PACKAGE INSERT

1. ARIPDON TABLETS 5MG

2 COMPOSITION
Each tablet contains 5 mg of aripiprazole.

3 PHARMACEUTICAL FORM
Blue round and biconvex tablets of 6.1 mm in diameter, engraved with "5" on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
ARIPDON is indicated for the treatment of schizophrenia. The efficacy of aripiprazole in the treatment of schizophrenia was established in four short-term (4- and 6-week) controlled trials in adults. Maintenance efficacy was demonstrated in one trial in adults.The physician who elects to use aripiprazole for extended periods should periodically re-evaluate the long- term usefulness of the drug for the individual patient.

ARIPDON is indicated for the treatment of acute manic and mixed episodes associated with Bipolar I Disorder and for maintaining stability or preventing recurrence, as monotherapy in adults,and as an adjunct to lithium or valproate in adults.
The efficacy of aripiprazole as monotherapy was established in four 3-week monotherapy trials in adults.Efficacy as adjunctive therapy was established in one 6-week adjunctive trial in adults.

Maintenance efficacy was demonstrated in one monotherapy maintenance trial and in one adjunctive maintenance trial in adults. Physicians who elect to use ARIPDON for extended periods, should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

4.2 Posology and method of administration

Schizophrenia

Usual dose
The recommended starting and target dose for aripiprazole is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. Aripiprazole has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, however, doses higher than 10 or 15 mg/day were not more effective than 10 or 15 mg/day. Dosage increases should generally not be made before 2 weeks, the time needed to achieve steady state.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, systematic evaluation of patients with schizophrenia who had been symptomatically stable on other antipsychotic medication, for periods of 3 months or longer, were discontinued from those medications, and were then administered aripiprazole 15 mg/day and observed for relapse during a period of up to 26 weeks, demonstrated a benefit of such maintenance treatment. Patients should be periodically reassessed to determine the need for maintenance treatment.

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to aripiprazole or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

Bipolar Disorder

Acute Treatment of Manic and Mixed Episodes

The recommended starting dose for aripiprazole is 15 mg given once daily as monotherapy and 10 to 15 mg given once daily as adjunctive therapy with lithium or valproate. Aripiprazole can be given without regard to meals. The recommended target dose of aripiprazole is 15 mg/day, as monotherapy or as adjunctive therapy with lithium or valproate. The dose may be increased to 30 mg/day based on clinical response. The safety of doses above 30 mg/day has not been evaluated in clinical trials.

Maintenance Therapy
The recommended dose for maintenance treatment is the same dose needed to stabilize patients during acute treatment for adult patients. Systematic evaluation of adult patients with Bipolar I Disorder experiencing a manic or mixed episode, who had been symptomatically stable on aripiprazole tablets (15 mg/day or 30 mg/day with a starting dose of 30 mg/day) for 6 consecutive weeks and then randomized to Aripiprazole Tablets (15 mg/day or 30 mg/day) or placebo for at least 6 months and up to an additional 17 months of observation for relapse, demonstrated a benefit of such maintenance treatment. Patients should be periodically reassessed to determine the need for maintenance treatment.

Hepatic and Renal impairment
No dosage adjustment for aripiprazole is required on the basis of a patient's hepatic function (mild to severe hepatic impairment, Child-Pugh score between 5 and 15), or renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute).

Elderly
No dosage adjustment is recommended for elderly patients. Aripiprazole is not approved for treatment of patients with psychosis associated with Alzheimer's disease.

Other Specific Populations
No dosage adjustment for aripiprazole is required on the basis of a patient's sex, race, or smoking status.

Dosage Adjustments for Cytochrome P450 Considerations

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1).When the co-administered drug is withdrawn from the combination therapy, aripiprazole dosage should then be adjusted to its original level. When the co-administered CYP3A4 inducer is withdrawn, aripiprazole dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favourable clinical response

Table 1: Dose Adjustments for Aripiprazole in Patients who are known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, CYP3A4 Inhibitors, and/or CYP3A4 Inducers

Factors	Dosage adjustments for Aripiprazole
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers taking concomitant strong CYP3A4 inhibitors (e.g. itraconazole, clarithromycin)	Administer a quarter of usual dose
Strong CYP2D6 (e.g. quinidine, fluoxetine, paroxetine) or CYP3A4 inhibitors (e.g. itraconazole, clarithromycin)	Administer half of usual dose
Strong CYP2D6 and CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers (e.g. carbamazepine, rifampin)	Double usual dose over 1 to 2 weeks

CYP2D6 Poor Metabolizers
Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3 to 8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). The rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Co-administration of Aripiprazole with known inhibitors of CYP2D6, such as quinidine or fluoxetine in EMs, approximately doubles aripiprazole plasma exposure, and dose adjustment is needed.

Similarly, PMs have higher exposure to aripiprazole compared to EMs; hence, PMs should have their initial dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Method of administration
Aripdon is for oral use.

4.3 Contraindications
Aripiprazole is contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

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.

Venous Thromboembolism
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
As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

Tardive dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, Aripiprazole should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on Aripiprazole, drug discontinuation should be considered. However, some patients may require treatment with aripiprazole despite the presence of the syndrome.

Extrapyramidal symptoms
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)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including ARIPIPRAZOLE. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. 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.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for

which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.

The safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with aripiprazole, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration.

Cerebrovascular Adverse Events, Including Stroke
In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78 to 88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.

Metabolic Changes
Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycaemia/diabetes mellitus, dyslipidaemia and body weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

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. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increase risk of treatment-emergent hyperglycaemia-related adverse events in the patients treated either the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In

some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidaemia
Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight gain
Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Orthostatic Hypotension
Aripiprazole may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. 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 medications medicinal products) or hypertension, including accelerated or malignant.

Leukopenia, Neutropenia, and Agranulocytosis
In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including aripiprazole. Agranulocytosis has also been reported.
Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) / absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of Aripiprazole at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue aripiprazole in patients with severe neutropenia (absolute neutrophil count < $1000/mm^3$) and follow their WBC counts until recovery.

Seizures
As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment
Aripiprazole, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with aripiprazole does not affect them adversely.

Body Temperature Regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration).

Suicide
The possibility of a suicide attempt is inherent in psychotic illnesses, bipolar disorder, and major depressive disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for aripiprazole should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Dysphagia
Oesophageal dysmotility and aspiration have been associated with antipsychotic medicinal product use, including aripiprazole. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling and impulse-control problems
Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. Because patients may not recognize these behaviours as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, or other urges, while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; In some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Compulsive behaviours 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.

Sleep apnoea and related disorders
Sleep apnoea and related disorders have been reported in patients treated with atypical antipsychotic drugs, including aripiprazole, with or without concomitant weight gain or prior history of sleep apnoea.
Aripiprazole should be used with caution in patients who have sleep apnoea or risk factors for developing sleep apnoea, which include: overweight/obesity, males, and concomitant use of central nervous system depressants.

Falls
Antipsychotics, including aripiprazole, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Hypersensitivity
As with other medicinal products, hypersensitivity reactions, characterized by allergic symptoms, may occur with aripiprazole.

4.5 Interaction with other medicinal products and other forms of interaction

Strong CYP3A4 Inhibitors (e.g., itraconazole, clarithromycin) or strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)
The concomitant use of aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of aripiprazole alone. With concomitant use of aripiprazole with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, reduce the aripiprazole dosage [see Posology section (4.2)].

Strong CYP3A4 Inducers (e.g., carbamazepine, rifampin)

The concomitant use of aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of aripiprazole alone. With concomitant use of aripiprazole with a strong CYP3A4 inducer, consider increasing the aripiprazole dosage [see Posology section (4.2)].

Antihypertensive Drugs
Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents. Monitor blood pressure and adjust dose accordingly.

Benzodiazepines (e.g., lorazepam)
The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone. Monitor sedation and blood pressure. Adjust dose accordingly.

Drugs Having No Clinically Important Interactions with Aripiprazole
Based on pharmacokinetic studies, no dosage adjustment of aripiprazole is required when administered concomitantly with famotidine, valproate, lithium, and lorazepam.

In addition, no dosage adjustment is necessary for substrates of CYP2D6 (e.g., dextromethorphan, fluoxetine, paroxetine or venlafaxine), CYP2C9 (e.g., warfarin), CYP2C19 (e.g., omeprazole, warfarin, escitalopram), or CYP3A4 (e.g., dextromethorphan) when co-administered with aripiprazole. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when co-administered with aripiprazole.

Fluoxetine, Paroxetine, and Sertraline
A population pharmacokinetic analysis in patients with major depressive disorder showed no substantial change in plasma concentrations of fluoxetine (20 mg/day or 40 mg/day), paroxetine CR (37.5 mg/day or 50 mg/day), or sertraline (100 mg/day or 150 mg/day) dosed to steady-state. The steady-state plasma concentrations of fluoxetine and norfluoxetine increased by about 18% and 36%, respectively and concentrations of paroxetine decreased by about 27%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were co-administered with aripiprazole. Aripiprazole dosing was 2 mg/day to 15 mg/day (when given with fluoxetine or paroxetine) or 2 mg/day to 20 mg/day (when given with sertraline).

Alcohol
There was no significant difference between aripiprazole co-administered with ethanol and placebo co-administered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking aripiprazole.

4.6 Fertility, pregnancy and lactation
Patients should be advised to notify their doctors if they become pregnant or intend to become pregnant during therapy with Aripiprazole

Neonates exposed to antipsychotic drugs including Aripiprazole during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization

Aripiprazole should be used during pregnancy only if the potential benefits justifies the potential risk to the foetus.

Breast-feeding
Aripiprazole is present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from aripiprazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

4.8 Undesirable effects

Adverse Reactions
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following adverse reactions are discussed in more details in other sections of the labelling (see section 4.4. Special warnings and precautions for use):

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- Cerebrovascular Adverse Events, Including Stroke
- Neuroleptic Malignant Syndrome (NMS)
- Tardive Dyskinesia
- Extrapyramidal symptoms
- Venous Thromboembolism
- Metabolic Changes
- Orthostatic Hypotension
- Leukopenia, Neutropenia, and Agranulocytosis
- Seizures
- Potential for Cognitive and Motor Impairment
- Body Temperature Regulation
- Suicide
- Dysphagia
- Pathological Gambling and Other Compulsive Behaviours
- Sleep apnoea and related disorders
- Falls

The most common adverse reactions in adult patients in clinical trials (≥ 10%) were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia and restlessness.

Aripiprazole has been evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials in schizophrenia, bipolar disorder, major depressive disorder, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7,619 patient-years of exposure to oral aripiprazole. A total of 3,390 patients were treated with oral aripiprazole for at least 180 days and 1,933 patients treated with oral aripiprazole had at least 1 year of exposure.

The conditions and duration of treatment with aripiprazole (monotherapy and adjunctive therapy with antidepressants or mood stabilizers) included (in overlapping categories) double-

blind, comparative and non-comparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, MedDRA dictionary terminology has been used to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; i.e., all reported events are included.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Clinical Trials Experience

Adult Patients with Schizophrenia
The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which Aripirazole was administered in doses ranging from 2 to 30 mg/day.

Commonly Observed Adverse Reactions
The only commonly observed adverse reaction associated with the use of aripiprazole in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (placebo 4%; aripiprazole 8%).

Adult Patients with Bipolar Mania

Monotherapy
The following findings are based on a pool of 3-week, placebo-controlled bipolar mania trials in which aripiprazole was administered at doses of 15 or 30 mg/day.

Commonly Observed Adverse Events
Commonly observed adverse reactions associated with the use of aripiprazole in patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table2.

Table2 : Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials in Patients with Bipolar Mania Treated with Aripiprazole Monotherapy

Preferred Term	Percentage of Patients Reporting Reactions	
	Aripiprazole (n=917)	Placebo (n=753)
Akathisia	13	4

Sedation	8	3
Restlessness	6	3
Tremor	6	3
Extrapyramidal Disorder	5	2

Less Common Adverse Reactions in Adults

Table 3 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those reactions that occurred in 2% or more of patients treated with aripiprazole (doses ≥ 2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 3: Treatment-Emergent Adverse Reactions in Short-Term, Placebo- Controlled Trials in Adult Patients Treated with Aripiprazole

	Percentage of Patients Reporting Reactions	
System Organ Class **Preferred Term**	**Aripiprazole** **(n=1843)**	**Placebo** **(n=1166)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13

Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

[a] Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction incidence on the basis of age, gender, or race.

Adult Patients with Adjunctive Therapy with Bipolar Mania
The following findings are based on a placebo-controlled trial of adult patients with bipolar disorder in which aripiprazole was administered at doses of 15 or 30 mg/day as adjunctive therapy with lithium or valproate.

Adverse Reactions Associated with Discontinuation of Treatment
In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 12% for patients treated with adjunctive aripiprazole compared to 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive aripiprazole-treated compared to placebo-treated patients were akathisia (5% and 1%, respectively) and tremor (2% and 1%, respectively).

Commonly Observed Adverse Reactions
The commonly observed adverse reactions associated with adjunctive aripiprazole and lithium or valproate in patients with bipolar mania (incidence of 5% or greater and incidence at least twice that for adjunctive placebo) were: akathisia, insomnia, and extrapyramidal disorder.

Less Common Adverse Reactions in Adult Patients with Adjunctive Therapy in Bipolar Mania

Table 4 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during acute treatment (up to 6 weeks), including only those reactions that occurred in 2% or more of patients treated with adjunctive aripiprazole (doses of 15 or 30 mg/day) and lithium or valproate and for which the incidence in patients treated with this combination was greater than the incidence in patients treated with placebo plus lithium or valproate.

Table 4: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**Aripiprazole + Li or Val*** **(n=253)**	**Placebo + Li or Val*** **(n=130)**
Gastrointestinal Disorders		
Nausea	8	5
Vomiting	4	0
Salivary Hypersecretion	4	2
Dry Mouth	2	1
Infections and Infestations		
Nasopharyngitis	3	2
Investigations		
Weight Increased	2	1
Nervous System Disorders		
Akathisia	19	5
Tremor	9	6

Extrapyramidal Disorder	5	1
Dizziness	4	1
Sedation	4	2
Psychiatric Disorders		
Insomnia	8	4
Anxiety	4	1
Restlessness	2	1

[a] Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.
* Lithium or Valproate

Dose-Related Adverse Reactions

Schizophrenia
Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed doses (2, 5, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence ([including sedation] placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

Extrapyramidal Symptoms

Schizophrenia
In the short-term, placebo-controlled trials of schizophrenia in adults, the incidence of reported EPS- related events, excluding events related to akathisia, for aripiprazole-treated patients was 13% vs. 12% for placebo. In the short-term, placebo-controlled trials in schizophrenia, the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo.

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05).

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

Bipolar Mania
In the short-term, placebo-controlled trials in bipolar mania in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for monotherapy aripiprazole-treated patients was 16% vs. 8% for placebo and the incidence of akathisia-related events for monotherapy aripiprazole-treated patients was 13% vs. 4% for placebo. In the 6-week, placebo-controlled trial in bipolar mania for adjunctive therapy with lithium or valproate, the incidence of reported EPS-related events, excluding events related to akathisia for adjunctive aripiprazole-treated patients was 15% vs. 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive Aripiprazole-treated patients was 19% vs. 5% for adjunctive placebo.

In the adult bipolar mania trials with monotherapy aripiprazole, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.50; placebo, – 0.01 and aripiprazole, 0.21; placebo, – 0.05). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups. In the bipolar mania trials with aripiprazole as adjunctive therapy with either lithium or valproate, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.73; placebo, 0.07 and aripiprazole, 0.30; placebo, 0.11). Changes in the Assessments of Involuntary Movement Scales were similar for adjunctive aripiprazole and adjunctive placebo.

Dystonia
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.

Additional Findings Observed in Clinical Trials

Adverse Reactions in Long-Term, Double-Blind, Placebo-Controlled Trials

The adverse reactions reported in a 26-week, double-blind trial comparing aripiprazole and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for aripiprazole vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤ 49 days), and were of limited duration (7/12 ≤ 10 days). Tremor infrequently led to discontinuation (< 1%) of aripiprazole. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for aripiprazole was 5% (40/859).

A similar profile was observed in a long-term monotherapy study and a long-term adjunctive study with lithium and valproate in bipolar disorder.

Summary of the safety profile
Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients
The most common adverse reactions in adult patients were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia and restlessness.

Tabulated list of adverse reactions

	Frequent	Infrequent	Rare
Blood and lymphatic system disorders			Thrombocytopenia
Immune system disorders			hypersensitivity
Metabolism and nutrition disorders	anorexia		hyponatremia, hypoglycaemia

Psychiatric disorders		Aggression, Loss of libido, delirium	libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking
Nervous system disorders		parkinsonism, memory impairment, cogwheel rigidity, hypokinesia, myoclonus, bradykinesia	akinesia, myoclonus, coordination abnormal, speech disorder, Grand Mal convulsion; <1/10,000 patients – choreoathetosis
Eye disorders		Photophobia	Diplopia
Cardiac disorders		bradycardia, palpitations, rare – atrial flutter, cardio-respiratory arrest, atrioventricular block, atrial fibrillation, angina pectoris, myocardial ischemia, myocardial infarction, cardiopulmonary failure	
Vascular disorders		Hypotension, hypertension	
Respiratory, thoracic and mediastinal disorders		nasal congestion, dyspnoea	
Gastrointestinal disorders		gastroesophageal reflux disease	
Hepatobiliary disorders			hepatitis, jaundice
Skin and subcutaneous tissue disorders		rash, hyperhidrosis, pruritus, photosensitivity reaction, alopecia	urticaria
Musculoskeletal and connective tissue disorders		muscular weakness, muscle tightness	rhabdomyolysis, mobility decreased
Renal and urinary disorders			urinary retention nocturia
Reproductive system and breast disorders		erectile dysfunction	gynaecomastia, menstruation irregular, amenorrhea, breast pain,priapism .

General disorders and administration site conditions	asthenia	peripheral oedema, chest pain	face oedema
Investigations	weight decreased	hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transferase increased,	blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated haemoglobin increased
Injury, Poisoning, and Procedural Complications		fall	heat stroke

Post-marketing Experience
The following adverse events were reported during the post marketing use of aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: occurrences of blood glucose fluctuation, allergic reaction (anaphylactic reaction, angioedema, laryngospasm or oropharyngeal spasm), hyper sexuality, pathological gambling, hepatic failure, hiccups, oculogyric crisis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), restless legs syndrome, blood prolactin decreased and sleep-related eating disorder (SRED), somnambulism (sleep walking) and sleep-related eating disorder.

4.9 Overdose

Common adverse reactions (reported in at least 5% of all overdose cases) reported with aripiprazole over dosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus and tachycardia.

Management of overdose
No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of over dosage and, if QTc interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of aripiprazole, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and Cmax of aripiprazole by 50%.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antipsychotics, ATC code: N05AX12

Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D_2 and serotonin $5HT_{1a}$ receptors and antagonism of serotonin $5HT_{2a}$ receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D_2 and D_3, serotonin $5HT_{1a}$ and $5HT_{2a}$ receptors and moderate affinity for dopamine D_4, serotonin $5HT_{2c}$ and $5HT_7$, alpha-1 adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}C-raclopride, a D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

5.2 Pharmacokinetic properties

Aripiprazole activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole is dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.

Absorption

Aripiprazole is well absorbed after administration of the tablet, with peak plasma concentrations occurring within 3 hours to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. Aripiprazole can be administered with or without food.

Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent D2-receptor occupancy indicating brain penetration of aripiprazole in humans.

Biotransformation

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

Clinical Studies

Schizophrenia

Adults
The efficacy of Aripirazole in the treatment of schizophrenia was evaluated in five short-term (4- and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Four of the five trials were able to distinguish ARIPIPRAZOLE from placebo, but one study, the smallest, did not. Three of these studies also included an active control group consisting of either risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for a comparison of aripiprazole and the active comparators.

In the four positive trials for aripiprazole, four primary measures were used for assessing psychiatric signs and symptoms. The Positive and Negative Syndrome Scale (PANSS) is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. The PANSS positive subscale is a subset of items in the PANSS that rates seven positive symptoms of schizophrenia (delusions, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution, and hostility). The PANSS negative subscale is a subset of items in the PANSS that rates seven negative symptoms of schizophrenia (blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, and stereotyped thinking). The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n = 414) comparing two fixed doses of aripiprazole (15 or 30 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score (Study 1 in Table 5), PANSS positive subscale, and CGI-severity score. In addition, the 15- mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n = 404) comparing two fixed doses of aripiprazole (20 or 30 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score (Study 2 in Table 5), PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n = 420) comparing three fixed doses of aripiprazole (10, 15, or 20 mg/day) to placebo, all three doses of aripiprazole were superior to placebo in the PANSS total score (Study 3 in Table5), PANSS positive subscale, and the PANSS negative subscale.

In a 6-week trial (n = 367) comparing three fixed doses of aripiprazole (2, 5, or 10 mg/day) to placebo, the 10-mg dose of aripiprazole was superior to placebo in the PANSS total score (Study 4 in Table 5), the primary outcome measure of the study. The 2-mg and 5-mg doses did not demonstrate superiority to placebo on the primary outcome measure.

Thus, the efficacy of 10-mg, 15-mg, 20-mg, and 30-mg daily doses was established in two studies for each dose. Among these doses, there was no evidence that the higher dose groups offered any advantage over the lowest dose group of these studies. An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, by history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to aripiprazole 15 mg or placebo for up to 26 weeks of observation for relapse. Relapse during the double-blind phase was defined as CGI-Improvement score of ≥ 5 (minimally worse), scores ≥ 5 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or ≥ 20% increase in the PANSS total score. Patients receiving ARIPIPRAZOLE 15 mg experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo.

Table 5: Schizophrenia Studies

Study number	**Treatment Group**	**Primary Efficacy Measure: PANSS**		
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95% CI)**
Study 1	Aripiprazole (15 mg/day)*	98.5 (17.2)	-15.5 (2.40)	-12.6 (-18.9, -6.2)
	Aripiprazole (30 mg/day)*	99.0 (19.2)	-11.4 (2.39)	-8.5 (-14.8, -2.1)
	Placebo	100.2(16.5)	-2.9 (2.36)	--
Study 2	Aripiprazole (20 mg/day)*	92.6 (19.5)	-14.5 (2.23)	-9.6 (-15.4, -3.8)
	Aripiprazole (30 mg/day)*	94.2 (18.5)	-13.9 (2.24)	-9.0 (-14.8, -3.1)
	Placebo	94.3 (18.5)	-5.0 (2.17)	--
Study 3	Aripiprazole (10 mg/day)*	92.7(19.5)	-15.0 (2.38)	-12.7 (-19.00, -6.41)
	Aripiprazole (15 mg/day)*	93.2 (21.6)	-11.7 (2.38)	-9.4 (-15.71, -3.08)
	Aripiprazole (20 mg/day)*	92.5 (20.9)	-14.4 (2.45)	-12.1 (-18.53, -5.68)
	Placebo	92.3 (21.8)	-2.3 (2.35)	--
Study 4	Aripiprazole (2 mg/day)*	90.7 (14.5)	-8.2 (1.90)	-2.9 (-8.29, 2.47)
	Aripiprazole (5 mg/day)*	92.0 (12.6)	-10.6 (1.93)	-5.2 (-10.7, 0.19)
	Aripiprazole (10 mg/day)*	90.0 (11.9)	-11.3 (1.88)	-5.9 (-11.3, -0.58)
	Placebo	90.8 (13.3)	-5.3 (1.97)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

Bipolar Disorder

Acute Treatment of Manic and Mixed Episodes

Adults

Monotherapy
The efficacy of aripiprazole as monotherapy in the acute treatment of manic episodes was established in four 3-week, placebo-controlled trials in hospitalized patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These studies included

patients with or without psychotic features and two of the studies also included patients with or without a rapid-cycling course.

The primary instrument used for assessing manic symptoms was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). A key secondary instrument included the Clinical Global Impression-Bipolar (CGI-BP) Scale.

In the four positive, 3-week, placebo-controlled trials (n = 268; n = 248; n = 480; n = 485) which evaluated aripiprazole in a range of 15 mg to 30 mg, once daily (with a starting dose of 30 mg/day in two studies and 15 mg/day in two studies), aripiprazole was superior to placebo in the reduction of Y-MRS total score (Studies 1 to 4 in Table 6) and CGI-BP Severity of Illness score (mania). In the two studies with a starting dose of 15 mg/day, 48% and 44% of patients were on 15 mg/day at endpoint. In the two studies with a starting dose of 30 mg/day, 86% and 85% of patients were on 30 mg/day at endpoint.

Adjunctive Therapy

The efficacy of adjunctive aripiprazole with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in a 6-week, placebo-controlled study (n = 384) with a 2-week lead-in mood stabilizer monotherapy phase in adult patients who met DSM-IV criteria for bipolar I disorder. This study included patients with manic or mixed episodes and with or without psychotic features.

Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 μg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (YMRS total score ≥ 16 and ≤ 25% improvement on the Y-MRS total score) to lithium or valproate were randomized to receive either aripiprazole (15 mg/day or an increase to 30 mg/day as early as day 7) or placebo as adjunctive therapy with open-label lithium or valproate. In the 6-week, placebo-controlled phase, adjunctive aripiprzole starting at 15 mg/day with concomitant lithium or valproate (in a therapeutic range of 0.6 to 1.0 mEq/L or 50 to 125 μg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score (Study 5 in Table 6) and CGI-BP Severity of Illness score (mania). Seventy-one percent of the patients co-administered valproate and 62% of the patients co-administered lithium were on 15 mg/day at 6-week endpoint.

Table 6: Bipolar Studies

Study number	**Treatment Group**	**Primary Efficacy Measure: Y-MRS**		
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95% CI)**
Study 1	Aripiprazole (30/15 mg/day)*	29.0(5.9)	-12.52 (1.05)	-5.33 (-7.90, -2.76)
	Placebo	28.5 (4.6)	-7.19 (1.07)	--
Study 2	Aripiprazole (30/15 mg/day)*	27.8(5.7)	-8.15 (1.23)	-4.80 (-7.80, -1.80)
	Placebo	29.1 (6.9)	-3.35 (1.22)	--
Study 3	Aripiprazole (15-30mg/day)*	28.5 (5.6)	- 12.64 (0.84)	- 3.63 (-5.75, -1.51)
	Placebo	28.9 (5.9)	9.01 (0.81)	--

Study 4	Aripiprazole (15-30mg/day)*	28.0 (5.8)	11.98 (0.80)	-2.28 (-4.44, -0.11)
	Placebo	28.3 (5.8)	-9.70 (0.83)	--
Study 5	Aripiprazole (15 or 30mg/day)*+ Lithium/Valproate	23.2 (5.7)	-13.31 (0.50)	-2.62 (-4.29, -0.95)
	Placebo + Lithium/Valproate	23.0 (4.9)	-10.7 (0.69)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses statistically significantly superior to placebo.

Maintenance Treatment of Bipolar I Disorder

Monotherapy Maintenance Therapy

A maintenance trial was conducted in adult patients meeting DSM-IV criteria for Bipolar I Disorder with a recent manic or mixed episode who had been stabilized on open-label aripiprazole and who had maintained a clinical response for at least 6 weeks. The first phase of this trial was an open-label stabilization period in which inpatients and outpatients were clinically stabilized and then maintained on open-label aripiprazole (15 or 30 mg/day, with a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one outpatients were then randomized in a double-blind fashion, to either the same dose of aripiprazole they were on at the end of the stabilization and maintenance period or placebo and were then monitored for manic or depressive relapse. During the randomization phase, aripiprazole was superior to placebo on time to the number of combined affective relapses (manic plus depressive), the primary outcome measure for this study. The majority of these relapses were due to manic rather than depressive symptoms. There is insufficient data to know whether aripiprazole is effective in delaying the time to occurrence of depression in patients with Bipolar I Disorder.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age and gender; however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess inter-group differences.

Adjunctive Maintenance Therapy

An adjunctive maintenance trial was conducted in adult patients meeting DSMIV criteria for bipolar I disorder with a recent manic or mixed episode. Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 μg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥ 16 and ≤ 35% improvement on the Y-MRS total score) to lithium or valproate received aripiprazole with a starting dose of 15 mg/day with the option to increase to 30 mg or reduce to 10 mg as early as day 4, as adjunctive therapy with open-label lithium or valproate. Prior to randomization, patients on the combination of single-blind Aripiprazole and lithium or valproate were required to maintain stability (Y-MRS and MADRS total scores ≤ 12) for 12 consecutive weeks. Three hundred thirty-seven patients were then randomized in a double-blind fashion, to either the same dose of aripiprazole they were on at the end of the stabilization period or placebo plus lithium or valproate and were then monitored for manic, mixed, or depressive relapse for a maximum of 52 weeks. Aripiprazole was superior to placebo on the primary endpoint, time from randomization to relapse to any mood. A mood event was defined as hospitalization for a manic, mixed, or depressive episode, study discontinuation due to lack of efficacy accompanied by Y-MRS score > 16 and/or a MADRS > 16, or an SAE of worsening disease accompanied by YMRS

score > 16 and/or a MADRS > 16. A total of 68 mood events were observed during the double-blind treatment phase. Twenty-five were from the aripiprazole group and 43 were from the placebo group. The number of observed manic episodes in the aripiprazole group (7) were fewer than that in the placebo group (19), while the number of depressive episodes in the aripiprazole group (14) was similar to that in the placebo group (18).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Crystalline Maltose
Microcrystalline cellulose
Pregelatinised starch
Croscarmellose Sodium
Magnesium stearate
Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.
Store below 30°C

6.5 Nature and contents of container

Carton of 28 tablets in PA/Alu/PVC- Aluminium foil perforated blisters (alu-alu blister)

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION NUMBER(S)

ARIPDON TABLETS 5MG: MAL*********
ARIPDON TABLETS 5MG: SINXXXXXP

8 MANUFACTURER

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