Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

ARIPITAS 10 (Aripiprazole Tablets USP 10 mg)

ARIPITAS 15 (Aripiprazole Tablets USP 15mg)

ARIPITAS 30 (Aripiprazole Tablets USP 30 mg)

2. Qualitative and quantitative composition

Each uncoated tablet contains: Aripiprazole USP 10 mg

Each uncoated tablet contains: Aripiprazole USP 15 mg

Each uncoated tablet contains: Aripiprazole USP 30 mg

Excipient with known effect

Each 10 mg tablet contains 44 mg lactose (as monohydrate).

Each 15 mg tablet contains 58 mg lactose (as monohydrate).

Each 30 mg tablet contains 110 mg lactose (as monohydrate).

For the full list of excipients, see Section 6.1.

3. Pharmaceutical form

Tablets

10mg: Brick red coloured, round, flat uncoated tablet having break line on one side and plain on other side.

15mg: Red coloured, round, flat uncoated tablet having break line on one side and plain on other side.
30mg: Brick red coloured, round, flat faced beveled edge uncoated tablet having break line on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

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

Aripiprazole Accord 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 Accord 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

Schizophrenia:

The recommended starting dose for Aripitas 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.

It 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 Aripitas 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.

Renal and hepatic impairment:

A similar dose schedule can be followed for patients with renal impairment, as clearance of donepezil hydrochloride is not affected by this condition.

Due to possible increased exposure in mild to moderate hepatic impairment, dose escalation should be performed according to individual tolerability. There are no data for patients with severe hepatic impairment.

Paediatric population

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

Aripiprazole Accord is effective in a dose range of 10 mg/day 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 Accord 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 Accord is 10 mg/day administered on a once-aday schedule without regard to meals. Treatment should be initiated at 2 mg (using aripiprazole oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg.

The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant 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

Accord 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 Accord 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 Accord 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 population

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 Accord 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 Accord is for oral use.

Orodispersible tablets or oral solution may be used as an alternative to Aripiprazole Accord tablets for patients who have difficulty swallowing Aripiprazole Accord 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.

The occurrence of suicidal behavior is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with Aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among adult patients with schizophrenia or bipolar disorder. There are insufficient paediatric data to evaluate this risk in younger patients (below 18 years of age), but there is evidence that the risk of suicide persists beyond

the first 4 weeks of treatment for atypical antipsychotics, including aripiprazole.

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

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

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

Tardive dyskinesia: in clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on ARIPITAS, dose reduction or discontinuation should be considered. 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 ARIPITAS, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical

manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including ARIPITAS, must be discontinued.

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

Elderly patients with dementia-related psychosis:

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

Cerebrovascular adverse reactions: in the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6% of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole.

Aripitas is not indicated for the treatment of dementia-related psychosis.

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

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

Weight gain: weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed Aripitas. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

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

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

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

Patients with ADHD comorbidity: despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of Aripitas and stimulants; therefore, extreme caution should be taken when these drugs are coadministered.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Potential for other medicinal products to affect ARIPITAS

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

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

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

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

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

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

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydroaripiprazole 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.

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

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

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 drugs, such as SSRI/SNRI, or with drugs that are known to increase aripiprazole concentrations (see section 4.8).

Potential for ARIPITAS to affect other medicinal products

In clinical studies, 10-30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), 2C9 (warfarin), 2C19 (omeprazole), and 3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not

show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Pregnancy and Lactation

Pregnancy

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

Neonates 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, newborns should be monitored carefully.

Breast-feeding

Aripiprazole is excreted in human breast milk. Patients should be advised not to breast feed if they are taking aripiprazole.

4.7 Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor

vehicles, until they are reasonably certain that aripiprazole does not affect them adversely. Some paediatric patients with Bipolar I Disorder have an increased incidence of somnolence and fatigue (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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 postmarketing 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 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 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) 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 placebocontrolled trial, the incidence of EPS was 18.2 % for aripiprazole-treated patients and 15.7 % for placebo-treated patients.

Akathisia

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

Dystonia

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

Prolactin

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

Laboratory parameters

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

Paediatric population

Schizophrenia in adolescents aged 15 years and older

In a short-term placebo-controlled clinical trial involving 302 adolescents (13 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 mg 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

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 D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for

dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole. Aripiprazole doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}C-raclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination

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

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

Following a single oral dose of [14C]-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

Paediatric population

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Older people

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

Gender

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

Smoking and Race

Population pharmacokinetic evaluation has revealed no evidence of clinically significant racerelated differences or effects from smoking upon 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 safety data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

Toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 to 60 mg/kg/day (3 to 10 times the mean steady-state AUC at the maximum recommended human dose) and

increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 7 times the human exposure at the recommended dose.

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m2). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6% of the bile

concentrations found in the monkeys in the 39-week study and are well below (6%) their limits of in vitro solubility.

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

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered nongenotoxic. 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 BP

Microcrystalline cellulose BP Ferric

Oxide Red USP Hydroxy Propyl

Cellulose BP Iso Propyl Alcohol BP

Croscarmellose Sodium USP Magnesium

Stearate BP Colloidal
Anhydrous Silica BP

6.2 Incompatibilities
Not applicable.
6.3 Shelf-Life
36 months

6.4 Special Precautions for storage
6.4.1.1.1.1.1 Do not store above 30°C.
6.5 Nature and Content of container

10 tablets in PVC-Alu blister pack
6.6 Special precautions for disposal and other handling
No special requirements.
7. Marketing Authorization Holder
Intas Pharmaceuticals Limited Corporate House,
Near Sola Bridge,
S.G. Highway, Thaltej, Ahmedabad380054, INDIA.

8. Marketing Authorization Number
9. 10mg: CTD1764 15mg: CTD-498 30mg: CTD-499

9. Date of first authorization/renewal of the authorization
13-Apr-14 /13-Jun-12/ 13-Jun-12
10. Date of revision of the test
1/4/2026