ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aripiprazole Zentiva 5 mg tablets
Aripiprazole Zentiva 10 mg tablets
Aripiprazole Zentiva 15 mg tablets
Aripiprazole Zentiva 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Aripiprazole Zentiva 5 mg tablets

Each tablet contains 5 mg of aripiprazole.

Excipient with known effect

Each tablet contains 33 mg of lactose (as monohydrate).

Aripiprazole Zentiva 10 mg tablets

Each tablet contains 10 mg of aripiprazole.

Excipient with known effect

Each tablet contains 66 mg of lactose (as monohydrate).

Aripiprazole Zentiva 15 mg tablets

Each tablet contains 15 mg of aripiprazole.

Excipient with known effect

Each tablet contains 99 mg of lactose (as monohydrate).

Aripiprazole Zentiva 30 mg tablets

Each tablet contains 30 mg of aripiprazole.

Excipient with known effect

Each tablet contains 198 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Aripiprazole Zentiva 5 mg tablets

White to off-white round flat bevel edged uncoated tablets with ‘5’ debossed on one side and plain on the other side with diameter approx. 6 mm.

Aripiprazole Zentiva 10 mg tablets

White to off-white round uncoated tablets with ‘10’ debossed on one side and snap tab breakline on the other side with diameter approx. 8 mm.
The score line is not intended for breaking the tablet.

Aripiprazole Zentiva 15 mg tablets

White to off-white round flat bevel edged uncoated tablets with ‘15’ debossed on one side and plain on the other side with diameter approx. 8.8 mm.

Aripiprazole Zentiva 30 mg tablets

White to off-white capsule shaped uncoated tablets with ‘30’ debossed on one side and snap tab breakline on the other side with dimensions approx. 15.5 x 8 mm.
The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aripiprazole Zentiva is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.

Aripiprazole Zentiva 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).

Aripiprazole Zentiva 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 Aripiprazole Zentiva 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.

Aripiprazole Zentiva 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 Aripiprazole Zentiva is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

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

Paediatric population

Schizophrenia in adolescents aged 15 years and older
The recommended dose for Aripiprazole Zentiva is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using an appropriate aripiprazole containing medicinal product) 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).

Aripiprazole Zentiva 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.

Aripiprazole Zentiva 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 Aripiprazole Zentiva is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using an appropriate aripiprazole containing medicinal product) 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 adverse reactions 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, Aripiprazole Zentiva 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 aripiprazole 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 aripiprazole 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.

Special populations

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 safety and efficacy of aripiprazole in the treatment of schizophrenia or manic episodes in 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 strong 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 strong 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

Aripiprazole Zentiva is for oral use.

The orodispersible tablets may be used as an alternative to Aripiprazole Zentiva tablets for patients who have difficulty swallowing Aripiprazole Zentiva 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 treatment.

Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions 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. 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 antipsychotics. 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 antipsychotics, 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 to 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 to 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 patients with dementia-related psychosis.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, 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 antipsychotics are not available to allow direct comparisons. Patients treated with any antipsychotics, including aripiprazole, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control (see section 4.8).

Hypersensitivity

Hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed 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 the use of antipsychotics, including aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling and other impulse control disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported, include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Impulse control disorders may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole (see section 4.8).

Patients with attention deficit hyperactivity disorder (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.

Falls

Aripiprazole may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls. Caution should be taken when treating patients at higher risk, and a lower starting dose should be considered (e.g., elderly or debilitated patients; see section 4.2).

Lactose

Aripiprazole Zentiva tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Potential for other medicinal products to affect aripiprazole

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

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

Quinidine and other CYP2D6 inhibitors
In a clinical trial in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%, respectively. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole with quinidine occurs. Other strong 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 strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other strong 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 strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors, may be expected to have similar effects and similar dose reductions should therefore be applied (see section 4.2).

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of aripiprazole should be increased to the level prior to the initiation of the concomitant therapy.

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

Carbamazepine and other CYP3A4 inducers
Following concomitant administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizoaffective disorder, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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. Concomitant administration of aripiprazole and other inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's

Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of strong CYP3A4 inducers, the dosage of aripiprazole should be reduced to the recommended dose.

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

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.

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 selective serotonin reuptake inhibitor/selective serotonin noradrenaline reuptake inhibitor (SSRI/SNRI), or with medicinal products that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with 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 (see section 4.8).

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Aripiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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

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

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

	Common	**Uncommon**	**Not known**
Blood and lymphatic system disorders			Leukopenia Neutropenia Thrombocytopenia
Immune system disorders			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, or urticaria)
Endocrine disorders		Hyperprolactinaemia Blood prolactin decreased	Diabetic hyperosmolar coma Diabetic ketoacidosis
Metabolism and nutrition disorders	Diabetes mellitus	Hyperglycaemia	Hyponatremia Anorexia
Psychiatric disorders	Insomnia Anxiety Restlessness	Depression Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) Pathological gambling Impulse-control disorder

	Common	Uncommon	Not known
			Binge eating Compulsive shopping Poriomania Aggression Agitation Nervousness
Nervous system disorders	Akathisia Extrapyramidal disorder Tremor Headache Sedation Somnolence Dizziness	Tardive dyskinesia Dystonia Restless legs syndrome	Neuroleptic Malignant Syndrome Grand mal convulsion Serotonin syndrome Speech disorder
Eye disorders	Vision blurred	Diplopia Photophobia	Oculogyric crisis
Cardiac disorders		Tachycardia	Sudden unexplained death Torsades de pointes Ventricular arrhythmia Cardiac arrest Bradycardia
Vascular disorders		Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Hypertension Syncope
Respiratory, thoracic and mediastinal disorders		Hiccups	Aspiration pneumonia Laryngospasm Oropharyngeal spasm
Gastrointestinal disorders	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting		Pancreatitis Dysphagia Diarrhoea Abdominal discomfort Stomach discomfort
Hepatobiliary disorders			Hepatic failure Hepatitis Jaundice
Skin and subcutaneous tissue disorders			Rash Photosensitivity reaction Alopecia Hyperhidrosis Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Rhabdomyolysis Myalgia Stiffness

	Common	Uncommon	Not known
Renal and urinary disorders			Urinary incontinence Urinary retention
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders			Priapism
General disorders and administration site conditions	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
Investigations			Weight decreased Weight gain Alanine Aminotransferase increased Aspartate Aminotransferase increased Gamma-glutamyltransferase increased Alkaline phosphatase increased QT prolonged Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Creatine phosphokinase increased

Description of selected adverse reactions

Adults

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 (see 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 to 17 years) with schizophrenia, the frequency and type of adverse reactions 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 (≥ 1/10), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly (≥ 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 (≥ 1/100, < 1/10).

In the pooled adolescent schizophrenia population (13 to 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 to 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 to 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 adverse reactions in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly (≥ 1/10) somnolence (23.0%),

extrapyramidal disorder (18.4%), akathisia (16.0%), and fatigue (11.8%); and commonly (≥ 1/100, < 1/10) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.

The following adverse reactions 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 to 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.

Pathological gambling and other impulse control disorders
Pathological gambling, hypersexuality, compulsive shopping and binge or compulsive eating can occur in patients treated with aripiprazole (see section 4.4).

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: Psycholeptics, 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_{1A} receptors and antagonism of serotonin 5-HT_{2A} 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_{1A} and 5-HT_{2A} receptors and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.
Aripiprazole doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}C-raclopride, a D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical efficacy and safety

Adults

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-Åsberg Depression Rating Scale (MADRS) 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, High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL).

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 randomisation, 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 (Young Mania Rating Scale [YMRS] and MADRS with

total scores ≤ 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure in Clinical Global Impression - Bipolar version (CGI-BP) Severity of Illness (SOI; mania) scores.
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 to 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 to 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 to 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 to 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 to 17 years), who met DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders) for Bipolar I Disorder with manic or mixed episodes with or without psychotic features and had a YMRS score ≥ 20 at baseline. Among the patients included in the primary efficacy analysis, 139 patients had a current comorbid 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 comorbidity of ADHD compared to the group without ADHD, where there was no difference from placebo. Recurrence prevention was not established.

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 to 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 to 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 to 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 the reference medicinal product containing aripiprazole 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 to 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 [^{14}C]-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

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.

Pharmacokinetics in special patient groups

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^2). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6% of the bile concentrations found in the monkeys in the 39-week study and are well below (6%) their limits of *in vitro* solubility.

In 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

Lactose monohydrate
Cellulose microcrystalline
Crospovidone
Hydroxypropyl cellulose
Silica colloidal anhydrous
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/Alu/PVC/Alu foil blisters (Alu-Alu blister), carton box.
Pack size: 14, 28, 49, 56, or 98 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

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

8. MARKETING AUTHORISATION NUMBER(S)

Aripiprazole Zentiva 5 mg tablets

EU/1/15/1009/001
EU/1/15/1009/002
EU/1/15/1009/003
EU/1/15/1009/004
EU/1/15/1009/005

Aripiprazole Zentiva 10 mg tablets

EU/1/15/1009/006
EU/1/15/1009/007
EU/1/15/1009/008
EU/1/15/1009/009
EU/1/15/1009/010

Aripiprazole Zentiva 15 mg tablets

EU/1/15/1009/011
EU/1/15/1009/012
EU/1/15/1009/013
EU/1/15/1009/014
EU/1/15/1009/015

Aripiprazole Zentiva 30 mg tablets

EU/1/15/1009/016
EU/1/15/1009/017
EU/1/15/1009/018
EU/1/15/1009/019
EU/1/15/1009/020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 June 2015
Date of latest renewal: 2 June 2020

10. DATE OF REVISION OF THE TEXT

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

Aripiprazole Zentiva 10 mg orodispersible tablets
Aripiprazole Zentiva 15 mg orodispersible tablets
Aripiprazole Zentiva 30 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Aripiprazole Zentiva 10 mg orodispersible tablets

Each orodispersible tablet contains 10 mg of aripiprazole.

Excipient with known effect

Each orodispersible tablet contains 37 mg of lactose (as monohydrate).

Aripiprazole Zentiva 15 mg orodispersible tablets

Each orodispersible tablet contains 15 mg of aripiprazole.

Excipient with known effect

Each orodispersible tablet contains 55.5 mg of lactose (as monohydrate).

Aripiprazole Zentiva 30 mg orodispersible tablets

Each orodispersible tablet contains 30 mg of aripiprazole.

Excipient with known effect

Each orodispersible tablet contains 111 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Aripiprazole Zentiva 10 mg orodispersible tablets

White to off-white round tablets debossed with ‘10’ on one side and snap break line on other side with diameter approx. 7 mm.
The score line is not intended for breaking the tablet.

Aripiprazole Zentiva 15 mg orodispersible tablets

White to off-white round flat bevel edged tablets debossed with ‘15’ on one side and plain on the other side with diameter approx. 8 mm.

Aripiprazole Zentiva 30 mg orodispersible tablets

White to off-white round tablets debossed with ‘30’ on one side and snap break line on the other side with diameter approx. 10.2 mm.
The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aripiprazole Zentiva is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.

Aripiprazole Zentiva 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).

Aripiprazole Zentiva 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 Aripiprazole Zentiva 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.

Aripiprazole Zentiva 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 Aripiprazole Zentiva is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

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

Paediatric population

Schizophrenia in adolescents aged 15 years and older
The recommended dose for Aripiprazole Zentiva is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using an appropriate aripiprazole containing medicinal product) 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).

Aripiprazole Zentiva 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.

Aripiprazole Zentiva 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 Aripiprazole Zentiva is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using an appropriate aripiprazole containing medicinal product) 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 adverse reactions 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, Aripiprazole Zentiva 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 aripiprazole 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 aripiprazole 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.

Special populations

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 safety and efficacy of aripiprazole in the treatment of schizophrenia or manic episodes in 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 strong 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 strong 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

Aripiprazole Zentiva 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.

The orodispersible tablets may be used as an alternative to Aripiprazole Zentiva tablets for patients who have difficulty swallowing Aripiprazole Zentiva 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 treatment.

Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities),

cerebrovascular disease, conditions 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. 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 antipsychotics. 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 antipsychotics, 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 to 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 to 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 patients with dementia-related psychosis.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, 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 antipsychotics are not available to allow direct comparisons. Patients treated with any antipsychotics, including aripiprazole, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control (see section 4.8).

Hypersensitivity

Hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed 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 the use of antipsychotics, including aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling and other impulse control disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported, include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Impulse control disorders may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole (see section 4.8).

Patients with attention deficit hyperactivity disorder (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.

Falls

Aripiprazole may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls. Caution should be taken when treating patients at higher risk, and a lower starting dose should be considered (e.g., elderly or debilitated patients; see section 4.2).

Lactose

Aripiprazole Zentiva orodispersible tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Potential for other medicinal products to affect aripiprazole

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

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

Quinidine and other CYP2D6 inhibitors
In a clinical trial in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107%, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32% and 47%, respectively. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole with quinidine occurs. Other strong 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 strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63% and 37%, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77% and 43%, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other strong 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 strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should therefore be applied (see section 4.2).

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of aripiprazole should be increased to the level prior to the initiation of the concomitant therapy.

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

Carbamazepine and other CYP3A4 inducers
Following concomitant administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizoaffective disorder, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when 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. Concomitant administration of aripiprazole and other inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of strong CYP3A4 inducers, the dosage of aripiprazole should be reduced to the recommended dose.

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

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.

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 selective serotonin reuptake inhibitor/selective serotonin noradrenaline reuptake inhibitor (SSRI/SNRI), or with medicinal products that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with 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 (see section 4.8).

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Aripiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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

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

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

	Common	**Uncommon**	**Not known**
Blood and lymphatic system disorders			Leukopenia Neutropenia Thrombocytopenia
Immune system disorders			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, or urticaria)
Endocrine disorders		Hyperprolactinaemia Blood prolactin decreased	Diabetic hyperosmolar coma Diabetic ketoacidosis
Metabolism and nutrition disorders	Diabetes mellitus	Hyperglycaemia	Hyponatremia Anorexia
Psychiatric disorders	Insomnia Anxiety Restlessness	Depression Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) Pathological gambling Impulse-control disorder Binge eating Compulsive shopping Poriomania Aggression Agitation Nervousness
Nervous system disorders	Akathisia Extrapyramidal disorder	Tardive dyskinesia Dystonia	Neuroleptic Malignant Syndrome Grand mal convulsion

	Common	Uncommon	Not known
	Tremor Headache Sedation Somnolence Dizziness	Restless legs syndrome	Serotonin syndrome Speech disorder
Eye disorders	Vision blurred	Diplopia Photophobia	Oculogyric crisis
Cardiac disorders		Tachycardia	Sudden death unexplained Torsades de pointes Ventricular arrhythmia Cardiac arrest Bradycardia
Vascular disorders		Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Hypertension Syncope
Respiratory, thoracic and mediastinal disorders		Hiccups	Aspiration pneumonia Laryngospasm Oropharyngeal spasm
Gastrointestinal disorders	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting		Pancreatitis Dysphagia Diarrhoea Abdominal discomfort Stomach discomfort
Hepatobiliary disorders			Hepatic failure Hepatitis Jaundice
Skin and subcutaneous tissue disorders			Rash Photosensitivity reaction Alopecia Hyperhidrosis Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Rhabdomyolysis Myalgia Stiffness
Renal and urinary disorders			Urinary incontinence Urinary retention
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders			Priapism
General disorders and administration site conditions	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia)

	Common	Uncommon	Not known
			Chest pain Peripheral oedema
Investigations			Weight decreased Weight gain Alanine Aminotransferase increased Aspartate Aminotransferase increased Gamma-glutamyltransferase increased Alkaline phosphatase increased QT prolonged Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Creatine phosphokinase increased

Description of selected adverse reactions

Adults

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 (see 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 to 17 years) with schizophrenia, the frequency and type of adverse reactions 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 (≥ 1/10), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly (≥ 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 (≥ 1/100, < 1/10).

In the pooled adolescent schizophrenia population (13 to 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 to 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 to 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 adverse reactions in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly (≥ 1/10) somnolence (23.0%), extrapyramidal disorder (18.4%), akathisia (16.0%), and fatigue (11.8%); and commonly (≥ 1/100, < 1/10) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.

The following adverse reactions 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 to 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.

Pathological gambling and other impulse control disorders
Pathological gambling, hypersexuality, compulsive shopping and binge or compulsive eating can occur in patients treated with aripiprazole (see section 4.4).

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: Psycholeptics, 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_{1A} receptors and antagonism of serotonin 5-HT_{2A} 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_{1A} and 5-HT_{2A} receptors and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.
Aripiprazole doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}C-raclopride, a D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical efficacy and safety

Adults

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-Åsberg Depression Rating Scale (MADRS) 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, High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL).

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 randomisation, 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 (Young Mania Rating Scale [YMRS] and MADRS with total scores ≤ 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46% decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65% decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure in Clinical Global Impression - Bipolar version (CGI-BP) Severity of Illness (SOI; mania) scores .
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 to 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 to 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 to 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 to 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 to 17 years), who met DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders) for Bipolar I Disorder with manic or mixed episodes with or without psychotic features and had a Y-MRS score ≥ 20 at baseline. Among the patients included in the primary efficacy analysis, 139 patients had a current comorbid 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 comorbidity of ADHD compared to the group without ADHD, where there was no difference from placebo. Recurrence prevention was not established.

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 to 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 to 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 to 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 the reference medicinal product containing aripiprazole 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 to 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 [^{14}C]-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

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.

Pharmacokinetics in special patient groups

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 non-tumorigenic 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^2). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6% of the bile concentrations found in the monkeys in the 39-week study and are well below (6%) their limits of *in vitro* solubility.

In 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

Lactose monohydrate
Cellulose microcrystalline
Crospovidone

Hydroxypropyl cellulose
Silica colloidal anhydrous
Croscarmellose sodium
Acesulfame potassium
Mango flavour (consisting of nature identical flavourings, maize maltodextrin, gum arabic (E 414), triacetin (E 1518), propylene glycol (E 1520) and moisture)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/Alu/PVC/Alu foil blisters (Alu-Alu blister), carton box.
Pack size: 14, 28 or 49 orodispersible 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

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

8. MARKETING AUTHORISATION NUMBER(S)

Aripiprazole Zentiva 10 mg orodispersible tablets

EU/1/15/1009/021
EU/1/15/1009/022
EU/1/15/1009/023

Aripiprazole Zentiva 15 mg orodispersible tablets

EU/1/15/1009/024
EU/1/15/1009/025

EU/1/15/1009/026

Aripiprazole Zentiva 30 mg orodispersible tablets

EU/1/15/1009/027
EU/1/15/1009/028
EU/1/15/1009/029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 June 2015
Date of latest renewal: 2 June 2020

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
S.C. Zentiva S.A.
B-dul Theodor Pallady nr.50, sector 3,
Bucureşti, cod 032266
Romania

LAMP SAN PROSPERO SPA
VIA DELLA PACE 25/A
SAN PROSPERO (MO)
41030
Italy

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 (PSURs)**

The requirements for submission PSURs 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 marketing authorisation holder (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

Aripiprazole Zentiva 5 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

14 tablets
28 tablets
49 tablets
56 tablets
98 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

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

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1009/001
EU/1/15/1009/002
EU/1/15/1009/003
EU/1/15/1009/004
EU/1/15/1009/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aripiprazole Zentiva 5 mg tablets

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

Aripiprazole Zentiva 5 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Zentiva logo

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

Aripiprazole Zentiva 10 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

14 tablets
28 tablets
49 tablets
56 tablets
98 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

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

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1009/006
EU/1/15/1009/007
EU/1/15/1009/008
EU/1/15/1009/009
EU/1/15/1009/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aripiprazole Zentiva 10 mg tablets

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

Aripiprazole Zentiva 10 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Zentiva logo

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

Aripiprazole Zentiva 15 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

14 tablets
28 tablets
49 tablets
56 tablets
98 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

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

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1009/011
EU/1/15/1009/012
EU/1/15/1009/013
EU/1/15/1009/014
EU/1/15/1009/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aripiprazole Zentiva 15 mg tablets

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

Aripiprazole Zentiva 15 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Zentiva logo

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

Aripiprazole Zentiva 30 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

14 tablets
28 tablets
49 tablets
56 tablets
98 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

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

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1009/016
EU/1/15/1009/017
EU/1/15/1009/018
EU/1/15/1009/019
EU/1/15/1009/020

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aripiprazole Zentiva 30 mg tablets

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

Aripiprazole Zentiva 30 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Zentiva logo

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

Aripiprazole Zentiva 10 mg orodispersible tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodipersible tablet contains 10 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

14 orodispersible tablets
28 orodispersible tablets
49 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

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

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1009/021
EU/1/15/1009/022
EU/1/15/1009/023

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aripiprazole Zentiva 10 mg orodispersible tablets

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

Aripiprazole Zentiva 10 mg orodispersible tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Zentiva logo

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

Aripiprazole Zentiva 15 mg orodispersible tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodipersible tablet contains 15 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

14 orodispersible tablets
28 orodispersible tablets
49 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

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

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1009/024
EU/1/15/1009/025
EU/1/15/1009/026

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aripiprazole Zentiva 15 mg orodispersible tablets

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

Aripiprazole Zentiva 15 mg orodispersible tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Zentiva logo

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

Aripiprazole Zentiva 30 mg orodispersible tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodipersible tablet contains 30 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

14 orodispersible tablets
28 orodispersible tablets
49 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

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

Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1009/027
EU/1/15/1009/028
EU/1/15/1009/029

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Aripiprazole Zentiva 30 mg orodispersible tablets

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

Aripiprazole Zentiva 30 mg orodispersible tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Zentiva logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Aripiprazole Zentiva 5 mg tablets
Aripiprazole Zentiva 10 mg tablets
Aripiprazole Zentiva 15 mg tablets
Aripiprazole Zentiva 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 Aripiprazole Zentiva is and what it is used for
2. What you need to know before you take Aripiprazole Zentiva
3. How to take Aripiprazole Zentiva
4. Possible side effects
5. How to store Aripiprazole Zentiva
6. Contents of the pack and other information

1. What Aripiprazole Zentiva is and what it is used for

Aripiprazole Zentiva 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.

Aripiprazole Zentiva 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 Aripiprazole Zentiva.

2. What you need to know before you take Aripiprazole Zentiva

Do not take Aripiprazole Zentiva
- 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 Aripiprazole Zentiva.
Suicidal thoughts and behaviours have been reported during aripiprazole treatment. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself.

Before treatment with Aripiprazole Zentiva, tell your doctor if you suffer from

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

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.

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

Aripiprazole may cause sleepiness, fall in blood pressure when standing up, dizziness and changes in your ability to move and balance, which may lead to falls. Caution should be taken, particularly if you are an elderly patient or have some debility.

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 Aripiprazole Zentiva
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: Aripiprazole Zentiva 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 Aripiprazole Zentiva with some medicines may mean the doctor will need to change your dose of Aripiprazole Zentiva or the other medicines. It is especially important to mention the following to your doctor:

- medicines to correct heart rhythm (such as quinidine, amiodarone, flecainide)

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

These medicines may increase the risk of side effects or reduce the effect of Aripiprazole Zentiva; if you get any unusual symptom taking any of these medicines together with Aripiprazole Zentiva, you should see your doctor.

Medicines that increase the level of serotonin are typically used in conditions including depression, generalised anxiety disorder, obsessive-compulsive disorder (OCD) and social phobia as well as migraine and pain:
- triptans, tramadol and tryptophan used for conditions including depression, generalised anxiety disorder, obsessive compulsive disorder (OCD) and social phobia as well as migraine and pain
- selective-serotonin-reuptake-inhibitors (SSRIs) (such as paroxetine and fluoxetine) used for depression, OCD, panic and anxiety
- other anti-depressants (such as venlafaxine and tryptophan) used in major depression
- tricyclic's (such as clomipramine and amitriptyline) used for depressive illness
- St John's Wort (Hypericum perforatum) used as a herbal remedy for mild depression
- pain killers (such as tramadol and pethidine) used for pain relief
- triptans (such as sumatriptan and zolmitripitan) used for treating migraine

These medicines may increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with Aripiprazole Zentiva, you should see your doctor.

Aripiprazole Zentiva with food, drink and alcohol
This medicine 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 Aripiprazole Zentiva 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.

If you are taking Aripiprazole Zentiva, your doctor will discuss with you whether you should breast feed considering the benefit to you of your therapy and the benefit to your baby of breast feeding. You should not do both. Talk to your doctor about the best way to feed your baby if you are taking this medicine.

Driving and using machines
Dizziness and vision problems may occur during treatment with this medicine (see section 4). This should be considered in cases where full alertness is required, e.g. when driving a car or handling machines.

Aripiprazole Zentiva contains lactose
If you have been told by your doctor that you have an intolerance to some sugars contact your doctor before taking this medicine.

Aripiprazole Zentiva contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Aripiprazole Zentiva

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 medicine 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 effect of Aripiprazole Zentiva is too strong or too weak, talk to your doctor or pharmacist.

Try to take Aripiprazole Zentiva 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 Aripiprazole Zentiva without first consulting your doctor.

Aripiprazole Zentiva 10 mg, 30 mg tablets: The score line is not intended for breaking the tablet.

If you take more Aripiprazole Zentiva than you should
If you realise you have taken more Aripiprazole Zentiva than your doctor has recommended (or if someone else has taken some of your Aripiprazole Zentiva), contact your doctor right away.
If you cannot reach your doctor, go to the nearest hospital and take the pack with you.
Patients who have taken too much aripiprazole have experienced the following symptoms:
- rapid heartbeat, agitation/aggressiveness, problems with speech.
- unusual movements (especially of the face or tongue) and reduced level of consciousness.

Other symptoms may include:
- acute confusion, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating,
- muscle stiffness, and drowsiness or sleepiness, slower breathing, choking, high or low blood pressure, abnormal rhythms of the heart.

Contact your doctor or hospital immediately if you experience any of the above.

If you forget to take Aripiprazole Zentiva
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 Aripiprazole Zentiva
Do not stop your treatment just because you feel better. It is important that you carry on taking Aripiprazole Zentiva 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,
- akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly),
- uncontrollable twitching, jerking or writhing movements,
- 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 or decreased 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),
- restless legs,
- double vision,
- eye sensitivity to light,
- 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 (frequency cannot be estimated from the available data)**:
- 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;
- 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,
- fixation of the eyeballs in one position,
- 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,
- skin sensitivity to light,
- baldness,
- excessive sweating,
- serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia),
- 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,
- inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences
  - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive
  - uncontrollable excessive shopping
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)
  - a tendency to wander away.

  Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms.

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 Aripiprazole Zentiva

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.

This medicine does not require any special storage conditions.

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 Aripiprazole Zentiva contains
- The active substance is aripiprazole. Each tablet contains 5 mg/10 mg/15 mg/30 mg of aripiprazole.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, crospovidone, hydroxypropyl cellulose, silica colloidal anhydrous, croscarmellose sodium, magnesium stearate.

What Aripiprazole Zentiva looks like and contents of the pack
Aripiprazole Zentiva 5 mg are white to off-white round flat bevel edged uncoated tablets with '5' debossed on one side and plain on the other side with diameter approx. 6 mm.

Aripiprazole Zentiva 10 mg tablets are white to off-white round uncoated tablets with '10' debossed on one side and snap tab breakline on the other side with diameter approx. 8 mm.

Aripiprazole Zentiva 15 mg tablets are white to off-white round flat bevel edged uncoated tablets with '15' debossed on one side and plain on the other side with diameter approx. 8.8 mm.

Aripiprazole Zentiva 30 mg tablets are white to off-white capsule shaped uncoated tablets with '30' debossed on one side and snap tab breakline on the other side with dimensions approx. 15.5 x 8 mm.

Pack size: 14, 28, 49, 56, or 98 tablets
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

Manufacturer
S.C. Zentiva S.A.
B-dul Theodor Pallady nr.50, sector 3
București, cod 032266
Romania

LAMP SAN PROSPERO SPA
VIA DELLA PACE 25/A
SAN PROSPERO (MO)
41030
Italy

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

België/Belgique/Belgien
Zentiva, k.s.
Tél/Tel: +32 280 86 420
PV-Belgium@zentiva.com

Lietuva
Zentiva, k.s.
Tel: +370 52152025
PV-Lithuania@zentiva.com

България
Zentiva, k.s.
Тел: +35924417136
PV-Bulgaria@zentiva.com

Česká republika
Zentiva, k.s.
Tel: +420 267 241 111
PV-Czech-Republic@zentiva.com

Danmark
Zentiva Denmark ApS
Tlf: +45 787 68 400
PV-Denmark@zentiva.com

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0) 800 53 53 010
PV-Germany@zentiva.com

Eesti
Zentiva, k.s.
Tel: +372 52 70308
PV-Estonia@zentiva.com

Ελλάδα
Zentiva, k.s.
Τηλ: +30 211 198 7510
PV-Greece@zentiva.com

España
Zentiva, k.s.
Tel: +34 931 815 250
PV-Spain@zentiva.com

France
Zentiva France
Tél: +33 (0) 800 089 219
PV-France@zentiva.com

Hrvatska
Zentiva d.o.o.
Tel: +385 1 6641 830
PV-Croatia@zentiva.com

Ireland
Zentiva, k.s.
Tel: +353 818 882 243
PV-Ireland@zentiva.com

Ísland
Zentiva Denmark ApS
Sími: +354 539 0650
PV-Iceland@zentiva.com

Luxembourg/Luxemburg
Zentiva, k.s.
Tél/Tel: +352 208 82330
PV-Luxembourg@zentiva.com

Magyarország
Zentiva Pharma Kft.
Tel.: +36 1 299 1058
PV-Hungary@zentiva.com

Malta
Zentiva, k.s.
Tel: +356 2778 0890
PV-Malta@zentiva.com

Nederland
Zentiva, k.s.
Tel: +31 202 253 638
PV-Netherlands@zentiva.com

Norge
Zentiva Denmark ApS
Tlf: +47 219 66 203
PV-Norway@zentiva.com

Österreich
Zentiva, k.s.
Tel: +43 720 778 877
PV-Austria@zentiva.com

Polska
Zentiva Polska Sp. z o.o.
Tel: + 48 22 375 92 00
PV-Poland@zentiva.com

Portugal
Zentiva Portugal, Lda
Tel: +351210601360
PV-Portugal@zentiva.com

România
ZENTIVA S.A.
Tel: +4 021.304.7597
PV-Romania@zentiva.com

Slovenija
Zentiva, k.s.
Tel: +386 360 00 408
PV-Slovenia@zentiva.com

Slovenská republika
Zentiva, a.s.
Tel: +421 2 3918 3010
PV-Slovakia@zentiva.com

Italia
Zentiva Italia S.r.l.
Tel: +39-02-38598801
PV-Italy@zentiva.com

Κύπρος
Zentiva, k.s.
Τηλ: +357 240 30 144
PV-Cyprus@zentiva.com

Latvija
Zentiva, k.s.
Tel: +371 67893939
PV-Latvia@zentiva.com

Suomi/Finland
Zentiva Denmark ApS
Puh/Tel: +358 942 598 648
PV-Finland@zentiva.com

Sverige
Zentiva Denmark ApS
Tel: +46 840 838 822
PV-Sweden@zentiva.com

United Kingdom (Northern Ireland)
Zentiva, k.s.
Tel: +44 (0) 800 090 2408
PV-United-Kingdom@zentiva.com

This leaflet was last revised in

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

Aripiprazole Zentiva 10 mg orodispersible tablets
Aripiprazole Zentiva 15 mg orodispersible tablets
Aripiprazole Zentiva 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 Aripiprazole Zentiva is and what it is used for
2. What you need to know before you take Aripiprazole Zentiva
3. How to take Aripiprazole Zentiva
4. Possible side effects
5. How to store Aripiprazole Zentiva
6. Contents of the pack and other information

1. What Aripiprazole Zentiva is and what it is used for

Aripiprazole Zentiva 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.

Aripiprazole Zentiva 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 Aripiprazole Zentiva.

2. What you need to know before you take Aripiprazole Zentiva

Do not take Aripiprazole Zentiva
- 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 Aripiprazole Zentiva.

Suicidal thoughts and behaviours have been reported during aripiprazole treatment. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself.

Before treatment with Aripiprazole Zentiva, tell your doctor if you suffer from

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

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.

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.

Aripiprazole may cause sleepiness, fall in blood pressure when standing up, dizziness and changes in your ability to move and balance, which may lead to falls. Caution should be taken, particularly if you are an elderly patient or have some debility.

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 Aripiprazole Zentiva
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: Aripiprazole Zentiva 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 Aripiprazole Zentiva with some medicines may mean the doctor will need to change your dose of Aripiprazole Zentiva or the other medicines. It is especially important to mention the following to your doctor:

- medicines to correct heart rhythm (such as quinidine, amiodarone, flecainide)

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

These medicines may increase the risk of side effects or reduce the effect of Aripiprazole Zentiva; if you get any unusual symptom taking any of these medicines together with Aripiprazole Zentiva tablets, you should see your doctor.

Medicines that increase the level of serotonin are typically used in conditions including depression, generalised anxiety disorder, obsessive-compulsive disorder (OCD) and social phobia as well as migraine and pain:
- triptans, tramadol and tryptophan used for conditions including depression, generalised anxiety disorder, obsessive compulsive disorder (OCD) and social phobia as well as migraine and pain
- selective-serotonin-reuptake-inhibitors (SSRIs) (such as paroxetine and fluoxetine) used for depression, OCD, panic and anxiety
- other anti-depressants (such as venlafaxine and tryptophan) used in major depression
- tricyclic's (such as clomipramine and amitriptyline) used for depressive illness
- St John's Wort (Hypericum perforatum) used as a herbal remedy for mild depression
- pain killers (such as tramadol and pethidine) used for pain relief
- triptans (such as sumatriptan and zolmitripitan) used for treating migraine.

These medicines may increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with Aripiprazole Zentiva, you should see your doctor.

Aripiprazole Zentiva with food, drink and alcohol
This medicine 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 Aripiprazole Zentiva 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.

If you are taking Aripiprazole Zentiva, your doctor will discuss with you whether you should breast feed considering the benefit to you of your therapy and the benefit to your baby of breast feeding. You should not do both. Talk to your doctor about the best way to feed your baby if you are taking this medicine.

Driving and using machines
Dizziness and vision problems may occur during treatment with this medicine (see section 4). This should be considered in cases where full alertness is required, e.g., when driving a car or handling machines.

Aripiprazole Zentiva contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Aripiprazole Zentiva contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Aripiprazole Zentiva

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 medicine 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 effect of Aripiprazole Zentiva is too strong or too weak, talk to your doctor or pharmacist.

Try to take Aripiprazole Zentiva 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. 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 Aripiprazole Zentiva without first consulting your doctor.

Aripiprazole Zentiva 10 mg, 30 mg orodispersible tablets: The score line is not intended for breaking the tablet.

If you take more Aripiprazole Zentiva than you should
If you realise you have taken more Aripiprazole Zentiva than your doctor has recommended (or if someone else has taken some of your Aripiprazole Zentiva), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.
Patients who have taken too much aripiprazole have experienced the following symptoms:
- rapid heartbeat, agitation/aggressiveness, problems with speech.
- unusual movements (especially of the face or tongue) and reduced level of consciousness.

Other symptoms may include:
- acute confusion, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating,
- muscle stiffness, and drowsiness or sleepiness, slower breathing, choking, high or low blood pressure, abnormal rhythms of the heart.

Contact your doctor or hospital immediately if you experience any of the above.

If you forget to take Aripiprazole Zentiva
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 Aripiprazole Zentiva
Do not stop your treatment just because you feel better. It is important that you carry on taking Aripiprazole Zentiva 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,
- akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly),
- uncontrollable twitching, jerking or writhing movements,
- 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 or decreased 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),
- restless legs,
- double vision,
- eye sensitivity to light,
- 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 (frequency cannot be estimated from the available data)**:

- 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,
- 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,
- fixation of the eyeballs in one position,
- 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,
- skin sensitivity to light,
- baldness,
- excessive sweating,
- serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased

levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia),
- 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,
- inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences
  - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive
  - uncontrollable excessive shopping
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)
  - a tendency to wander away.

  Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms.

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 Aripiprazole Zentiva

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.

This medicine does not require any special storage conditions.

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 Aripiprazole Zentiva contains
- The active substance is aripiprazole. Each orodispersible tablet contains 10 mg/15 mg/30 mg of aripiprazole.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, crospovidone, hydroxypropyl cellulose, silica colloidal anhydrous, croscarmellose sodium, acesulfame potassium, mango flavour (consisting of nature identical flavourings, maize maltodextrin, gum arabic (E 414), triacetin (E 1518), propylene glycol (E 1520) and moisture), magnesium stearate.

What Aripiprazole Zentiva looks like and contents of the pack
Aripiprazole Zentiva 10 mg orodispersible tablets are white to off-white round tablets debossed with '10' on one side and snap break line on other side with diameter approx. 7 mm.

Aripiprazole Zentiva 15 mg orodispersible tablets are white to off-white round flat bevel edged tablets debossed with '15' on one side and plain on the other side with diameter approx. 8 mm.

Aripiprazole Zentiva 30 mg orodispersible tablets are white to off-white round tablets debossed with '30' on one side and snap break line on the other side with diameter approx. 10.2 mm.

Pack size: 14, 28 or 49 orodispersible tablets
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Zentiva, k.s.
U Kabelovny 130
102 37 Prague 10
Czech Republic

Manufacturer
S.C. Zentiva S.A.
B-dul Theodor Pallady nr.50, sector 3
Bucureşti, cod 032266
Romania

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

België/Belgique/Belgien
Zentiva, k.s.
Tél/Tel: +32 280 86 420
PV-Belgium@zentiva.com

Lietuva
Zentiva, k.s.
Tel: +370 52152025
PV-Lithuania@zentiva.com

България
Zentiva, k.s.
Тел: +35924417136
PV-Bulgaria@zentiva.com

Luxembourg/Luxemburg
Zentiva, k.s.
Tél/Tel: +352 208 82330
PV-Luxembourg@zentiva.com

Česká republika
Zentiva, k.s.
Tel: +420 267 241 111
PV-Czech-Republic@zentiva.com

Danmark
Zentiva Denmark ApS
Tlf: +45 787 68 400
PV-Denmark@zentiva.com

Deutschland
Zentiva Pharma GmbH
Tel: +49 (0) 800 53 53 010
PV-Germany@zentiva.com

Eesti
Zentiva, k.s.
Tel: +372 52 70308
PV-Estonia@zentiva.com

Ελλάδα
Zentiva, k.s.
Τηλ: +30 211 198 7510
PV-Greece@zentiva.com

España
Zentiva, k.s.
Tel: +34 931 815 250
PV-Spain@zentiva.com

France
Zentiva France
Tél: +33 (0) 800 089 219
PV-France@zentiva.com

Hrvatska
Zentiva d.o.o.
Tel: +385 1 6641 830
PV-Croatia@zentiva.com

Ireland
Zentiva, k.s.
Tel: +353 818 882 243
PV-Ireland@zentiva.com

Ísland
Zentiva Denmark ApS
Sími: +354 539 0650
PV-Iceland@zentiva.com

Italia
Zentiva Italia S.r.l.
Tel: +39-02-38598801
PV-Italy@zentiva.com

Magyarország
Zentiva Pharma Kft.
Tel.: +36 1 299 1058
PV-Hungary@zentiva.com

Malta
Zentiva, k.s.
Tel: +356 2778 0890
PV-Malta@zentiva.com

Nederland
Zentiva, k.s.
Tel: +31 202 253 638
PV-Netherlands@zentiva.com

Norge
Zentiva Denmark ApS
Tlf: +47 219 66 203
PV-Norway@zentiva.com

Österreich
Zentiva, k.s.
Tel: +43 720 778 877
PV-Austria@zentiva.com

Polska
Zentiva Polska Sp. z o.o.
Tel: + 48 22 375 92 00
PV-Poland@zentiva.com

Portugal
Zentiva Portugal, Lda
Tel: +351210601360
PV-Portugal@zentiva.com

România
ZENTIVA S.A.
Tel: +4 021.304.7597
PV-Romania@zentiva.com

Slovenija
Zentiva, k.s.
Tel: +386 360 00 408
PV-Slovenia@zentiva.com

Slovenská republika
Zentiva, a.s.
Tel: +421 2 3918 3010
PV-Slovakia@zentiva.com

Suomi/Finland
Zentiva Denmark ApS
Puh/Tel: +358 942 598 648
PV-Finland@zentiva.com

Κύπρος
Zentiva, k.s.
Τηλ: +357 240 30 144
PV-Cyprus@zentiva.com

Latvija
Zentiva, k.s.
Tel: +371 67893939
PV-Latvia@zentiva.com

Sverige
Zentiva Denmark ApS
Tel: +46 840 838 822
PV-Sweden@zentiva.com

United Kingdom (Northern Ireland)
Zentiva, k.s.
Tel: +44 (0) 800 090 2408
PV-United-Kingdom@zentiva.com

This leaflet was last revised in

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