients treated with placebo. For patients receiving aripiprazole, the median time to onset was 30 days and median duration was 194 days.

#### *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  $\leq 12$ ) 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.

#### 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.

In a 60- to 89-week, randomised, double-blind, placebo-controlled trial in adolescent subjects (n = 146; ages 13-17 years) with schizophrenia, there was a statistically significant difference in the rate of relapse of psychotic symptoms between the aripiprazole (19.39 %) and placebo (37.50 %) groups. The point estimate of the hazard ratio (HR) was 0.461 (95% confidence interval, 0.242-0.879) in the full population. In subgroup analyses the point estimate of the HR was 0.495 for subjects 13 to 14 years of age compared to 0.454 for subjects 15 to 17 years of age. However, the estimation of the HR for the younger (13-14 years) group was not precise, reflecting the smaller number of subjects in that group (aripiprazole, n = 29; placebo, n = 12), and the confidence interval for this estimation (ranging from 0.151 to 1.628) did not allow conclusions to be drawn on the presence of a treatment effect. In contrast the 95 % confidence interval for the HR in the older subgroup (aripiprazole, n = 69; placebo, n = 36) was 0.242 to 0.879 and hence a treatment effect could be concluded in the older patients.

#### *Manic episodes in Bipolar I Disorder in children and adolescents with oral aripiprazole*

Aripiprazole was studied in a 30-week placebo-controlled trial involving 296 children and adolescents (10-17 years), who met DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes with or without psychotic features and had a Y-MRS score  $\geq 20$  at baseline. Among the patients included in the primary efficacy analysis, 139 patients had a current co-morbid diagnosis of ADHD.

Aripiprazole was superior to placebo in change from baseline at week 4 and at week 12 on the Y-MRS total score. In a post-hoc analysis, the improvement over placebo was more pronounced in the patients with associated co-morbidity of ADHD compared to the group without ADHD, where there was no difference from placebo. Recurrence prevention was not established.

**Table 1: Mean improvement from baseline YMRS score by psychiatric comorbidity**

<b>Psychiatric comorbidities</b>	Week 4	Week 12	<b>ADHD</b>	Week 4	Week 12
ABILIFY 10 mg (n = 48)	14.9	15.1	ABILIFY 10 mg (n = 44)	15.2	15.6
ABILIFY 30 mg (n = 51)	16.7	16.9	ABILIFY 30 mg (n = 48)	15.9	16.7
Placebo (n = 52) <sup>a</sup>	7.0	8.2	Placebo (n = 47) <sup>b</sup>	6.3	7.0
<b>No psychiatric comorbidities</b>	Week 4	Week 12	<b>No ADHD</b>	Week 4	Week 12
ABILIFY 10 mg (n = 27)	12.8	15.9	ABILIFY 10 mg (n = 37)	12.7	15.7
ABILIFY 30 mg (n = 25)	15.3	14.7	ABILIFY 30 mg (n = 30)	14.6	13.4
Placebo (n = 18)	9.4	9.7	Placebo (n = 25)	9.9	10.0

<sup>a</sup>n = 51 at Week 4

<sup>b</sup>n = 46 at Week 4

The most common treatment-emergent adverse events among patients receiving 30 mg were extrapyramidal disorder (28.3 %), somnolence (27.3 %), headache (23.2 %), and nausea (14.1 %). Mean weight gain in the 30 weeks treatment-interval was 2.9 kg as compared to 0.98 kg in patients treated with placebo.

The European Medicines Agency has deferred the obligation to submit the results of studies with ABILIFY in one or more subsets of the paediatric population in the treatment of schizophrenia and in the treatment of bipolar affective disorder (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

ABILIFY 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

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

#### Biotransformation

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. 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 [<sup>14</sup>C]-labelled aripiprazole, approximately 27 % of the administered radioactivity was recovered in the urine and approximately 60 % in the faeces. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged in the faeces.

#### Pharmacokinetics in special patient groups

##### *Paediatric population*

The pharmacokinetics of oral aripiprazole and dehydro-aripiprazole in paediatric patients 10 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*

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

##### *Race*

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

##### *Renal impairment*

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 impairment*

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 ABILIFY 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 data reveal no special hazard for humans based on conventional oral aripiprazole studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, 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/m<sup>2</sup>). 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 reactions 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  $\beta$ -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.

For storage conditions after first opening of the medicinal product, see section 6.3.

## **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.

Each carton contains one single-use type I glass vial with a rubber butyl stopper and a "tear-off" aluminium seal.

## **6.6 Special precautions for disposal**

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

## **7. MARKETING AUTHORISATION HOLDER**

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

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/276/036

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 04 June 2004

Date of latest renewal: 04 June 2009

## **10. DATE OF REVISION OF THE TEXT**

{MM/YYYY}

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

## **ANNEX II**

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

### Name and address of the manufacturers responsible for batch release

Bristol-Myers Squibb S.r.l.  
Contrada Fontana del Ceraso  
I-03012 Anagni-Frosinone - Italy

AndersonBrecon (UK) Limited  
Wye Valley Business Park, Brecon Road, Hay-on-Wye  
Hereford - Herefordshire HR3 5PG - United Kingdom

Elaiapharm  
2881 Route des Crêtes, Z.I. Les Bouilides-Sophia Antipolis,  
06560 Valbonne - France

Zambon S.p.A.  
Via della Chimica, 9  
I-36100 Vicenza(VI) - Italy

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

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

### **• Periodic Safety Update Reports**

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

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

### **• Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

ABILIFY 5 mg tablets

aripiprazole

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/276/001 (5 mg, 14 x 1 tablets)  
EU/1/04/276/002 (5 mg, 28 x 1 tablets)  
EU/1/04/276/003 (5 mg, 49 x 1 tablets)  
EU/1/04/276/004 (5 mg, 56 x 1 tablets)  
EU/1/04/276/005 (5 mg, 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

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:



**MINIMUM PARTICULARS TO APPEAR ON 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(S)**

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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/276/006 (10 mg, 14 x 1 tablets)  
EU/1/04/276/007 (10 mg, 28 x 1 tablets)  
EU/1/04/276/008 (10 mg, 49 x 1 tablets)  
EU/1/04/276/009 (10 mg, 56 x 1 tablets)  
EU/1/04/276/010 (10 mg, 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

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON 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(S)**

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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/276/011 (15 mg, 14 x 1 tablets)  
EU/1/04/276/012 (15 mg, 28 x 1 tablets)  
EU/1/04/276/013 (15 mg, 49 x 1 tablets)  
EU/1/04/276/014 (15 mg, 56 x 1 tablets)  
EU/1/04/276/015 (15 mg, 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

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON 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(S)**

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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/276/016 (30 mg, 14 x 1 tablets)  
EU/1/04/276/017 (30 mg, 28 x 1 tablets)  
EU/1/04/276/018 (30 mg, 49 x 1 tablets)  
EU/1/04/276/019 (30 mg, 56 x 1 tablets)  
EU/1/04/276/020 (30 mg, 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

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON 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(S)**

Each tablet contains 10 mg of aripiprazole.

**3. LIST OF EXCIPIENTS**

Contains aspartame and lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 x 1 orodispersible tablets

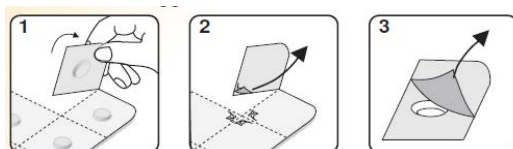
28 x 1 orodispersible tablets

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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/276/024 (10 mg, 14 x 1 orodispersible tablets)  
EU/1/04/276/025 (10 mg, 28 x 1 orodispersible tablets)  
EU/1/04/276/026 (10 mg, 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

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON 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(S)**

Each tablet contains 15 mg of aripiprazole.

**3. LIST OF EXCIPIENTS**

Contains aspartame and lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 x 1 orodispersible tablets

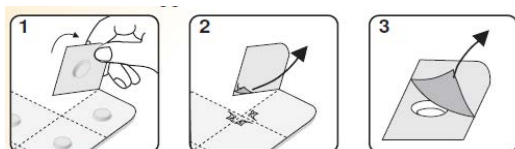
28 x 1 orodispersible tablets

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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/276/027 (15 mg, 14 x 1 orodispersible tablets)  
EU/1/04/276/028 (15 mg, 28 x 1 orodispersible tablets)  
EU/1/04/276/029 (15 mg, 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

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON 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(S)**

Each tablet contains 30 mg of aripiprazole.

**3. LIST OF EXCIPIENTS**

Contains aspartame and lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 x 1 orodispersible tablets

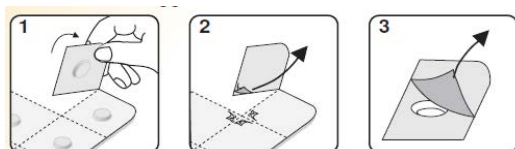
28 x 1 orodispersible tablets

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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/276/030 (30 mg, 14 x 1 orodispersible tablets)  
EU/1/04/276/031 (30 mg, 28 x 1 orodispersible tablets)  
EU/1/04/276/032 (30 mg, 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

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON 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(S)**

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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

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.  
Gallions, Wexham Springs, Framewood Road,  
Wexham, SL3 6PJ - 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

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER 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**

Read the package leaflet before use.

Intramuscular use.

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/276/036

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**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 / 1.3 ml

**6. OTHER**



**B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

**ABILIFY 5 mg tablets**  
**ABILIFY 10 mg tablets**  
**ABILIFY 15 mg tablets**  
**ABILIFY 30 mg tablets**

aripiprazole

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### What is in this leaflet

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

### 1. What ABILIFY tablets are and what they are used for

ABILIFY tablets contain the active substance aripiprazole and belong to a group of medicines called antipsychotics. It is used to treat adults and adolescents aged 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 tablets are used to treat adults and adolescents aged 13 years and older 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. In adults it also prevents this condition from returning in patients who have responded to the treatment with ABILIFY tablets.

### 2. What you need to know before you take ABILIFY tablets

#### Do not take ABILIFY tablets

- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

#### Warnings and precautions

Talk to your doctor before taking ABILIFY tablets 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
- past experience of excessive gambling

If you notice you are gaining weight, develop unusual movements, experience somnolence that interferes with normal daily activities, 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**

Do not use this medicine in children and adolescents under 13 years of age. It is not known if it is safe and effective in these patients.

### **Other medicines and ABILIFY tablets**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY tablets 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 tablets with some medicines may need to change your dose of ABILIFY tablets. 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

Medicines that increase the level of serotonin: triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline), pethidine, St John's Wort and venlafaxine. These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ABILIFY tablets, you should see your doctor.

### **ABILIFY tablets with food, drink and alcohol**

ABILIFY tablets can be taken regardless of meals.  
Alcohol should be avoided.

### **Pregnancy, breast-feeding and fertility**

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

The following symptoms may occur in newborn babies, of mothers that have used ABILIFY tablets in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY tablets, you should not breast-feed.

### **Driving and using machines**

Do not drive or use any tools or machines, until you know how ABILIFY tablets affect you.

### **ABILIFY tablets contain lactose**

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 tablets**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**The recommended 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 and adolescents**

This medicinal product may be started at a low dose with the oral solution (liquid) form.

The dose may be gradually increased to **the recommended 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 effects of your ABILIFY tablets are too strong or too weak, talk to your doctor or pharmacist.

**Try to take your ABILIFY tablets 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 tablets without first consulting your doctor.

### **If you take more ABILIFY tablets 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 your ABILIFY tablets**

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 stop taking ABILIFY tablets**

Do not stop your treatment just because you feel better. It is important that you carry on taking your ABILIFY tablets for as long as your doctor has told you to.

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

## **4. Possible side effects**

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

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

- diabetes mellitus,
- difficulty sleeping,
- feeling anxious,

- feeling restless and unable to keep still, difficulty sitting still,
- uncontrollable twitching, jerking or writhing movements, restless legs,
- trembling,
- headache,
- tiredness,
- sleepiness,
- light-headedness,
- shaking and blurred vision,
- decreased number of or difficulty making bowel movements,
- indigestion,
- feeling sick,
- more saliva in mouth than normal,
- vomiting,
- feeling tired.

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

- increased blood levels of the hormone prolactin,
- too much sugar in the blood,
- depression,
- altered or increased sexual interest,
- uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia),
- muscle disorder causing twisting movements (dystonia),
- double vision,
- fast heart beat,
- a fall in blood pressure on standing up which causes dizziness, light-headedness or fainting,
- hiccups.

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

- low levels of white blood cells,
- low levels of blood platelets,
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives),
- onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma,
- high blood sugar,
- not enough sodium in the blood,
- loss of appetite (anorexia),
- weight loss,
- weight gain,
- thoughts of suicide, suicide attempt and suicide,
- excessive gambling,
- feeling aggressive,
- agitation,
- nervousness,
- combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate, fainting (neuroleptic malignant syndrome),
- seizure,
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles),
- speech disorder,
- sudden unexplained death,
- life-threatening irregular heart beat,
- heart attack,
- slower heart beat,

- 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),
- high blood pressure,
- fainting,
- accidental inhalation of food with risk of pneumonia (lung infection),
- spasm of the muscles around the voice box,
- inflammation of the pancreas,
- difficulty swallowing,
- diarrhoea,
- abdominal discomfort,
- stomach discomfort,
- liver failure,
- inflammation of the liver,
- yellowing of the skin and white part of eyes,
- reports of abnormal liver tests values,
- skin rash,
- sensitivity to light,
- baldness,
- excessive sweating,
- abnormal muscle breakdown which can lead to kidney problems,
- muscle pain,
- stiffness,
- involuntary loss of urine (incontinence),
- difficulty in passing urine,
- withdrawal symptoms in newborn babies in case of exposure during pregnancy,
- prolonged and/or painful erection,
- difficulty controlling core body temperature or overheating,
- chest pain,
- swelling of hands, ankles or feet,
- in blood tests: fluctuating blood sugar, increased glycosylated haemoglobin.

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.

#### **Additional side effects in children and adolescents**

Adolescents aged 13 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness, uncontrollable twitching or jerking movements, restlessness, and tiredness were very common (greater than 1 in 10 patients) and upper abdominal pain, dry mouth, increased heart rate, weight gain, increased appetite, muscle twitching, uncontrolled movements of the limbs, and feeling dizzy, especially when getting up from a lying or sitting position, were common (greater than 1 in 100 patients).

#### **Reporting of side effects**

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

### **5. How to store ABILIFY tablets**

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

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

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

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

## 6. Contents of the pack and other information

### What ABILIFY tablets contain

- The active substance is aripiprazole.  
Each tablet contains 5 mg of aripiprazole.  
Each tablet contains 10 mg of aripiprazole.  
Each tablet contains 15 mg of aripiprazole.  
Each tablet contains 30 mg of aripiprazole.
- The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropylcellulose and magnesium stearate.

#### Tablet coat

ABILIFY 5 mg tablets:	Indigo carmine aluminium lake (E 132)
ABILIFY 10 mg tablets:	Red iron oxide (E 172)
ABILIFY 15 mg tablets:	Yellow iron oxide (E 172)
ABILIFY 30 mg tablets:	Red iron oxide (E 172)

### What ABILIFY tablets looks like and contents of the pack

ABILIFY 5 mg tablets are rectangular and blue, marked with 'A-007' and '5' on one side.  
ABILIFY 10 mg tablets are rectangular and pink, marked with 'A-008' and '10' on one side.  
ABILIFY 15 mg tablets are round and yellow, marked with 'A-009' and '15' on one side.  
ABILIFY 30 mg tablets are round and pink, marked with 'A-011' and '30' on one side.

ABILIFY tablets are supplied in perforated unit dose blisters packed in cartons containing 14 x 1, 28 x 1, 49 x 1, 56 x 1, or 98 x 1 tablets.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder

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

### Manufacturer

Bristol-Myers Squibb S.r.l.  
Contrada Fontana del Ceraso  
I-03012 Anagni-Frosinone - Italy

### AndersonBrecon (UK) Limited

Wye Valley Business Park, Brecon Road, Hay-on-Wye  
Hereford - Herefordshire HR3 5PG - United Kingdom

### Elaiapharm

2881 Route des Crêtes, Z.I. Les Bouilides-Sophia Antipolis,  
06560 Valbonne - France

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

**België/Belgique/Belgien**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**България**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Česká republika**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Danmark**

Otsuka Pharma Scandinavia AB  
Tlf: +46 854 528 660

**Deutschland**

Otsuka Pharma GmbH  
Tel: +49 (0)69 170086-0

**Eesti**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Ελλάδα**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**España**

Otsuka Pharmaceutical, S.A.  
Tel: +34 93 550 01 00

**France**

Otsuka Pharmaceutical France SAS  
Tél: +33(0)1 47 08 00 00

**Hrvatska**

Otsuka Pharmaceutical Europe Ltd.  
Tel: +44 (0)203 747 5000

**Ireland**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Ísland**

Vistor hf.  
Sími: +354 535 7000

**Italia**

Otsuka Pharmaceutical Italy S.r.l.  
Tel: +39 02 00 63 27 10

**Κύπρος**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Lietuva**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Luxembourg/Luxemburg**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Magyarország**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Malta**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Nederland**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Norge**

Otsuka Pharma Scandinavia AB  
Tlf: +46 854 528 660

**Österreich**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Polska**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Portugal**

Lundbeck Portugal Lda  
Tel: +351 21 00 45 900

**România**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Slovenija**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Slovenská republika**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Suomi/Finland**

Otsuka Pharma Scandinavia AB  
Puh/Tel: +46 854 528 660

**Sverige**

Otsuka Pharma Scandinavia AB  
Tel: +46 854 528 660



**Latvija**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**United Kingdom**

Otsuka Pharmaceuticals (UK) Ltd.  
Tel: +44 (0)203 747 5300

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

**Other sources of information**

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

## Package leaflet: Information for the user

**ABILIFY 10 mg orodispersible tablets**

**ABILIFY 15 mg orodispersible tablets**

**ABILIFY 30 mg orodispersible tablets**

aripiprazole

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### **What is in this leaflet**

1. What ABILIFY orodispersible tablets are and what they are used for
2. What you need to know before you take ABILIFY orodispersible tablets
3. How to take ABILIFY orodispersible tablets
4. Possible side effects
5. How to store ABILIFY orodispersible tablets
6. Contents of the pack and other information

### **1. What ABILIFY orodispersible tablets are and what they are used for**

ABILIFY orodispersible tablets contain the active substance aripiprazole and belong to a group of medicines called antipsychotics. It is used to treat adults and adolescents aged 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 orodispersible tablets are used to treat adults and adolescents aged 13 years and older 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. In adults it also prevents this condition from returning in patients who have responded to the treatment with ABILIFY orodispersible tablets.

### **2. What you need to know before you take ABILIFY orodispersible tablets**

#### **Do not take ABILIFY orodispersible tablets**

- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

#### **Warnings and precautions**

Talk to your doctor before taking ABILIFY orodispersible tablets 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

- past experience of excessive gambling

If you notice you are gaining weight, develop unusual movements, experience somnolence that interferes with normal daily activities, 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**

Do not use this medicine in children and adolescents under 13 years of age. It is not known if it is safe and effective in these patients.

### **Other medicines and ABILIFY orodispersible tablets**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY orodispersible tablets 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 orodispersible tablets with some medicines may need to change your dose of ABILIFY orodispersible tablets. 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

Medicines that increase the level of serotonin: triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline), pethidine, St John's Wort and venlafaxine. These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ABILIFY orodispersible tablets, you should see your doctor.

### **ABILIFY orodispersible tablets with food, drink and alcohol**

ABILIFY orodispersible tablets can be taken regardless of meals.  
Alcohol should be avoided.

### **Pregnancy, breast-feeding and fertility**

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

The following symptoms may occur in newborn babies, of mothers that have used ABILIFY orodispersible tablets in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY orodispersible tablets, you should not breast-feed.

### **Driving and using machines**

Do not drive or use any tools or machines, until you know how ABILIFY orodispersible tablets affect you.

### **ABILIFY orodispersible tablets contain aspartame**

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.**

### **ABILIFY orodispersible tablets contain lactose**

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 orodispersible tablets**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**The recommended 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 and adolescents**

This medicinal product may be started at a low dose with the oral solution (liquid) form.

The dose may be gradually increased to **the recommended 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 effects of your ABILIFY orodispersible tablets are too strong or too weak, talk to your doctor or pharmacist.

**Try to take your ABILIFY orodispersible tablets 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 orodispersible tablets without first consulting your doctor.

### **If you take more ABILIFY orodispersible tablets 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 orodispersible tablets**

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 stop taking ABILIFY orodispersible tablets**

Do not stop your treatment just because you feel better. It is important that you carry on taking ABILIFY orodispersible tablets for as long as your doctor has told you to.

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

#### 4. Possible side effects

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

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

- diabetes mellitus,
- difficulty sleeping,
- feeling anxious,
- feeling restless and unable to keep still, difficulty sitting still,
- uncontrollable twitching, jerking or writhing movements, restless legs,
- trembling,
- headache,
- tiredness,
- sleepiness,
- light-headedness,
- shaking and blurred vision,
- decreased number of or difficulty making bowel movements,
- indigestion,
- feeling sick,
- more saliva in mouth than normal,
- vomiting,
- feeling tired.

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

- increased blood levels of the hormone prolactin,
- too much sugar in the blood,
- depression,
- altered or increased sexual interest,
- uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia),
- muscle disorder causing twisting movements (dystonia),
- double vision,
- fast heart beat,
- a fall in blood pressure on standing up which causes dizziness, light-headedness or fainting,
- hiccups.

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

- low levels of white blood cells,
- low levels of blood platelets,
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives),
- onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma,
- high blood sugar,
- not enough sodium in the blood,
- loss of appetite (anorexia),
- weight loss,
- weight gain,
- thoughts of suicide, suicide attempt and suicide,
- excessive gambling,
- feeling aggressive,
- agitation,
- nervousness,

- combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate, fainting (neuroleptic malignant syndrome),
- seizure,
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles),
- speech disorder,
- sudden unexplained death,
- life-threatening irregular heart beat,
- heart attack,
- slower heart beat,
- 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),
- high blood pressure,
- fainting,
- accidental inhalation of food with risk of pneumonia (lung infection),
- spasm of the muscles around the voice box,
- inflammation of the pancreas,
- difficulty swallowing,
- diarrhoea,
- abdominal discomfort,
- stomach discomfort,
- liver failure,
- inflammation of the liver,
- yellowing of the skin and white part of eyes,
- reports of abnormal liver tests values,
- skin rash,
- sensitivity to light,
- baldness,
- excessive sweating,
- abnormal muscle breakdown which can lead to kidney problems,
- muscle pain,
- stiffness,
- involuntary loss of urine (incontinence),
- difficulty in passing urine,
- withdrawal symptoms in newborn babies in case of exposure during pregnancy,
- prolonged and/or painful erection,
- difficulty controlling core body temperature or overheating,
- chest pain,
- swelling of hands, ankles or feet,
- in blood tests: fluctuating blood sugar, increased glycosylated haemoglobin.

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.

#### **Additional side effects in children and adolescents**

Adolescents aged 13 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness, uncontrollable twitching or jerking movements, restlessness, and tiredness were very common (greater than 1 in 10 patients) and upper abdominal pain, dry mouth, increased heart rate, weight gain, increased appetite, muscle twitching, uncontrolled movements of the limbs, and feeling dizzy, especially when getting up from a lying or sitting position, were common (greater than 1 in 100 patients).

#### **Reporting of side effects**

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

this medicine.

## 5. How to store ABILIFY orodispersible tablets

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

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

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

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

## 6. Contents of the pack and other information

### What ABILIFY orodispersible tablets contain

- The active substance is aripiprazole.  
Each orodispersible tablet contains 10 mg of aripiprazole.  
Each orodispersible tablet contains 15 mg of 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 and magnesium stearate.

#### Tablet coat

ABILIFY 10 mg orodispersible tablets:	Red iron oxide (E 172)
ABILIFY 15 mg orodispersible tablets:	Yellow iron oxide (E 172)
ABILIFY 30 mg orodispersible tablets:	Red iron oxide (E 172)

### What ABILIFY orodispersible tablets 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.

ABILIFY 15 mg orodispersible tablets are round and yellow, marked with "A" over "641" on one side and '15' on the other.

ABILIFY 30 mg orodispersible tablets are round and pink, marked with "A" over "643" on one side and '30' on the other.

ABILIFY orodispersible tablets are supplied in perforated unit dose blisters packed in cartons containing 14 x 1, 28 x 1, or 49 x 1 orodispersible tablets.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder

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

### Manufacturer

Bristol-Myers Squibb S.r.l.  
Contrada Fontana del Ceraso  
I-03012 Anagni-Frosinone - Italy

### Elaiapharm

2881 Route des Crêtes, Z.I. Les Bouilides-Sophia Antipolis,

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

**België/Belgique/Belgien**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**България**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Česká republika**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Danmark**

Otsuka Pharma Scandinavia AB  
Tlf: +46 854 528 660

**Deutschland**

Otsuka Pharma GmbH  
Tel: +49 (0)69 170086-0

**Eesti**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Ελλάδα**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**España**

Otsuka Pharmaceutical, S.A.  
Tel: +34 93 550 01 00

**France**

Otsuka Pharmaceutical France SAS  
Tél: +33(0)1 47 08 00 00

**Hrvatska**

Otsuka Pharmaceutical Europe Ltd.  
Tel: +44 (0)203 747 5000

**Ireland**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Ísland**

Vistor hf.  
Sími: +354 535 7000

**Italia**

Otsuka Pharmaceutical Italy S.r.l.  
Tel: +39 02 00 63 27 10

**Lietuva**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Luxembourg/Luxemburg**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Magyarország**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Malta**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Nederland**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Norge**

Otsuka Pharma Scandinavia AB  
Tlf: +46 854 528 660

**Österreich**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Polska**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Portugal**

Lundbeck Portugal Lda  
Tel: +351 21 00 45 900

**România**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Slovenija**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Slovenská republika**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Suomi/Finland**

Otsuka Pharma Scandinavia AB  
Puh/Tel: +46 854 528 660



**Κύπρος**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Sverige**

Otsuka Pharma Scandinavia AB  
Tel: +46 854 528 660

**Latvija**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**United Kingdom**

Otsuka Pharmaceuticals (UK) Ltd.  
Tel: +44 (0)203 747 5300

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

**Other sources of information**

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

## 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 because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

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

#### **1. What ABILIFY oral solution is and what it is used for**

ABILIFY oral solution contains the active substance aripiprazole and belongs to a group of medicines called antipsychotics. It is used to treat adults and adolescents aged 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 oral solution is used to treat adults and adolescents aged 13 years and older 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. In adults it also prevents this condition from returning in patients who have responded to the treatment with ABILIFY oral solution.

#### **2. What you need to know before you take ABILIFY oral solution**

##### **Do not take ABILIFY oral solution**

- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

##### **Warnings and precautions**

Talk to your doctor before taking ABILIFY oral solution 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
- past experience of excessive gambling

If you notice you are gaining weight, develop unusual movements, experience somnolence that

interferes with normal daily activities, 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**

Do not use this medicine in children and adolescents under 13 years of age. It is not known if it is safe and effective in these patients.

### **Other medicines and ABILIFY oral solution**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY oral solution 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 oral solution with some medicines may need to change your dose of ABILIFY oral solution. 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

Medicines that increase the level of serotonin: triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline), pethidine, St John's Wort and venlafaxine. These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ABILIFY oral solution, you should see your doctor.

### **ABILIFY oral solution with food, drink and alcohol**

ABILIFY oral solution 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.

### **Pregnancy, breast-feeding and fertility**

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

The following symptoms may occur in newborn babies, of mothers that have used ABILIFY oral solution in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY oral solution, you should not breast-feed.

### **Driving and using machines**

Do not drive or use any tools or machines until you know how ABILIFY oral solution affects you.

**ABILIFY oral solution contains fructose, sucrose and parahydroxybenzoates**

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 oral solution**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

**The recommended 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 and adolescents**

**The recommended dose for adolescents is 10 ml solution (corresponding to 10 mg aripiprazole) once a day.** However your doctor may prescribe a lower or higher dose to a maximum of 30 ml (i.e. 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 oral solution 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 oral solution without first consulting your doctor.

**If you take more ABILIFY oral solution 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 oral solution**

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 stop taking ABILIFY oral solution**

Do not stop your treatment just because you feel better. It is important that you carry on taking ABILIFY oral solution for as long as your doctor has told you to.

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

**4. Possible side effects**

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

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

- diabetes mellitus,

- difficulty sleeping,
- feeling anxious,
- feeling restless and unable to keep still, difficulty sitting still,
- uncontrollable twitching, jerking or writhing movements, restless legs,
- trembling,
- headache,
- tiredness,
- sleepiness,
- light-headedness,
- shaking and blurred vision,
- decreased number of or difficulty making bowel movements,
- indigestion,
- feeling sick,
- more saliva in mouth than normal,
- vomiting,
- feeling tired.

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

- increased blood levels of the hormone prolactin,
- too much sugar in the blood,
- depression,
- altered or increased sexual interest,
- uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia),
- muscle disorder causing twisting movements (dystonia),
- double vision,
- fast heart beat,
- a fall in blood pressure on standing up which causes dizziness, light-headedness or fainting,
- hiccups.

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

- low levels of white blood cells,
- low levels of blood platelets,
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives),
- onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma,
- high blood sugar,
- not enough sodium in the blood,
- loss of appetite (anorexia),
- weight loss,
- weight gain,
- thoughts of suicide, suicide attempt and suicide,
- excessive gambling,
- feeling aggressive,
- agitation,
- nervousness,
- combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate, fainting (neuroleptic malignant syndrome),
- seizure,
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles),
- speech disorder,
- sudden unexplained death,
- life-threatening irregular heart beat,
- heart attack,
- slower heart beat,

- 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),
- high blood pressure,
- fainting,
- accidental inhalation of food with risk of pneumonia (lung infection),
- spasm of the muscles around the voice box,
- inflammation of the pancreas,
- difficulty swallowing,
- diarrhoea,
- abdominal discomfort,
- stomach discomfort,
- liver failure,
- inflammation of the liver,
- yellowing of the skin and white part of eyes,
- reports of abnormal liver tests values,
- skin rash,
- sensitivity to light,
- baldness,
- excessive sweating,
- abnormal muscle breakdown which can lead to kidney problems,
- muscle pain,
- stiffness,
- involuntary loss of urine (incontinence),
- difficulty in passing urine,
- withdrawal symptoms in newborn babies in case of exposure during pregnancy,
- prolonged and/or painful erection,
- difficulty controlling core body temperature or overheating,
- chest pain,
- swelling of hands, ankles or feet,
- in blood tests: fluctuating blood sugar, increased glycosylated haemoglobin.

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.

#### **Additional side effects in children and adolescents**

Adolescents aged 13 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness, uncontrollable twitching or jerking movements, restlessness, and tiredness were very common (greater than 1 in 10 patients) and upper abdominal pain, dry mouth, increased heart rate, weight gain, increased appetite, muscle twitching, uncontrolled movements of the limbs, and feeling dizzy, especially when getting up from a lying or sitting position, were common (greater than 1 in 100 patients).

#### **Reporting of side effects**

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

### **5. How to store ABILIFY oral solution**

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

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

This medicine does not require any special storage conditions.  
Use within 6 months after first opening.

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

## 6. Contents of the pack and other information

### What ABILIFY oral solution 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 oral solution 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.  
Gallions, Wexham Springs, Framewood Road,  
Wexham, SL3 6PJ - United Kingdom

### Manufacturer

Bristol-Myers Squibb S.r.l.  
Contrada Fontana del Ceraso  
I-03012 Anagni-Frosinone - Italy

### Elaiapharm

2881 Route des Crêtes, Z.I. Les Bouilides-Sophia Antipolis,  
06560 Valbonne - France

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

### België/Belgique/Belgien

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### Lietuva

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### България

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### Luxembourg/Luxemburg

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### Česká republika

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### Magyarország

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Danmark**

Otsuka Pharma Scandinavia AB  
Tlf: +46 854 528 660

**Deutschland**

Otsuka Pharma GmbH  
Tel: +49 (0)69 170086-0

**Eesti**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Ελλάδα**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**España**

Otsuka Pharmaceutical, S.A.  
Tel: +34 93 550 01 00

**France**

Otsuka Pharmaceutical France SAS  
Tél: +33(0)1 47 08 00 00

**Hrvatska**

Otsuka Pharmaceutical Europe Ltd.  
Tel: +44 (0)203 747 5000

**Ireland**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Ísland**

Vistor hf.  
Sími: +354 535 7000

**Italia**

Otsuka Pharmaceutical Italy S.r.l.  
Tel: +39 02 00 63 27 10

**Κύπρος**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Latvija**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Malta**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Nederland**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Norge**

Otsuka Pharma Scandinavia AB  
Tlf: +46 854 528 660

**Österreich**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Polska**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Portugal**

Lundbeck Portugal Lda  
Tel: +351 21 00 45 900

**România**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Slovenija**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Slovenská republika**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Suomi/Finland**

Otsuka Pharma Scandinavia AB  
Puh/Tel: +46 854 528 660

**Sverige**

Otsuka Pharma Scandinavia AB  
Tel: +46 854 528 660

**United Kingdom**

Otsuka Pharmaceuticals (UK) Ltd.  
Tel: +44 (0)203 747 5300

This leaflet was last revised in{MM/YYYY}

**Other sources of information**

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

<http://www.ema.europa.eu>.



## **Package leaflet: Information for the user**

### **ABILIFY 7.5 mg/ml solution for injection** aripiprazole

**Read all of this leaflet carefully before you receive this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

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

#### **1. What ABILIFY solution for injection is and what it is used for**

ABILIFY solution for injection contains the active substance aripiprazole and belongs to 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 is not appropriate. Your doctor will change your treatment to oral ABILIFY as soon as appropriate.

#### **2. What you need to know before you are given ABILIFY solution for injection**

##### **Do not use ABILIFY solution for injection**

- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

##### **Warnings and precautions**

Talk to your doctor before you are given ABILIFY solution for injection.

Before treatment with ABILIFY solution for injection, tell your doctor if you suffer from

- high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite, and feeling weak) or family history of diabetes
- fits (seizures) since your doctor may want to monitor you more closely
- involuntary, irregular muscle movements, especially in the face
- cardiovascular diseases (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure
- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots
- past experience of excessive gambling

If you notice you are gaining weight, develop unusual movements, experience somnolence that interferes with normal daily activities, 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 solution for injection.

### **Other medicines and ABILIFY solution for injection**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Blood pressure-lowering medicines: ABILIFY solution for injection 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.

Using ABILIFY solution for injection with some medicines may need to change your dose of ABILIFY solution for injection. 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

Medicines that increase the level of serotonin: triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline), pethidine, St John's Wort and venlafaxine. These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ABILIFY solution for injection, you should see your doctor.

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 solution for injection if your doctor tells you that you can.

### **ABILIFY solution for injection with food, drink and alcohol**

ABILIFY solution for injection can be administered regardless of meals.

Alcohol should be avoided.

### **Pregnancy, breast-feeding and fertility**

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

The following symptoms may occur in newborn babies, of mothers that have used ABILIFY solution

for injection in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Be sure to tell your doctor immediately if you are breast-feeding.

If you are taking ABILIFY solution for injection, 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 ABILIFY solution for injection is given**

Your doctor will decide how much ABILIFY solution for injection you need and how long you need it for. The recommended 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 given more ABILIFY solution for injection than you need**

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

### **If you miss an injection of ABILIFY solution for injection**

It is important not to miss your dose. If you miss an injection, you should contact your doctor to arrange your next injection as soon as you can.

### **If you stop receiving ABILIFY solution for injection**

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

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

## **4. Possible side effects**

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

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

- diabetes mellitus,
- difficulty sleeping,
- feeling anxious,
- feeling restless and unable to keep still, difficulty sitting still,
- uncontrollable twitching, jerking or writhing movements, restless legs,
- trembling,
- headache,
- tiredness,
- sleepiness,
- light-headedness,
- shaking and blurred vision,
- decreased number of or difficulty making bowel movements,

- indigestion,
- feeling sick,
- more saliva in mouth than normal,
- vomiting,
- feeling tired.

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

- increased blood levels of the hormone prolactin,
- too much sugar in the blood,
- depression,
- altered or increased sexual interest,
- uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia),
- muscle disorder causing twisting movements (dystonia),
- double vision,
- fast heart beat,
- increased diastolic blood pressure,
- a fall in blood pressure on standing up which causes dizziness, light-headedness or fainting,
- hiccups,
- dry mouth.

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

- low levels of white blood cells,
- low levels of blood platelets,
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives),
- onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma,
- high blood sugar,
- not enough sodium in the blood,
- loss of appetite (anorexia),
- weight loss,
- weight gain,
- thoughts of suicide, suicide attempt and suicide,
- excessive gambling,
- feeling aggressive,
- agitation,
- nervousness,
- combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate, fainting (neuroleptic malignant syndrome),
- seizure,
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles),
- speech disorder,
- sudden unexplained death,
- life-threatening irregular heart beat,
- heart attack,
- slower heart beat,
- 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),
- high blood pressure,
- fainting,
- accidental inhalation of food with risk of pneumonia (lung infection),
- spasm of the muscles around the voice box,
- inflammation of the pancreas,
- difficulty swallowing,

- diarrhoea,
- abdominal discomfort,
- stomach discomfort,
- liver failure,
- inflammation of the liver,
- yellowing of the skin and white part of eyes,
- reports of abnormal liver tests values,
- skin rash,
- sensitivity to light,
- baldness,
- excessive sweating,
- abnormal muscle breakdown which can lead to kidney problems,
- muscle pain,
- stiffness,
- involuntary loss of urine (incontinence),
- difficulty in passing urine,
- withdrawal symptoms in newborn babies in case of exposure during pregnancy,
- prolonged and/or painful erection,
- difficulty controlling core body temperature or overheating,
- chest pain,
- swelling of hands, ankles or feet,
- in blood tests: increased or fluctuating blood sugar, increased glycosylated haemoglobin.

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.

#### **Additional side effects in children and adolescents**

Adolescents aged 13 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness, uncontrollable twitching or jerking movements, restlessness, and tiredness were very common (greater than 1 in 10 patients) and upper abdominal pain, dry mouth, increased heart rate, weight gain, increased appetite, muscle twitching, uncontrolled movements of the limbs, and feeling dizzy, especially when getting up from a lying or sitting position, were common (greater than 1 in 100 patients).

#### **Reporting of side effects**

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

### **5. How to store ABILIFY solution for injection**

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

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

Keep the vial in the outer carton in order to protect from light.

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

### **6. Contents of the pack and other information**

#### **What ABILIFY solution for injection 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  $\beta$ -cyclodextrin (SBECD), tartaric acid, sodium hydroxide, and water for injections.

### **What ABILIFY solution for injection 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.

Each carton contains one single-use type I glass vial with a rubber butyl stopper and a "tear-off" aluminium seal.

### **Marketing Authorisation Holder**

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

### **Manufacturer**

Bristol-Myers Squibb S.r.l.  
Contrada Fontana del Ceraso  
I-03012 Anagni-Frosinone - Italy

Zambon S.p.A.

Via della Chimica, 9  
I-36100 Vicenza(VI) - Italy

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

### **België/Belgique/Belgien**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### **България**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### **Česká republika**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### **Danmark**

Otsuka Pharma Scandinavia AB  
Tlf: +46 854 528 660

### **Deutschland**

Otsuka Pharma GmbH  
Tel: +49 (0)69 170086-0

### **Eesti**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### **Lietuva**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### **Luxembourg/Luxemburg**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### **Magyarország**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### **Malta**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### **Nederland**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

### **Norge**

Otsuka Pharma Scandinavia AB  
Tlf: +46 854 528 660

**Ελλάδα**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**España**

Otsuka Pharmaceutical, S.A.  
Tel: +34 93 550 01 00

**France**

Otsuka Pharmaceutical France SAS  
Tél: +33(0)1 47 08 00 00

**Hrvatska**

Otsuka Pharmaceutical Europe Ltd.  
Tel: +44 (0)203 747 5000

**Ireland**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Ísland**

Vistor hf.  
Sími: +354 535 7000

**Italia**

Otsuka Pharmaceutical Italy S.r.l.  
Tel: +39 02 00 63 27 10

**Κύπρος**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Latvija**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Österreich**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Polska**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Portugal**

Lundbeck Portugal Lda  
Tel: +351 21 00 45 900

**România**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Slovenija**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Slovenská republika**

Otsuka Pharmaceutical Europe Ltd.  
Tel: + 44 (0)203 747 5000

**Suomi/Finland**

Otsuka Pharma Scandinavia AB  
Puh/Tel: +46 854 528 660

**Sverige**

Otsuka Pharma Scandinavia AB  
Tel: +46 854 528 660

**United Kingdom**

Otsuka Pharmaceuticals (UK) Ltd.  
Tel: +44 (0)203 747 5300

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**Other sources of information**

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