

SUMMARY OF PRODUCT CHARACTERISTICS

- 1. Name of the medicinal Product Brand Name:** PRAXAL-30
Generic Name: ARIPIPAZOLE TABLETS USP 30 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Aripiprazole USP 30 mg Excipients

Q.S.

Colour: Red oxide of Iron

3. Pharmaceutical form

Oral Film coated tablet

4. Clinical particulars

4.1 Therapeutic indications

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

Aripiprazole 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 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

Adults

Schizophrenia: the recommended starting dose for Aripiprazole 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 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. Paediatric population

Schizophrenia in adolescents aged 15 years and older: the recommended dose for Aripiprazole is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg 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.

Aripiprazole 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 is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy.

Method of administration

Aripiprazole Milpharm tablets are for oral use.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precautions for use

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

Suicidality:

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 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 pediatric 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, characterized 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.

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 behaviors. 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 recognized. 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 coadministered.

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

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α 1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive 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 strong 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 mg/day to 30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3methoxymorphinan 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 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.

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

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

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

	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, 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 disorders 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 arrhythmias 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
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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 olanzapinetreated patients.

Manic episodes in Bipolar I Disorder - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium. In the long term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2% for aripiprazole-treated patients and 15.7% for placebo-treated patients.

Akathisia

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

Dystonia

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

Prolactin

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

Laboratory parameters

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

4.9 Overdose and Treatments:

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 Pharmacodynamics 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 mg to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of 11Craclopride, a D2/D3 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-Asberg 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 nonresponsive 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.

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 [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.

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: dosedependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 mg/kg/day 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 steadystate 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 mg/kg/day 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 reactions 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
Maize starch BP
Croscarmellose sodium BP
Hydroxy Propyl Cellulose (LH-11) BP
Purified Water BP
Magnesium Stearate BP
Purified Talc BP
Colloidal Anhydrous Silica BP
Colorezy White 17F580001 IH
Colour Lake of red oxide of iron IH Isopropyl alcohol BP
Methylene Chloride BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Refer to the outer carton.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container<and special equipment for use, administration or implantation>

3 x 10 Tablets in Alu-Alu Blister Pack

6.6 Special precautions for disposal <and other handling> special requirements.

No

**7 <APPLICANT/MANUFACTURER> STALLION
LABORATORIES PVT. LTD.**

C-1B, 305/2, 3, 4 & 5, G.I.D.C.,
KERALA (BAVLA),
DIST.: AHMEDABAD, GUJARAT, INDIA.