Aripiprazole tablets 10mg/15mg

1. Name of the medicinal product

Aripiprazole 10 mg tablets TajPharma

Aripiprazole 15 mg tablets TajPharma

2. Qualitative and quantitative composition

a) Each film coated tablet contains:
Aripiprazole   10mg
Excipients   q.s.
Colour: Yellow Oxide of Iron

b) Each film coated tablet contains:
Aripiprazole   15mg
Excipients   q.s.
Colour: Yellow Oxide of Iron

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet

4. Clinical particulars

4.1 Therapeutic indications
Aripiprazole 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
Posology

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.

Manic episodes in Bipolar I Disorder: the recommended starting dose for aripiprazole 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 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 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 (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 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. (Alternative products with the same ingredient should be used for required doses not achievable with this product.)

The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant undesirable effects including EPS related events, somnolence, fatigue and weight gain (see section 4.8). Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring (see sections 4.4, 4.8 and 5.1).

Younger patients are at increased risk of experiencing adverse events associated with aripiprazole.

Therefore, aripiprazole 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.

Hepatic impairment

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

Renal impairment

No dosage adjustment is required in patients with renal impairment.

Elderly

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

Gender

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

Smoking Status

According to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions

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

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

Method of administration

Aripiprazole tablets are for oral use.

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 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 aripiprazole and preventive measures undertaken.

QT prolongation

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

Tardive dyskinesia

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

Other extrapyramidal symptoms

In paediatric clinical trials of aripiprazoleakathisia and parkinsonism were observed. If signs and symptoms of other EPS

appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, 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.

Elderly patients with dementia-related psychosis

Increased mortality:

In three placebo-controlled trials (n= 938; mean age: 82.4 years; range: 56-99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in aripiprazole-treated patients was 3.5% compared to 1.7% in the placebo group. Although the causes of deaths were varied, most

of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8).

Cerebrovascular adverse reactions

In the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6% of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole (see section 4.8).

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

Hyperglycaemia and diabetes mellitus

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

Hypersensitivity

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

Weight gain

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to 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

Oesophagealdysmotility and aspiration have been associated with antipsychotic treatment, including aripiprazole. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling

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

Patients with ADHD comorbidity

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

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 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 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%.Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to

have similar effects and similar dose reductions should therefore be applied.

Ketoconazole and other CYP3A4 inhibitors:

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

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

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

Carbamazepine and other CYP3A4 inducers:

Following concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole were 68% and 73% lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of C_{max} and AUC after carbamazepine co-administration were 69% and 71% lower, respectively, than those following treatment with aripiprazole alone.

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

Valproate and lithium:

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

Serotonin syndrome:

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

Potential for Aripiprazole to affect other medicinal products

In clinical studies, 10-30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), CYP 2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

change in valproate, lithium or lamotrigine concentrations.

4.6 Fertility, pregnancy and lactation
Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established.

Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

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

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 convention, 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 (≥1/100 to <1/10)	Uncommon (≥1/1,000 to < 1/100)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Leukopenia Neutropenia Thrombocytopenia
Immune system disorders			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema,

System Organ Class	Common	Uncommon	Rare / Unknown
			face oedema, pruritus, or urticaria)
Endocrine disorders		Hyperprolactinaemia	Diabetic hyperosmolar coma, Diabetic ketoacidosis, Hyperglycaemia
Metabolism and nutrition disorders	Diabetes mellitus	Hyperglycaemia	Hyponatremia, Anorexia, Weight decreased, Weight gain
Psychiatric disorders	Insomnia, Anxiety, Restlessness	Depression, Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4), Pathological gambling, Aggression, Agitation, Nervousness
Nervous system disorders	Akathisia, Extrapyramidal disorder, Tremor, Headache, Sedation, Somnolence, Dizziness	Tardive dyskinesia, Dystonia	Neuroleptic Malignant Syndrome (NMS), Grand mal convulsion, Serotonin syndrome, Speech disorder
Eye	Vision	Diplopia	

System Organ Class	Common	Uncommon	Rare / Unknown
disorders	blurred		
Cardiac disorders		Tachycardia	Sudden unexplained death, Torsades de pointes, QT prolongation, 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			Hepatic failure

disorders			Hepatitis Jaundice Increased Alanine Aminotransferase (ALT) Increased Aspartate Aminotransferase (AST) Increased Gamma GlutamylTransferase (GGT) Increased alkaline phosphatase
Skin and subcutaneous tissue disorders			Rash Photosensitivity reaction Alopecia Hyperhidrosis
Musculoskeletal and connective tissue disorders			Rhabdomyolysis Myalgia Stiffness
Renal and urinary disorders			Urinary incontinence Urinary retention
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system			Priapism

and breast disorders			
General disorders and administration site conditions	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
Investigations			Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Increased creatine phosphokinase

Description of selected adverse reactions

Extrapyramidal symptoms (EPS)

Schizophrenia: in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%). In a long term 26-week placebo-controlled trial, the incidence of EPS was 19% for aripiprazole-treated patients and 13.1% for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8% for aripiprazole-treated patients and 15.1% for olanzapine-treated patients.

Manic episodes in Bipolar I Disorder - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and

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

Akathisia

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

Dystonia

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

Prolactin

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

Laboratory parameters

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

Paediatric population

Schizophrenia in adolescents aged 15 years and older

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

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

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

In the pooled adolescent schizophrenia population (13-17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 29.5% and 48.3%, respectively. In the adolescent (13-17 years) schizophrenia population with aripiprazole exposure of 5 to 30 mg up to 72 months, incidence of low serum prolactin levels in females (<3 ng/ml) and males (<2 ng/ml) was 25.6 % and 45.0 %, respectively.

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

(< 2 ng/ml) was 37.0 % and 59.4 %, respectively.

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

The frequency and type of undesirable effects in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly (≥ 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 undesirable effects had a possible dose response relationship; extrapyramidal disorder (incidences were 10 mg, 9.1%, 30 mg, 28.8%, placebo, 1.7%,); and akathisia (incidences were 10 mg, 12.1%, 30 mg, 20.3%, placebo, 1.7%).

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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 aripiprazoleC_{max} by about 41% and AUC by about 51%, suggesting that charcoal may be effective in the treatment of overdose.

Haemodialysis

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

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other antipsychotics.

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.

Clinical efficacy and safety

Schizophrenia

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

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

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

Weight gain

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

Lipid parameters

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

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

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

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

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

Manic episodes in Bipolar I Disorder

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

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

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

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

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

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

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

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

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

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.

Paediatric population

Schizophrenia in adolescents

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

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

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

Manic episodes in Bipolar I Disorder in children and adolescents

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

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

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

Psychiatric comorbidities	Week 4	Week 12	ADHD	Week 4	Week 12
Aripiprazole 10 mg (n=48)	14.9	15.1	Aripiprazole 10 mg (n=44)	15.2	15.6

Aripiprazole 30 mg (n=51)	16.7	16.9	Aripiprazole 30 mg (n=48)	15.9	16.7
Placebo (n=52)[a]	7.0	8.2	Placebo (n=47)[b]	6.3	7.0
No psychiatric comorbidities	Week 4	Week 12	**No ADHD**	Week 4	Week 12
Aripiprazole 10 mg (n=27)	12.8	15.9	Aripiprazole 10 mg (n=37)	12.7	15.7
Aripiprazole 30 mg (n=25)	15.3	14.7	Aripiprazole 30 mg (n=30)	14.6	13.4
Placebo (n=18)	9.4	9.7	Placebo (n=25)	9.9	10.0

[a] n=51 at Week 4

[b] n=46 at Week 4

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

Irritability associated with autistic disorder in paediatric patients (see section 4.2)

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

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

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

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

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

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

The European Medicines Agency has deferred the obligation to submit the results of studies with 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 3-5 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]-labelledaripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

Paediatric population

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

Elderly

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

pharmacokinetic analysis in schizophrenic patients.

Gender

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

Smoking

Population pharmacokinetic evaluation has revealed no evidence of clinically significant effects from smoking upon 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 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/m^2). However, the concentrations of the sulphate conjugates of hydroxyaripiprazole 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
Cellulose microcrystalline, Tartaric acid, Croscarmellose sodium, Allura red AC aluminium lake.

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-Aluminium-PVC/Aluminium blister pack.

Pack sizes: 14, 28, 30, 49, 56, 98, 100, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufactured in India by:
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