PRODUCT MONOGRAPH

[Pr]pms-ARIPIPRAZOLE
Aripiprazole Tablets, House Standard
2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg

Antipsychotic Agent

PHARMASCIENCE INC.
6111 Royalmount Ave., Suite 100
Montréal, Canada
H4P 2T4

www.pharmascience.com

Date of Revision:
February 14, 2018

Submission Control No: 189870, 213225

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Oral	Tablet 2 mg, 5 mg , 10 mg, 15 mg, 20 mg and 30 mg	Croscarmellose Sodium, Hydroxypropyl-Cellulose, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. In addition, the following strengths contain: 2 mg: Indigo Carmine, Iron Oxide Yellow. 5 mg: Indigo Carmine. 10 mg: Iron Oxide Red. 15 mg: Iron Oxide Yellow. 30 mg: Iron Oxide Red.

INDICATIONS AND CLINICAL USE

Adults

Schizophrenia
pms-ARIPIPRAZOLE (aripiprazole) is indicated for the treatment of schizophrenia and related psychotic disorders in adults. In controlled clinical trials, aripiprazole was found to improve both positive and negative symptoms.

Aripiprazole has been shown to be more effective than placebo in maintaining clinical improvement for up to 26 weeks in adults.

Pediatrics (< 18 years of age):

When prescribing to adolescents with schizophrenia (15-17 years of age), clinicians must take into account the safety concerns associated with all antipsychotic drugs which include: weight gain; hyperlipidemia; hyperglycemia; and, extrapyramidal effects which can be more frequent or more severe in this patient population than in adults (see WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS). pms-ARIPIPRAZOLE should only be prescribed to adolescents with schizophrenia by clinicians who are experienced in the diagnosis and treatment of adolescents with psychiatric illness and who are experienced in

the early detection and management of the above-mentioned safety issues associated with this class of drugs.

Schizophrenia
pms-ARIPIPRAZOLE is indicated for the treatment of schizophrenia in adolescents 15-17 years of age.

Safety and efficacy were evaluated in one 6-week clinical trial in adolescents (13-17 years of age) with schizophrenia. pms-ARIPIPRAZOLE is not indicated for the treatment of schizophrenia in adolescents less than 15 years of age due to insufficient safety and efficacy data (see ADVERSE REACTIONS; CLINICAL TRIALS, Schizophrenia, Adolescents).

The safety and efficacy of aripiprazole during long term treatment have not been systematically evaluated in adolescents with schizophrenia. The physician who elects to use pms-ARIPIPRAZOLE for extended periods in adolescents with schizophrenia should periodically re-evaluate the long term usefulness of the drug for the individual patient.

Geriatrics (≥ 65years of age):

pms-ARIPIPRAZOLE is not indicated in elderly patients with dementia. (See WARNINGS AND PRECAUTIONS, Serious Warnings and Precaution Box and Special populations). The safety and efficacy of aripiprazole in patients 65 years of age or older has not been established. Caution should be used when treating geriatric patients (see WARNINGS AND PRECAUTIONS, Special Populations and ACTION AND CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

pms-ARIPIPRAZOLE (aripiprazole) is contraindicated in those patients with a known hypersensitivity to this drug or the excipients of the product. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia
Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-treated patients. Although the causes of death 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 WARNINGS AND PRECAUTIONS, Special Populations, Use in Elderly Patients with Dementia).

General

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 pms-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) (see ADVERSE REACTIONS).

Carcinogenesis and Mutagenesis

For animal data, see Part II: TOXICOLOGY section.

Cardiovascular

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. Aripiprazole may induce orthostatic hypotension, tachycardia, dizziness, and sometimes syncope, especially at the initiation of treatment. The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral aripiprazole (n=2,643) included (aripiprazole incidence, placebo incidence): orthostatic hypotension (1.0%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.3%); of adolescent patients (13-17 years of age) with schizophrenia on oral aripiprazole (n=202) included (aripiprazole 10 mg/day incidence, aripiprazole 30 mg/day incidence, placebo incidence): orthostatic hypotension (0%, 2.9%, 0%), postural dizziness (0%, 2%, 0%), and syncope (1%, 0%, 0%). The risk of orthostatic hypotension may be reduced by more gradual titration to the target dose.

The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 bpm when comparing standing to supine values) for oral aripiprazole was (aripiprazole incidence, placebo incidence): 3.7%, 2.3% in adults; 0% (0/202), 0% (0/100) in adolescent patients (13-17 years of age) with schizophrenia.

pms-ARIPIPRAZOLE should be used with caution in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Patients with a history of clinically significant cardiovascular disorders were excluded from clinical trials.

QT Interval

In clinical trials with aripiprazole involving patients with schizophrenia, the incidence of QT prolongation was comparable to placebo. In post-marketing experience, QT prolongation has been reported very rarely with aripiprazole treatment. As with other antipsychotics, caution should be

exercised when pms-ARIPIPRAZOLE is prescribed in patients with a history of cardiac arrhythmias, in patients with congenital or family history of long QT syndrome, and in concomitant use with drugs known to prolong the QT interval (see ADVERSE REACTIONS, ECG Changes; ADVERSE REACTIONS, Post-market Adverse Drug Reactions).

Dependence/Tolerance

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of pms-ARIPIPRAZOLE misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

Pathological Gambling and Other Impulse-Control Disorders

Post-marketing reports of pathological gambling have been reported in patients treated with aripiprazole. These reports suggest that patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. With regards to pathological gambling, patients with a prior history of gambling disorder may be at increased risk and should be monitored carefully. Other urges, reported very rarely, include: increased sexual urges, compulsive spending, binge or compulsive eating, and other impulsive and compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive spending, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Although impulse-control disorders have been reported very rarely, impulse-control disorders may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole.

Endocrine and Metabolism

Hyperglycemia and Diabetes Mellitus

Diabetic ketoacidosis has occurred in patients with no reported history of hyperglycemia. As with some other antipsychotics, exacerbation of pre-existing diabetes and hyperglycemia have been reported rarely and diabetic ketoacidosis and diabetic coma including some fatal cases, have been reported very rarely during the use of aripiprazole (see ADVERSE REACTIONS).

Assessment of the relationship between atypical antipsychotic 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 these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related

adverse events is not completely understood. However, epidemiological studies which did not include aripiprazole suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients should have baseline and periodic monitoring of blood glucose and body weight. Any patient treated with atypical antipsychotics should also be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. 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. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Weight, glucose and lipid changes in adolescents with schizophrenia
There are limited data for aripiprazole in adolescents with schizophrenia (13-17 years of age) from acute placebo controlled, fixed dose clinical trials (4 to 6 weeks, 10 mg/day and 30 mg/day) and from extension studies (up to 26 weeks of treatment) to assess the effects of aripiprazole on weight, glucose, and lipid metabolism. Data for these parameters from the acute placebo controlled clinical trials were from approximately 50 to 100 patients per treatment group, and in the adolescent schizophrenia trial the majority of patients had received treatment with other antipsychotic medications prior to inclusion in this study. Therefore, these data cannot be considered entirely predictive of the effects of aripiprazole on weight, glucose and lipid metabolism during use in adolescents with schizophrenia (see ADVERSE REACTIONS, Weight Gain, Glucose, and Lipids). Published studies have demonstrated that the adverse effects of atypical antipsychotic drugs on weight, glucose and lipid metabolism can be greater in antipsychotic-naïve pediatric and adolescent patients than in patients who have been treated previously with antipsychotic drugs.

Clinical monitoring of weight, glucose and lipids at baseline and at regular intervals is recommended for adolescents with schizophrenia who are treated with antipsychotics including pms-ARIPIPRAZOLE.

<u>Weight Gain</u>
During acute placebo controlled and extension phase studies in pediatric and adolescent patients with schizophrenia, the proportion of patients with potentially clinically significant weight gain (≥ 7% increase from baseline weight) was greater among those treated with aripiprazole compared to those that received placebo (see ADVERSE REACTIONS, Weight Gain).

<u>Glucose</u>
See ADVERSE REACTIONS, Glucose.

Lipids
See ADVERSE REACTIONS, Lipids.

Genitourinary

Priapism
Rare cases of priapism have been reported with antipsychotic use such as aripiprazole. As with other psychotropic drugs, this adverse reaction did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic

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 (see ADVERSE REACTIONS, Post-market Adverse Drug Reactions). Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting pms-ARIPIPRAZOLE and then periodically throughout treatment.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of pms-ARIPIPRAZOLE should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1,000/mm^3) should discontinue pms-ARIPIPRAZOLE and have their WBC followed until recovery.

Venous thromboembolism
Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including aripiprazole in case reports and/or observational studies. When prescribing pms-ARIPIPRAZOLE all potential risk factors for VTE should be identified and preventative measures undertaken.

Neurologic

Neuroleptic Malignant Syndrome (NMS)
Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including 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.

In arriving at a diagnosis, it is important to identify 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 all antipsychotic drugs including pms-ARIPIPRAZOLE and other drugs not essential to 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 for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential re-introduction of therapy should be very carefully considered. The patient should be carefully monitored, since recurrence of NMS has been reported.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome is 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 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.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome 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, pms-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 pms-ARIPIPRAZOLE drug discontinuation should be considered. However, some patients may require treatment with pms-ARIPIPRAZOLE despite the presence of the syndrome.

Extrapyramidal Symptoms
The rate of extrapyramidal-related adverse events in adolescents (13-17 years of age) with schizophrenia was greater than the rate reported in adult patients (see ADVERSE REACTIONS, Extrapyramidal Symptoms, Dose-Related Adverse Events, and Additional Findings Observed in Clinical Trials).

Pediatric and adolescent patients are known to be at greater risk of experiencing certain adverse events related to the use of atypical antipsychotics, including extrapyramidal symptoms (see ADVERSE REACTIONS).

Seizure/Convulsion
In short-term, placebo-controlled trials of patients treated with oral aripiprazole, seizures/convulsions occurred in 0.1% (3/2,643) of adult patients and in 0% (0/202) of adolescent (13-17 years of age) patients with schizophrenia. There were confounding factors that may have contributed to the occurrence of seizures in some of these patients.

As with other antipsychotic drugs, pms-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
Like other antipsychotics drugs, pms-ARIPIPRAZOLE has the potential to impair judgment, thinking, or motor skills. Somnolence was a commonly reported adverse event in patients treated with aripiprazole in clinical trials. Somnolence (including sedation) adverse events were reported more frequently in adolescents with schizophrenia (13-17 years of age) than in adult patients (see ADVERSE REACTIONS, Somnolence).

Because pms-ARIPIPRAZOLE may cause somnolence, and impair motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that pms-ARIPIPRAZOLE therapy does not affect them adversely.

Psychiatric

Suicide
The possibility of a suicide attempt is inherent in psychotic illnesses. Also, depression may be co-morbid with schizophrenia. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Close supervision and appropriate clinical management of high-risk patients should accompany drug therapy. Prescriptions for pms-ARIPIPRAZOLE should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Special Populations

Pregnant Women

Teratogenic effects

There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits (see TOXICOLOGY).

Non-teratogenic effects

Neonates exposed to antipsychotic drugs, including pms-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.

pms-ARIPIPRAZOLE should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

Labor and Delivery

The effect of aripiprazole on labor and delivery in humans is unknown.

Nursing Women

Aripiprazole is excreted in human breast milk. It is recommended that women receiving pms-ARIPIPRAZOLE should not breast-feed.

Pediatrics (< 18 years of age)

When prescribing to adolescents with schizophrenia (15-17 years of age), clinicians must take into account the safety concerns associated with all antipsychotic drugs which include: weight gain; hyperlipidemia; hyperglycemia; and, extrapyramidal effects which can be more frequent or more severe in this patient population than in adults (see ADVERSE REACTIONS).
pms-ARIPIPRAZOLE should only be prescribed to adolescents with schizophrenia by clinicians who are experienced in the diagnosis and treatment of adolescents with psychiatric illness and who are experienced in the early detection and management of the above-mentioned safety issues associated with this class of drugs.

Weight gain has been observed with atypical antipsychotic use in pediatric and adolescent patient populations. Independent of any drug-specific effects, weight gain can be associated with adverse changes in other metabolic parameters (e.g., glucose and lipid metabolism). Abnormal childhood weight and metabolic status can have adverse effects on cardiovascular outcomes in adulthood. Weight gain and adverse effects on other metabolic parameters associated with atypical antipsychotics can be more frequent or severe in pediatric and adolescent patients than in the adult patients.

The long-term safety, including cardiometabolic effects and effects on growth, maturation and behavioural development in patients under 18 years of age has not been systematically evaluated.

Safety and efficacy have been evaluated in one 6-week placebo-controlled clinical trial in adolescents (13-17 years of age) with schizophrenia. aripiprazole is not indicated for the treatment of schizophrenia in adolescents under 15 years of age due to insufficient safety and efficacy data (see ADVERSE REACTIONS; CLINICAL TRIALS, Schizophrenia, Adolescents (13-17 years of age)).

Geriatrics (≥65 years of age)
In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box; DOSAGE AND ADMINISTRATION, Geriatric (≥ 65 years of age)).

Placebo-controlled studies of oral aripiprazole in schizophrenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Nevertheless, geriatric patients generally have decreased cardiac, hepatic and renal function, and more frequent use of concomitant medication. The presence of multiple factors that might increase the pharmacodynamic response to aripiprazole, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for elderly patients. The safety and efficacy of aripiprazole in patients 65 years of age or older have not been established. Caution should be used when treating geriatric patients.

Use in Elderly Patients with Dementia
Overall Mortality
Elderly patients with dementia treated with atypical antipsychotic drugs showed increased mortality compared to placebo in a meta-analysis of 13 placebo-controlled trials of various atypical antipsychotic drugs. In three placebo-controlled studies of aripiprazole in elderly patients with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the rate of death in aripiprazole-treated patients was 3.5%, compared to a rate of 1.7% in the placebo group during or within 30 days after termination from the double-blind phase of the studies. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. pms-ARIPIPRAZOLE is not indicated for the treatment of patients with dementia (see Serious Warnings and Precautions).

Cerebrovascular Adverse Events, Including Stroke in Elderly Patients with Dementia
In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of elderly patients with dementia, there was an increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients. In the fixed-

dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. pms-ARIPIPRAZOLE is not indicated for the treatment of patients with dementia (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions).

Frequent Treatment Emergent Adverse Events in Elderly Patients with Dementia
In the placebo-controlled studies of elderly patients with dementia (n=595 treated with aripiprazole, n=343 treated with placebo), the following treatment-emergent adverse events were reported at an incidence of ≥3% and aripiprazole incidence at least twice that for placebo: lethargy [placebo 2%, aripiprazole 5%], somnolence (including sedation) [placebo 3%, aripiprazole 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole 5%], excessive salivation [placebo 0%, aripiprazole 4%], and lightheadedness [placebo 1%, aripiprazole 4%].

Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including aripiprazole. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. pms-ARIPIPRAZOLE and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see ADVERSE REACTIONS).

The emergence of difficulty swallowing or excessive somnolence could predispose patients to accidental injury or aspiration (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions).

Use in Patients with Renal Impairment
No dosage adjustment is required in subjects with renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special populations and Conditions, Renal Impairment).

Use in Patients with Hepatic Impairment
No dosage adjustment is required in subjects with hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special populations and Conditions, Hepatic Impairment).

Use in Patients with Concomitant Illness
Clinical experience with aripiprazole in patients with certain concomitant systemic illnesses is limited. Aripiprazole has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from pre-marketing clinical studies (see WARNINGS AND PRECAUTIONS, Cardiovascular, Orthostatic Hypotension).

Gender
C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

Race
Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation did not demonstrate important race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

Lactose
pms-ARIPIPRAZOLE tablets contain lactose (70 mg, 67 mg, 62 mg, 93 mg, 124 mg and 187 mg for the 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg tablets respectively). Patients with rare hereditary problems of galactose intolerance or glucose-galactose malabsorption should not take pms-ARIPIPRAZOLE.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Aripiprazole was evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials, and who had approximately 7,619 patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole injection. 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 included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed - and flexible-dose studies, and short - and longer-term exposure.

Aripiprazole was evaluated for safety in 202 adolescent patients (13-17 years of age) with schizophrenia in a 6 week placebo controlled clinical trial. Adolescent patients from this study were also treated with oral aripiprazole in uncontrolled, open label studies for more than 26 weeks (n=178) and more than 52 weeks (n=79). Treatment emergent adverse event frequencies are reported for adolescent patients, 13-17 years of age, with schizophrenia that were included in these studies, but the majority of patients were 15 - 17 years of age.

pms-ARIPIPRAZOLE is not indicated for the treatment of schizophrenia in adolescent patients under 15 years due to insufficient safety and efficacy data (see ADVERSE REACTIONS; CLINICAL TRIALS, Schizophrenia, Adolescents (13-17 years of age)).

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 events 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 reporting adverse events.

The stated frequencies of adverse events represent the proportion of individuals who reported 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 events meeting the defined criteria, regardless of investigator causality are included.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Short-Term, Placebo-Controlled Trials of 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 aripiprazole was administered orally in doses ranging from 2 to 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment

Overall, there was little difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

Commonly Reported Adverse Events

The only commonly observed adverse event 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%).

Adverse Events Reported at an Incidence of 2% or More Among Adult Aripiprazole-Treated Patients and Greater than Placebo in Short-Term, Schizophrenia Placebo-Controlled Trials

Table 1 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that were reported during acute therapy (up to 6 weeks in schizophrenia), including only those events that were reported 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 1: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials in Adult Patients with Schizophrenia [a] Treated with Oral Aripiprazole

	Percentage of Patients Reporting Event[b]	
System Organ Class	**Aripiprazole**	**Placebo**
Preferred Term	**(n=1843)**	**(n=1166)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11

	Percentage of Patients Reporting Event[b]	
System Organ Class	**Aripiprazole**	**Placebo**
Preferred Term	**(n=1843)**	**(n=1166)**
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] 926 aripiprazole-treated patients and 413 placebo treated patients
[b] Events reported by at least 2% of patients treated with oral aripiprazole, except events which had an incidence equal to or less than placebo.

An examination of population subgroups did not demonstrate a difference in the incidence of adverse events based on age, gender, or race.

Patients should be advised of the risk of severe constipation during aripiprazole treatment and that they should tell their doctor if constipation occurs or worsens as they may need laxatives.

Short-Term, Placebo-Controlled Trial of Adolescent Patients (13-17 years of age) with Schizophrenia

The following findings are based on one 6-week placebo-controlled trial in which oral aripiprazole was administered in doses ranging from 2 mg/day to 30 mg/day. Doses were titrated to fixed doses of 10 mg/day or 30 mg/day aripiprazole.

Adverse Events Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse events was 7% for patients treated with 10 mg/day aripiprazole, 3.9% for patients treated with 30 mg/day aripiprazole and 2% for patients treated with placebo.

Commonly Observed Adverse Events

Commonly observed adverse events associated with the use of aripiprazole in adolescent patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were extrapyramidal disorder, somnolence, and tremor.

Adverse Events Reported at an Incidence of 1% or More Among Aripiprazole-Treated Patients and Greater than Placebo in a Short-Term, Schizophrenia Placebo-Controlled Trial in Adolescents (13-17 years of age)

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that were reported during acute therapy (up to 6 weeks in schizophrenia) with 10 mg/day and 30 mg/day aripiprazole compared to placebo. Only adverse events that were reported in 1% or more of adolescent 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 are included in Table 2.

Table 2: Treatment-Emergent Adverse Events in a 6-week, Placebo-Controlled Trial in Adolescent Patients[a] with Schizophrenia Treated with Oral Aripiprazole

	Percentage of Patients Reporting Event [b]		
System Organ Class	**Aripiprazole 10 mg**	**Aripiprazole 30 mg**	**Placebo**
Preferred Term	**(n=100)**	**(n=102)**	**(n=100)**
Cardiac Disorders			
Tachycardia	2	0	0
Sinus bradycardia	1	1	0
Eye Disorders			
Vision blurred	2	0	0
Gastrointestinal Disorders			
Nausea	9	10	6
Constipation	3	2	1
Diarrhea	2	3	0
Dry Mouth	1	3	1
Salivary Hypersecretion	1	3	1
Stomach discomfort	1	1	0
General Disorders and Administration Site Conditions			
Fatigue	4	3	1
Pain	1	1	0

	Percentage of Patients Reporting Event [b]		
System Organ Class	**Aripiprazole 10 mg**	**Aripiprazole 30 mg**	**Placebo**
Preferred Term	**(n=100)**	**(n=102)**	**(n=100)**
Infections and Infestations			
Nasopharyngitis	5	5	4
Upper Respiratory Tract Infection	1	2	0
Influenza	1	1	0
Viral Infection	1	1	0
Investigations			
Blood Glucose Increased	3	0	0
Blood insulin increased	2	0	0
Weight Increased	1	2	0
Metabolism and Nutrition Disorders			
Increased Appetite	4	2	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	1	1	0
Muscle rigidity	1	1	0
Muscle weakness	1	1	0
Pain in Extremity	0	3	1
Nervous System Disorders			
Extrapyramidal Disorder	13	22	5
Somnolence[c]	11	22	6
Headache	16	11	10
Akathisia	5	12	5
Tremor	2	12	2
Dizziness	7	4	3
Dystonia	3	1	0
Dizziness postural	0	2	0
Drooling	0	3	0
Dysarthria	2	0	0
Dyskinesia	1	2	0
Psychiatric Disorders			
Hallucination, auditory	2	0	0
Respiratory, Thoracic and Mediastinal Disorders			
Hiccups	0	2	0
Skin and Subcutaneous Tissue Disorders			
Rash	3	1	0
Ecchymosis	1	1	0
Vascular Disorders			
Orthostatic Hypotension	0	3	0

[a] Treatment emergent adverse event incidences are based on the safety population that included patients 13 - 17 years of age, but 75% patients were 15 - 17 years of age. aripiprazole is not indicated for patients with schizophrenia < 15 years of age due to insufficient safety and efficacy data.

[b] Events reported by at least 1% of 202 adolescent patients treated with oral aripiprazole, except events which had an incidence equal to or less than placebo.

[c] Incidence of somnolence does not include sedation. Sedation was reported in one patient receiving 10 mg/day aripiprazole.

Dose-Related Adverse Events

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 oral doses (2, 5, 10, 15, 20, or 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg/day, was somnolence [including sedation]; (incidences were placebo, 7.4%; 10 mg/day, 8.5%; 15 mg/day, 8.7%; 20 mg/day, 7.5%; 30 mg/day, 12.6%).

In the study of adolescent patients with schizophrenia, four adverse events appeared to have a possible dose response relationship: extrapyramidal disorder (incidences were placebo, 5.0%; 10 mg/day, 13.0%; 30 mg/day, 21.6%); somnolence (incidences were placebo, 6.0%; 10 mg/day, 11.0%; 30 mg/day, 21.6%); akathisia (incidences were placebo, 5.0%; 10 mg/day, 5.0%; 30 mg/day, 11.8%); and tremor (incidences were placebo, 2.0%; 10 mg/day, 2.0%; 30 mg/day, 11.8%). Orthostatic hypotension adverse events also appeared to have a possible dose response relationship (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Extrapyramidal Symptoms

Tables 3 and 4 provide the percentage of patients reporting treatment-emergent extrapyramidal symptoms in short-term placebo-controlled trials in adults and pediatrics, respectively.

Table 3: Percentage of Adult Patients Reporting Treatment-EmergentExtrapyramidal Symptoms in Short-Term Placebo-Controlled Trials

	Percentage of Patients Reporting Event	
	Schizophrenia (dose range 2-30 mg/day)	
	Aripiprazole	Placebo
EPS-related AEsa (excluding akathisia)	14	14
Akathisia-related events	8	4

a EPS-related AEs included Parkinsonism events, dystonic events, dyskinetic events and residual events such as muscle twitching and myoclonus.

The incidence of reported EPS-related events in the placebo controlled trial in adolescent patients with schizophrenia was greater than the incidence reported for adult schizophrenia (Tables 3 and 4).

Table 4: Percentage of Children and Adolescent Patients Reporting Treatment-Emergent Extrapyramidal Symptoms in Short-Term Placebo-Controlled Trials

	Percentage of Patients Reporting Event		
	Schizophrenia[a]		
	Aripiprazole		
	10 mg	30 mg	Placebo
EPS-related AEs[b] (excluding akathisia)	18	32	7
Akathisia-related events	6	12	6

a Six-week schizophrenia trial of adolescent patients age 13-17

b EPS-related AEs included Parkinsonism events, dystonic events, dyskinetic events and residual events such as muscle twitching and myoclonus.

Commonly reported treatment emergent extrapyramidal symptoms in adolescent schizophrenia patients were generally dose-related (see ADVERSE REACTIONS, Dose-Related Adverse Events).

Tables 5 and 6 provide the mean change from baseline to endpoint score on the Simpson Angus Rating Scale (for EPS) (SAS), Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesia) (AIMS) from short-term, placebo-controlled trials in adults and pediatrics, respectively.

Table 5: Mean change from baseline to endpoint score on the SAS, Barnes Akathisia Scale, and AIMS from short-term placebo-controlled trials in adults

	Mean Change from Baseline to Endpoint Score	
	Schizophrenia (dose range 2-30 mg/day)	
	Aripiprazole	Placebo
SAS	-0.06	-0.08
Barnes	0.08	-0.05
AIMS	-0.44[1]	-0.02

* A negative score indicates improvement.

1 $p \leq 0.01$

Table 6: Mean change from baseline to endpoint score on the SAS, Barnes Akathisia Scale, and AIMS from short-term placebo-controlled trials in children and adolescents

	Mean Change from Baseline to Endpoint Score		
	Schizophrenia a		
	Aripiprazole		Placebo
	10 mg n=99	30 mg n=97	n=98
SAS	0.5[1]	0.3[2]	-0.3
Barnes	0.1	0.1	0.0
AIMS	-0.2	-0.1	-0.1

a Six-week schizophrenia trial of adolescent patients age 13-17

* A negative score indicates improvement.

1 $p \leq 0.01$

2 $p \leq 0.05$

In a long-term (26-week), placebo-controlled trial in adult patients with schizophrenia, data from the Simpson Angus Rating Scale, the Barnes Akathisia Scale, and the Assessments of Involuntary Movement Scales did not show a difference between aripiprazole and 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 and younger age groups.

Somnolence
Somnolence (including sedation) was a commonly reported adverse event in patients treated with aripiprazole in clinical trials and was reported more frequently in children and adolescents than in adults.

Table 7: Percentage of Adult Patients Reporting Somnolence Adverse Events(including sedation) in Short-Term Placebo-Controlled Trials

	Percentage of Patients Reporting Event	
	Schizophrenia (dose range 2-30 mg/day)	
	Aripiprazole	Placebo
Somnolence (including sedation)	9.6 (89/926)	7.7 (32/413)

Somnolence (including sedation) led to discontinuation of treatment for (aripiprazole-treated, placebo-treated) 0.1% and 0.2% of adult schizophrenia patients.

Table 8: Percentage of Children and Adolescent Patients Reporting Somnolence Adverse Events (including sedation) in Short-Term Placebo-Controlled Trials

	Percentage of Patients Reporting Event		
	Schizophrenia[a]		
	Aripiprazole		
	10 mg	30 mg	Placebo
Somnolence (including sedation)	12 (12/100)	22 (22/102)	6 (6/100)

a Six-week schizophrenia trial of adolescent patients age 13-17

Somnolence (including sedation) led to discontinuation of treatment for (aripiprazole-treated, placebo-treated) 0.5% and 0% of adolescent patients with schizophrenia.

Weight Gain
Adults
In 4- to 6-week trials in adults with schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively) and also a

statistically significant difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)].

In a long-term (26-week) placebo-controlled study of aripiprazole in adults with schizophrenia, a categorization of patients with schizophrenia at baseline on the basis of body mass index [BMI <23 ("low"); 23-27 ("normal"); >27 ("high")] revealed mean weight losses in patients treated with aripiprazole and patients on placebo ("low" BMI, -0.5 kg weight loss in both treatment groups; "normal" BMI, mean weight loss of -1.3 kg in aripiprazole-treated patients and -0.6 kg in placebo-treated patients; "high" BMI, mean weight loss of -2.1 kg in aripiprazole-treated patients and -1.5 kg in placebo-treated patients).

In a long-term (52-week) study of aripiprazole and haloperidol in adults, a categorization of patients with schizophrenia at baseline on the basis of BMI revealed the greatest mean weight gain in patients with low BMI compared to normal or overweight patients in both groups (patients with "low" BMI, mean weight gain 2.6 kg in aripiprazole-treated patients and 1.5 kg in haloperidol-treated patients; "normal" BMI, a mean weight gain of 1.4 kg in aripiprazole-treated patients and 0.2 kg in haloperidol-treated patients; "high" BMI, weight loss of -1.2 kg in aripiprazole-treated patients and -0.8 kg in haloperidol-treated patients).

In both long-term schizophrenia studies, the highest incidence of clinically significant weight gain (>7% of body weight) was in patients with a low BMI (<23) compared to normal (23-27) or overweight patients (>27).

Adolescents

Changes in weight in the 6-week, placebo controlled clinical trial in adolescent patients with schizophrenia are summarized in Table 9.

Table 9: Change in weight (kg) and proportion of patients with ≥ 7% increase in body weight in acute placebo controlled trials in children and adolescent patients

Schizophrenia[a]	**Placebo**	**Aripiprazole**	
		10 mg	**30 mg**
	N=100	N=100	N=102
Weight (kg)	n=98	n=99	n=97
Change from baseline to Last Visit	-0.8	0.0	0.2
Proportion of patients with ≥7% increase from baseline weight at Last Visit	1% (1/98)	4% (4/99)	5.2% (5/97)

a Six-week schizophrenia trial of adolescent patients age 13-17

There was a mean increase in weight of +2.03 kg from baseline to Week 26 during an uncontrolled, 26-week, flexible dose, open label extension study of adolescent patients with schizophrenia that completed the 6-week placebo controlled clinical trial. At Week 26, 26% (47/181) of adolescent patients with schizophrenia had a ≥7% increase in weight from baseline, not adjusted for normal growth (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Weight, glucose and lipid changes in adolescents with schizophrenia).

Glucose

In the 4- and 6-week placebo controlled clinical trials with adolescent schizophrenia patients, there were no patients with fasting serum glucose levels that shifted from normal baseline to clinically significant high values (<5.55 mmol/L to ≥6.99 mmol/L) at endpoint in any treatment group. In these studies fasting glucose data were from approximately 50 patients per treatment group. Therefore, these data cannot be considered entirely predictive of the effects of aripiprazole on glucose metabolism during use in adolescent patients with schizophrenia. In a 26-week open label extension trial that included adolescent patients with schizophrenia treated with aripiprazole, a shift from normal to high fasting glucose at Week 26 was reported for 1.9% (3/155) of them.

There was a mean increase of +0.12 mmol/L in fasting glucose at Week 26 during the 26-week uncontrolled, open label extension study in adolescent schizophrenia patients (n=166, mean baseline 4.87 mmol/L) (see WARNINGS AND PRECAUTIONS, Weight, glucose and lipid changes in adolescents with schizophrenia).

Lipids

Table 10 shows the proportion of pediatric and adolescent patients with changes in total cholesterol, fasting triglycerides and fasting HDL cholesterol in 4- and 6-week placebo-controlled trials in adolescent patients (13-17 years) with schizophrenia, and the 26-week uncontrolled, open-label extension trial that included both patient populations. In the 4- and 6- week placebo controlled clinical trials lipid data were from approximately 30 to 50 patients per treatment group. Therefore, these data cannot be considered entirely predictive of the effects of aripiprazole on lipid metabolism during use in adolescent patients with schizophrenia.

Table 10: Changes in Blood Lipid Parameters in Adolescent Patients[a]

Adolescent Patients with Schizophrenia				
Category Change (at least once) from Baseline	**Trial Type and Duration**	**Treatment Arm**	**n/N**	**%**
Total Cholesterol Normal to High (<4.40 mmol/L to ≥5.17 mmol/L)	6-week placebo-controlled trial	10 mg Aripiprazole	2/52	3.8
		30 mg Aripiprazole	1/52	1.9
		Placebo	0/55	0.0
	26-week open-label trial	Aripiprazole	4/139	3
Fasting Triglycerides Normal to High (<1.70 mmol/L to ≥2.26 mmol/L)	6-week placebo-controlled trial	10 mg Aripiprazole	0/33	0.0
		30 mg Aripiprazole	0/27	0.0
		Placebo	0/28	0.0
	26-week open-label trial	Aripiprazole	0/80	0.0
Fasting HDL Normal to low (>1.03 mmol/L to ≤1.03 mmol/L)	6-week placebo-controlled trial	10 mg Aripiprazole	5/34	14.7
		30 mg Aripiprazole	2/28	7.1
		Placebo	9/27	33.3
	26-week open-label trial	Aripiprazole	5/69	7.2

a Incidence rates are the number of patients with baseline values within the specified range and evaluated for the given lab test at Week 6 for adolescent schizophrenia patients.

During the, 26-week, uncontrolled, open label extension study, there were mean decreases in total cholesterol (fasting and nonfasting) at Week 26 in adolescent schizophrenia patients (n=176, mean baseline 3.81 mmol/L; mean decrease -0.0013 mmol/L). There were mean decreases in fasting triglycerides at Week 26 in adolescent schizophrenia patients (n=97, mean baseline 1.19 mmol/L; mean decrease -0.12 mmol/L). There was a mean increase in fasting HDL cholesterol at Week 26

in adolescent schizophrenia patients (n=97, mean baseline 1.23 mmol/L; mean increase +0.015 mmol/L) (see WARNINGS AND PRECAUTIONS, Weight, glucose and lipid changes in adolescents with schizophrenia).

ECG Changes
Between-group comparisons for a pooled analysis of placebo-controlled trials in adult patients with schizophrenia, and in the acute (4-6 week) placebo controlled trials in adolescent patients with schizophrenia, revealed no significant differences between oral aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. In adults aripiprazole was associated with a median increase in heart rate of 2 beats per minute compared to no increase among placebo patients.

Prolactin
In the 6-week placebo-controlled clinical trial in adolescents (13-17 years of age) with schizophrenia, there was a greater incidence of low serum prolactin levels in males (<86.96 pmol/L) and females (<130.434 pmol/L) treated with aripiprazole compared to placebo. Low serum prolactin levels were reported for 38.6% (17/44), 31.7% (19/60) and 7% (4/57) of males that received 10 mg/day aripiprazole, 30 mg/day aripiprazole or placebo, respectively. Low serum prolactin levels were reported for 29.6% (16/54), 17.1% (6/35) and 10.3% (4/39) of females that received 10 mg/day aripiprazole, 30 mg/day aripiprazole or placebo, respectively.

During a 26-week, open-label study of aripiprazole in adolescent schizophrenic patients, there was a mean decrease in prolactin levels (-27.83 pmol/L) relative to baseline (274.78 pmol/L).

The clinical significance of low prolactin levels in adolescence is not known. However, animal studies and case reports suggest a possible association between significantly low prolactin levels and failure to lactate, menstrual cycle disruption, and pubertal development.

Additional Findings Observed in Clinical Trials

Adverse Events in Long-Term, Double-Blind, Placebo-Controlled Trials in Adults
The adverse events reported in a 26-week, double-blind trial comparing oral aripiprazole and placebo in adult 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).

Adverse Events in a 26-Week Open-Label Extension Trial in Adolescent Patients with Schizophrenia
The safety profile in adolescent patients (13-17 years of age) with schizophrenia in a 26-week, uncontrolled, open-label extension trial, which included patients that completed the 6 week placebo controlled trial, was generally similar to that observed in the 6 week, placebo-controlled trial.

Adverse events such as extrapyramidal disorder, somnolence, and tremor were reported at similar frequencies in both the 6-week placebo-controlled trial and during the 26-week open label extension trial (19.2% extrapyramidal disorder; 13.8% somnolence; 6.3% tremor). The majority of these adverse events observed in the open-label 26-week study had a first onset during that study.

Other Adverse Events Observed During the Pre-marketing Evaluation of Oral Aripiprazole
Following is a list of MedDRA terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 13,543 adult patients. All events assessed as possible adverse drug reactions have been included. In addition, medically/clinically meaningful events particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in Tables 1 to 2 or other parts of the ADVERSE REACTIONS section have been excluded. Although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in less than 1/100 but at least 1/1,000 patients; rare events are those occurring in less than 1/1,000.

Adults – Oral Administration

Blood and Lymphatic System Disorders

Infrequent: leukopenia, neutropenia, thrombocytopenia

Cardiac Disorders

Infrequent: bradycardia, palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, sinus tachycardia, atrial fibrillation, angina pectoris, myocardial ischemia;

Rare: atrial flutter, supraventricular tachycardia, ventricular tachycardia

Endocrine Disorders

Infrequent: diabetes mellitus (including blood insulin increased, carbohydrate tolerance decreased, diabetes mellitus non-insulin-dependent, glucose tolerance impaired, glycosuria, glucose urine, glucose urine present), hyperglycemia, hypoglycemia, polydipsia;

Rare: - diabetic ketoacidosis, diabetic hyperosmolar coma

Eye Disorders

Infrequent: photophobia, diplopia, eyelid edema, photopsia

Gastrointestinal Disorders

Infrequent: gastroesophageal reflux disease, dysphagia, swollen tongue, esophagitis;

Rare: pancreatitis

General Disorders and Administration Site Conditions:
Frequent: asthenia, peripheral edema, irritability, chest pain;
Infrequent: feeling jittery, face edema, thirst, angioedema;
Rare: hypothermia

Hepatobiliary Disorders:
Rare: hepatitis, jaundice

Immune System Disorders:
Infrequent: hypersensitivity

Injury, Poisoning, and Procedural Complications:
Frequent: fall;
Infrequent: self mutilation;
Rare: heat stroke

Investigations:
Frequent: weight decreased;
Infrequent: hepatic enzyme increased (increased ALT, increased AST), blood glucose increased, blood prolactin increased, blood urea increased, electrocardiogram QT prolonged, blood creatinine increased, blood bilirubin increased;
Rare: blood lactate dehydrogenase increased, glycosylated hemoglobin increased, gamma-glutamyl transferase (GGT) increased

Metabolism and Nutrition Disorders:
Infrequent: hyperlipidemia, anorexia, hypokalemia, hyponatremia

Musculoskeletal and Connective Tissue Disorders:
Infrequent: muscle rigidity, muscular weakness, muscle tightness, mobility decreased;
Rare: rhabdomyolysis

Nervous System Disorders:
Frequent: coordination abnormal;
Infrequent: speech disorder, dyskinesia, parkinsonism, memory impairment, cogwheel rigidity, cerebrovascular accident, convulsion, hypokinesia, tardive dyskinesia, hypotonia, myoclonus, hypertonia, akinesia, bradykinesia;
Rare: Grand Mal convulsion, choreoathetosis, neuroleptic malignant syndrome

Psychiatric Disorders:
Frequent: suicidal ideation;
Infrequent: aggression, loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self-injury, completed suicide, tic, homicidal ideation;
Rare: catatonia, sleep walking

Renal and Urinary Disorders:
Infrequent: urinary incontinence, urinary retention, polyuria, nocturia

Reproductive System and Breast Disorders:
Infrequent: menstruation irregular, erectile dysfunction, amenorrhea, breast pain;
Rare: gynaecomastia, priapism

Respiratory, Thoracic, and Mediastinal Disorders:
Frequent: nasal congestion, dyspnea, pneumonia aspiration

Skin and Subcutaneous Tissue Disorders:
Frequent: rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis;
Infrequent: pruritus, photosensitivity reaction, alopecia, urticaria

Vascular Disorders:
Frequent: hypertension;
Infrequent: hypotension, syncope

Adolescent schizophrenia patients (13-17 years of age) - Oral Administration
Most adverse reactions observed in the pooled database of 281 adolescent patients aged 13-17 years were also observed in the adult population (see Tables 1 and 2; Other Adverse Events Observed During the Pre-marketing Evaluation of Oral Aripiprazole-Adults, Oral administration). Additional adverse reactions observed in the adolescent population are listed below.

General Disorders and Administration Site Conditions:
Infrequent: feeling abnormal

Metabolism and Nutrition Disorders:
Infrequent: hypertriglyceridemia

Nervous System Disorders:
Infrequent: sleep talking

Respiratory, Thoracic, and Mediastinal Disorders:
Frequent: rhinorrhea

Skin and Subcutaneous Tissue Disorders:
Infrequent: hirsutism

Abnormal Hematologic and Clinical Chemistry Findings

Between-group comparisons for 3- to 6-week, placebo-controlled trials in adult patients with schizophrenia and a 6-week placebo-controlled trial in adolescent patients with schizophrenia (13-

17 years of age) revealed no differences between the aripiprazole and placebo groups in the proportions of patients experiencing clinically important changes in most routine serum chemistry, hematology, or urinalysis parameters (including changes in fasting glucose, triglyceride, HDL, LDL and total cholesterol measurements) with the exception of prolactin. Low prolactin levels were reported more frequently in adolescents treated with aripiprazole than with placebo (see ADVERSE REACTIONS, Prolactin).

Similarly, there were no differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis.

In a long-term (26-week), placebo-controlled trial in adult patients with schizophrenia, there were no clinically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, and total cholesterol measurements (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism; ADVERSE REACTIONS, Prolactin).

Higher percentages of elevated creatine phosphokinase were observed in aripiprazole-treated adult patients compared to placebo-treated patients in short-term and long-term clinical trials. The most common AEs that were temporally associated with elevated CPK levels were musculoskeletal stiffness, myalgia, chest pain, fall, and muscle rigidity.

Post-Market Adverse Drug Reactions

The adverse events presented in Table 11 were reported during the post-marketing use of aripiprazole. Because these events 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.

Table 11: Post-Introduction Treatment-Emergent Adverse Events

Investigations:	*Rare:* Blood glucose fluctuation
Skin and Subcutaneous Tissue Disorders:	*Rare:* Allergic reaction (e.g., anaphylactic reaction, angioedema, laryngospasm, oropharyngeal spasm)
Psychiatric Disorders:	*Unknown:* Pathological gambling, Hypersexuality, Impulse control disorders
Hepatobiliary Disorders:	*Unknown:* Hepatic failure

Isolated cases of Serotonin Syndrome have been reported with the concomitant use of aripiprazole and serotonergic drugs such as Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) and Selective Serotonin Reuptake Inhibitor (SSRI).

As with other antipsychotics, sudden death, torsades de pointes, ventricular tachycardia, arrhythmia, cardiopulmonary arrest and QT prolongation have been reported during treatment with aripiprazole. These events during aripiprazole treatment have been very rare or isolated. Many of the patients had pre-existing cardiovascular disease, were on concomitant medications known to prolong the QT interval, had risk factors for QT prolongation, took an overdose of aripiprazole,

and/or were morbidly obese. Very rarely, QT prolongation has been reported in the absence of confounding factors.

Complex sleep-related behaviours such as somnambulism and sleep-related eating disorder have been associated with the use of atypical antipsychotic drugs, including aripiprazole.

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. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting aripiprazole and then periodically throughout treatment (see WARNINGS AND PRECAUTIONS, Hematologic).

Atypical antipsychotic drugs, including aripiprazole, have been associated with cases of sleep apnea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnea, pms-ARIPIPRAZOLE should be prescribed with caution.

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

Potential for Other Drugs to Affect pms-ARIPIPRAZOLE
Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism (see ACTION AND CLINICAL PHARMACOLOGY).

Agents that induce CYP3A4 (e.g., carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). CYP2D6 metabolizing capacity should be considered when aripiprazole is co-administered with drugs that inhibit CYP2D6.

Ketoconazole and Other CYP3A4 Inhibitors
Co-administration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When

ketoconazole is administered concomitantly with aripiprazole, pms-ARIPIPRAZOLE dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and require similar dose reductions; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the pms-ARIPIPRAZOLE dose should be increased.

Quinidine and Other CYP2D6 Inhibitors

Co-administration of quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, with a 10-mg single dose of aripiprazole increased the AUC of aripiprazole by 107% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 32%. The dose of pms-ARIPIPRAZOLE should be reduced to one-half of its normal dose when quinidine is administered concomitantly with pms-ARIPIPRAZOLE.

Concomitant administration of other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased.

Carbamazepine

Co-administration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, the dose of aripiprazole should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced.

Potential for pms-ARIPIPRAZOLE to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10-mg/day to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*.

Due to its alpha-1 adrenergic receptor antagonist activity, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Drugs having no clinically important interactions with pms-ARIPIPRAZOLE

Famotidine

Co-administration of aripiprazole (given in a single dose of 15 mg) with a 40-mg single dose of the H2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption. The C_{max} of aripiprazole and dehydro-aripiprazole, was reduced by 37% and 21%, respectively. The extent of absorption (AUC) of aripiprazole and dehydro-aripiprazole, was reduced by 13% and 15%, respectively. No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

Valproate
When valproate (500-1,500 mg/day) and aripiprazole (30 mg/day) were co-administered, at steady state the C_{max} and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

When aripiprazole (30 mg/day) and valproate (1,000 mg/day) were co-administered, at steady state there were no clinically important changes in the C_{max} or AUC of valproate. No dosage adjustment of valproate is required when administered concomitantly with aripiprazole.

Lithium
A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Co-administration of therapeutic doses of lithium (1200-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically important changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C_{max} and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

Co-administration of aripiprazole (30 mg/day) with lithium (900 mg/day) did not result in clinically important changes in the pharmacokinetics of lithium. No dosage adjustment of lithium is required when administered concomitantly with aripiprazole.

Lamotrigine
Co-administration of 10 to 30 mg daily oral doses of aripiprazole for 14 days to subjects with bipolar I disorder had no effect on the steady-state pharmacokinetics 100 to 400 mg once daily lamotrigine, a UDP-glucuronosyltransferase 1A4 substrate. No dosage adjustment of lamotrigine is required if aripiprazole and lamotrigine are administered concomitantly. Dosing recommendations for lamotrigine should be followed closely if valproate is also to be administered.

Venlafaxine
Co-administration of 10 to 20 mg daily oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg once daily venlafaxine XR, a CYP2D6 substrate. No dosage adjustment of venlafaxine is required if aripiprazole is administered concomitantly with venlafaxine.

Escitalopram
Co-administration of 10 mg daily oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of 10 mg once daily escitalopram, a substrate of CYP2C19 and CYP3A4. No dosage adjustment of escitalopram is required if aripiprazole and escitalopram are administered concomitantly.

Dextromethorphan
Aripiprazole at doses of 10 to 30 mg per day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-

methyoxymorphan, a pathway dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with pms-ARIPIPRAZOLE.

Warfarin
Aripiprazole 10 mg per day for 14 days had no effect on the pharmacokinetics of R- and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with pms-ARIPIPRAZOLE.

Omeprazole
Co-administration of aripiprazole (10 mg per day for 15 days) and a single 20-mg dose of omeprazole, a CYP2C19 substrate, had no effect on the pharmacokinetics of omeprazole in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with pms-ARIPIPRAZOLE.

Lorazepam
Co-administration of oral lorazepam (2 mg) and oral aripiprazole (15 mg) to healthy subjects (n=24 males; ages 18-43 years old) did not result in clinically important changes in the pharmacokinetics of either drug. No dosage adjustment of either drug is required when they are administered concomitantly. However, the intensity of sedation was greater with the combination as compared to that observed with aripiprazole alone and the incidence of orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone (see WARNINGS AND PRECAUTIONS).

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).

Drug-Food Interactions

pms-ARIPIPRAZOLE can be administered with or without food (see ACTION AND CLINICAL PHARMACOLOGY).

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been identified

Drug-Lifestyle Interactions

Alcohol/CNS Drugs
Given the primary CNS effects of aripiprazole, as with most psychoactive medications, combination use of aripiprazole with alcohol or other CNS drugs with overlapping undesirable effects such as sedation, should be avoided.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

The efficacy and safety of aripiprazole, at doses greater than 30 mg/day, have not been established.

Pediatric and adolescent patients are at greater risk of experiencing certain adverse events related to the use of atypical antipsychotics including pms-ARIPIPRAZOLE. Some of these adverse events appear to be dose related (see WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS).

pms-ARIPIPRAZOLE can be taken without regard to meals. Tablets should not be crushed or cut; they should be swallowed whole.

Refer to DRUG INTERACTION section for dosage adjustment in patients taking pms-ARIPIPRAZOLE concomitantly with strong CYP3A4 inhibitors (such as ketoconazole or clarithromycin), with potential CYP2D6 inhibitors (such as quinidine, fluoxetine, or paroxetine) or with potential CYP3A4 inducers (such as carbamazepine).

Schizophrenia
Adults
Usual Dose: The recommended starting and target dose for pms-ARIPIPRAZOLE is 10 or 15 mg/day administered on a once-a-day schedule. Doses in the range of 10 to 30 mg/day have been established as effective in clinical trials. However, greater efficacy has not been demonstrated at doses higher than 10 mg/day. Dosage increases, if needed, should only be made after 2 weeks, the time needed to achieve steady state. The maximum daily dose should not exceed 30 mg/day.

Patients should be maintained on the lowest effective dose that provides optimal clinical response and tolerability and should be periodically reassessed to determine the need for maintenance treatment.

Adolescents (15 - 17 years of age)
Usual dose: The recommended target dose of pms-ARIPIPRAZOLE is 10 mg/day administered on a once-a-day schedule. The recommended starting daily dose is 2 mg/day, titrated to 5 mg/day after 2 days and to the target dose of 10 mg/day after 2 additional days. Subsequent dose increases should be administered, if needed and as tolerated, in 5 mg/day increments. Both the 10 mg/day and 30 mg/day doses have been shown to be effective in a double-blind, placebo-controlled clinical trial**;** however the 30 mg/day dose was not shown to be more efficacious than the 10 mg/day dose.

The maximum daily dose should not exceed 30 mg/day. Patients should be maintained on the lowest effective dose that provides optimal clinical response and tolerability.

The safety and efficacy of aripiprazole during long term treatment have not been systematically evaluated in adolescent patients with schizophrenia. The physician who elects to use pms-ARIPIPRAZOLE for extended periods in adolescent patients with schizophrenia should periodically re-evaluate the long term usefulness of the drug for the individual patient.

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.

Dosing Considerations in Special Populations

Pediatrics (< 18 years of age)
Safety and efficacy were evaluated in adolescent (13-17 years of age) patients with schizophrenia in one 6-week clinical trial. pms-ARIPIPRAZOLE is not indicated for the treatment of schizophrenia in adolescent patients under 15 years of age due to insufficient safety and efficacy data (see ADVERSE REACTIONS; CLINICAL TRIALS, Schizophrenia, Adolescents (13-17 years of age)).

Geriatric (≥ 65 years of age)
Safety and efficacy of aripiprazole in the treatment of schizophrenia in patients 65 years of age or older have not been established. Given the greater sensitivity of this population, a lower starting dose may be considered when clinical factors warrant (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics (≥65 years of age)).

pms-ARIPIPRAZOLE is not indicated in elderly patients with dementia (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions).

Patients with hepatic impairment
No dosage adjustment is required for patients with hepatic impairment.

Patients with renal impairment
No dosage adjustment is required in patients with renal impairment.

Gender
No dosage adjustment is required for female patients as compared to male patients.

Smoking status
No dosage adjustment is required for smokers (see DRUG INTERACTIONS, Drug Lifestyle Interaction).

CYP2D6 poor metabolizers
Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). CYP2D6 metabolizing capacity should be considered when pms-ARIPIPRAZOLE is co-administered with drugs that inhibit CYP2D6 (see DRUG INTERACTIONS).

Missed Dose

If a patient misses a dose by a few hours, the patient should be advised to take their dose as soon as he/she remembers. If most of the day has passed, he/she should be advised to wait until the next scheduled dose. Patients should be advised to not take 2 doses of pms-ARIPIPRAZOLE at once.

OVERDOSAGE

Human Experience

In clinical studies, no deaths were associated with accidental or intentional acute overdosage of aripiprazole alone. In clinical trials, in the patient taking the largest confirmed amount of aripiprazole, 1,080 mg, ingested with alcohol, the only symptom reported was vomiting.

In post-marketing experience, there is a single case of death that was possibly associated with accidental or intentional acute overdosage of aripiprazole alone. The patient ingested 900 mg of aripiprazole, was hospitalized in the intensive care unit for 10 to 14 days and died. The patient's medical history included excessive alcohol use, although it is unclear whether alcohol was present at the time of overdosage. In the patient taking the largest confirmed amount of aripiprazole, 1,680 mg, the only symptoms reported were vomiting, fatigue, and dizziness. In addition, a report of non-fatal accidental overdose with aripiprazole alone (up to 195 mg) in a 2.5 year old child has been received. Vomiting, somnolence, lethargy, transient loss of consciousness and CNS depression were reported for this patient. Other potentially medically important signs and symptoms that have been observed during overdose included blood pressure increased and tachycardia. In the patients who were evaluated in hospital settings, there were no reported observations indicating clinically important adverse change in vital signs, laboratory assessments, or electrocardiogram.

Management of Overdosage

No specific information is available on the treatment of overdose with aripiprazole. Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple drug involvement should be considered. Therefore, cardiovascular monitoring should commence 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.

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 C_{max} of aripiprazole by 50%.

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

For up-to-date information on the management of a suspected drug overdose, contact the regional Poison Control Centre.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia is unknown. However, it has been proposed that the efficacy of aripiprazole may be mediated through a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5- HT2A receptors; however, the clinical relevance of these interactions has not been established. Actions at receptors other than D2, 5-HT1A, and 5-HT2A may explain some of the other clinical effects of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha1 receptors). The clinical relevance of these receptor interactions with aripiprazole is unknown.

Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D2 and D3, serotonin 5-HT1A and 5-HT2A receptors (Ki values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, alpha1-adrenergic and histamine H1 receptors (Ki values of 44,

15, 39, 57, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (Ki=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC50>1,000 nM). Aripiprazole functions as a partial agonist at the dopamine D2 and the serotonin 5-HT1A receptors, and as an antagonist at serotonin 5-HT2A receptor. The clinical relevance of these receptor interactions with aripiprazole is unknown.

Pharmacokinetics

Aripiprazole activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has 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 are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

Absorption

Aripiprazole is well absorbed after oral administration of the tablet, with peak plasma concentrations occurring within 3 to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. Aripiprazole can be administered with or without food. Administration of a 15-mg aripiprazole Tablet with a standard high-fat meal did not significantly affect the C_{max} or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed T_{max} by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

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. The clinical relevance of this receptor occupancy by aripiprazole is unknown.

Metabolism and Elimination

Aripiprazole is metabolized 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 catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas 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, like quinidine in EMs, results in a 112% increase in aripiprazole plasma exposure, and dose adjustment is needed (see DRUG INTERACTIONS). The mean elimination half-life for aripiprazole is about 75 hours in EMs and 146 hours in PMs. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Following a single oral dose of [^{14}C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

Special Populations and Conditions

Geriatrics

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), clearance of aripiprazole was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). However, there was no effect of age in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics (≥65 years of age); DOSAGE AND ADMINISTRATION).

Gender

C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. However, these differences are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation did not demonstrate clinically important race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

Renal Impairment

In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro- aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

Hepatic Impairment

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

Smoking

Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not demonstrate any significant pharmacokinetic differences between smokers and non-smokers. No dosage adjustment is recommended based on smoking status.

STORAGE AND STABILITY

Store between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

2 mg

Each green, rectangular shaped, biconvex, uncoated tablet, debossed with "AR" over "2" on one side, and plain on the other, contains: aripiprazole 2 mg, and the following non-medicinal ingredients: Croscarmellose sodium, Hydroxypropyl-Cellulose, Indigo Carmine, Iron Oxide Yellow, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. Bottles of 30 tablets.

5 mg

Each blue, rectangular shaped, biconvex, uncoated tablet, debossed with "AR" over "5" on one side, and plain on the other, contains: aripiprazole 5 mg, and the following non-medicinal ingredients: Croscarmellose Sodium, Hydroxypropyl-Cellulose, Indigo Carmine, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. Bottles of 30 tablets.

10 mg

Each pink, rectangular shaped, biconvex, uncoated tablet, debossed with "AR" over "10" on one side, and plain on the other, contains: aripiprazole 10 mg, and the following non-medicinal ingredients: Croscarmellose Sodium, Hydroxypropyl-Cellulose, Iron Oxide Red, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. Bottles of 30 tablets.

15 mg

Each yellow, round shaped, biconvex, uncoated tablet, debossed with "AR" over "15" on one side, and plain on the other, contains: aripiprazole 15 mg, and the following non-medicinal ingredients: Croscarmellose Sodium, Hydroxypropyl-Cellulose, Iron Oxide Yellow, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. Bottles of 30 tablets.

20 mg

Each white, round shaped, biconvex, uncoated tablet, debossed with "AR" over "20" on one side, and plain on the other, contains: aripiprazole 20 mg, and the following non-medicinal ingredients: Croscarmellose Sodium, Hydroxypropyl-Cellulose, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. Bottles of 30 tablets.

30 mg
Each pink, round shaped, biconvex, uncoated tablet, debossed with "AR" over "30" on one side, and plain on the other, contains: aripiprazole 30 mg, and the following non-medicinal ingredients: Croscarmellose Sodium, Hydroxypropyl-Cellulose, Iron Oxide Red, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. Bottles of 30 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

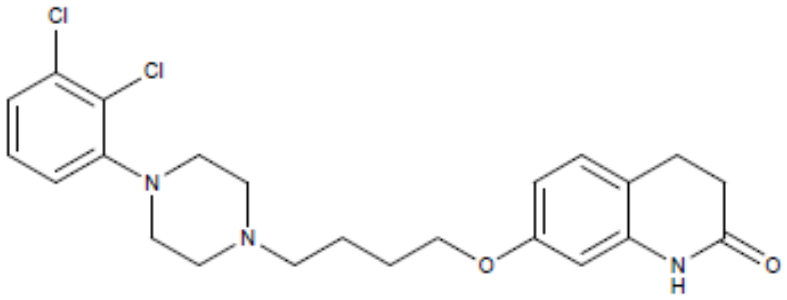
Proper name: aripiprazole

Chemical name: 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril

Molecular formula: C23H27Cl2N3O2

Molecular mass: 448.39 g/mol

Structural formula:



Physicochemical properties: Aripiprazole is a white to off white crystalline powder. Aripiprazole is freely soluble in dichloromethane, sparingly soluble in toluene, very slightly soluble in ethanol (96%), and practically insoluble in methanol and water. The pKa was determined to be 7.6.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single center, randomized, single oral dose, double-blind, two-treatment, two-period, two-sequence, crossover bioequivalence study comparing pms-ARIPIPRAZOLE 5 mg tablets (Pharmascience Inc.) to the Canadian reference product, [Pr]Abilify (aripiprazole) 5 mg tablets (Bristol-Myers Squibb Canada). The study drugs were administered as a single 5 mg dose to 24 healthy, adult male subjects under fasting conditions with 23 subjects completing the study. The bioavailability data were measured in plasma and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Aripiprazole (1 x 5 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_{0-72} (ng·h/mL)	1315.9 1342.1 (20.3)	1295.6 1321.1 (19.4)	101.6	97.5 – 105.8
AUC_I (ng·h/mL)	3160.7 3357.8 (36.6)	2798.4 2916.1 (29.4)	112.9	103.7 – 123.0
C_{MAX} (ng/mL)	33.0 33.9 (22.1)	32.4 33.5 (26.1)	101.8	95.1 – 109.0
T_{MAX}§ (h)	4.00 (1.50 – 5.00)	3.00 (1.00 – 12.00)		
$T_{½}$2 (h)	100.4 (38.1)	82.9 (39.8)		

* pms-ARIPIPRAZOLE 5 mg tablets, Pharmascience Inc., Montreal, QC, Canada

† [Pr']Abilify (aripiprazole) 5 mg tablets, Bristol-Myers Squibb Canada, Montreal, QC, Canada, and was purchased in Canada

§ Expressed as the median (range) only

2 Expressed as the arithmetic mean (CV%) only

A single center, randomized, single oral dose, double-blind, two-treatment, two-period, two-sequence, crossover bioequivalence study comparing pms-ARIPIPRAZOLE 10 mg tablets (Pharmascience Inc.) to the Canadian reference product, [Pr]Abilify (aripiprazole) 10 mg tablets (Bristol-Myers Squibb Canada, Canada). The study drugs were administered as a single 10 mg dose to 20 healthy, adult male subjects under fasting conditions. The bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Aripiprazole (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_{0-72} (ng·h/mL)	2472.5 2521.9 (18.7)	2208.7 2270.6 (24.5)	111.9	104.2 – 120.2
AUC_I (ng·h/mL)	6278.1 6919.3 (47.8)	5889.9 6466.7 (44.8)	106.6	93.3 – 121.7
C_{MAX} (ng/mL)	62.2 63.4 (21.0)	53.6 55.5 (27.6)	116.0	105.4 – 127.6
T_{MAX}§ (h)	2.7 (1.5 – 8.0)	4.0 (1.5 – 8.0)		
$T_{½}$[2] (h)	110.1 (56.9)	121.4 (73.1)		

* pms-ARIPIPRAZOLE 10 mg tablets, Pharmascience Inc., Montreal, QC, Canada

† [Pr]Abilify (aripiprazole) 10 mg tablets, Bristol-Myers Squibb Canada, Montreal, QC, Canada, and was purchased in Canada

§ Expressed as either the median (range) only

2 Expressed as the arithmetic mean (CV%) only

Schizophrenia

Adults

The efficacy of aripiprazole 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 behavior, 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, 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) and haloperidol (10 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score, 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) and risperidone (6 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score, 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, 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, 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.

In a fifth study, a 4-week trial (n=103) comparing aripiprazole in a range of 5 to 30 mg/day or haloperidol 5 to 20 mg/day to placebo, haloperidol was superior to placebo, in the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis, and in a responder analysis based on the CGI-severity score, the primary outcomes for that trial. Aripiprazole

was only significantly different compared to placebo in a responder analysis based on the CGI-severity score.

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 demonstrate 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/day 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/day experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo.

Adolescents (13-17 years of age)
The efficacy of aripiprazole in the treatment of schizophrenia was evaluated in one 6-week, placebo-controlled trial that included outpatients, 13 - 17 years of age, who met DSM-IV criteria for schizophrenia and had a PANSS score ≥70 at baseline. The majority of patients included in this trial (75%) were 15 - 17 years of age. Seventy-four percent of patients had received antipsychotic treatment for previous episodes. In this trial comparing two fixed doses of aripiprazole (10 mg/day, n=100 or 30 mg/day, n=102) to placebo (n=100), aripiprazole was titrated starting from 2 mg/day to the target dose in 5 days in the 10 mg/day treatment arm and in 11 days in the 30 mg/day treatment arm.

Both doses of aripiprazole were superior to placebo in the PANSS total score, the primary outcome measure of the study. The 30 mg/day dose was not shown to be more efficacious than the 10 mg/day dose. Maintenance of efficacy has not been systematically evaluated in adolescent patients.

pms-ARIPIPRAZOLE is not indicated for the treatment of schizophrenia in adolescents less than 15 years of age due to insufficient safety and efficacy data (see INDICATIONS AND CLINICAL USE; WARNINGS AND PRECAUTIONS, Special Populations; ADVERSE REACTIONS).

DETAILED PHARMACOLOGY

Nonclinical pharmacodynamics

Extensive *in vitro* and *in vivo* studies demonstrated that aripiprazole is a potent partial agonist at dopamine D2 and serotonin 5-HT1A receptors and an antagonist at serotonin 5-HT2 receptors.

Aripiprazole binds with high affinity to dopamine D2 and D3 and serotonin 5-HT1A and 5-HT2A receptors; with moderate affinity to dopamine D4, serotonin 5-HT2C and 5-HT7, alpha1-adrenergic and histamine H1 receptors and the serotonin transporter and with low affinity to muscarinic receptors. As a D2 partial agonist, aripiprazole blocks postsynaptic D2 receptors at a dose comparable to that at which it acts as agonist at presynaptic dopamine receptors. Aripiprazole exhibits the properties of an agonist in animal models of dopaminergic hypoactivity and the properties of an antagonist in animal models of dopaminergic hyperactivity. In multiple behavioral models, aripiprazole exhibits an antipsychotic profile and is several fold less potent than atypical antipsychotics in animal models predictive of extrapyramidal side effect liability.

Cardiorespiratory System

Aripiprazole and OPC-14857 inhibited the HERG/IKr current at 140- and 461-fold multiples of the maximum steady-state plasma free-drug concentration, respectively, and there were no effects on action potential duration (APD) in the rabbit Purkinje fiber assay. OPC-3373 demonstrated no *in vitro* inhibition of HERG/IKr current or prolongation of APD at concentrations up to 10 mcM. Neither aripiprazole nor the main human metabolites (OPC-14857, OPC-3373) accumulate in rat cardiac tissue following single or repeat (13 days) dosing. Potential cardiovascular effects were also assessed *in vitro* and *in vivo* safety pharmacology (anesthetized dogs) and toxicology studies (39-week treatment in monkeys) in which no significant changes were observed.

Central and Peripheral Nervous Systems

In animals, aripiprazole was less potent than chlorpromazine and haloperidol in producing behavioral signs consistent with CNS depression, in inducing catalepsy, and in suppressing spontaneous motor activity and, unlike these comparators, did not cause convulsions. Additionally, it reduced motor coordination and prolonged the duration of hexobarbital-induced hypnosis with a potency comparable to chlorpromazine. In contrast, aripiprazole demonstrated less potential than chlorpromazine or haloperidol to induce muscular relaxation and analgesia.

Other Systems and Tissues

In vitro and *in vivo* safety pharmacology studies were conducted to assess the potential of aripiprazole to alter gastric secretion, gastrointestinal motility, smooth muscle contractility, and urine volume and electrolyte excretion. These studies indicated that aripiprazole has little potential to cause gastrointestinal or renal side effects or affect smooth muscle contractility.

Nonclinical Pharmacokinetics

The absorption, distribution, metabolism and excretion properties of aripiprazole were evaluated in a series of *in vitro* and *in vivo* studies in mice, rats, rabbits, dogs, minipigs, and monkeys. Aripiprazole had only moderate intrinsic membrane permeability *in vitro*, but was well absorbed following oral administration in animals and humans.

Following intravenous administration of aripiprazole, its elimination half-life (1 to 5 hours) was shorter and its plasma clearance (14 to 110 mL/min/kg) was more rapid in animals than in humans

(75 hours and 0.7 mL/min/kg, respectively). As in humans, the steady-state volumes of distribution in animals suggest extensive extravascular distribution.

The exposure of mice, rats, and monkeys to aripiprazole after oral dosing was dose-related. In rats, possibly due to saturation of presystemic metabolism and/or clearance, the increase in exposure was greater than the dose increment; however, in mice and monkeys, exposure increased in a generally dose-proportional manner. After repeated daily doses, exposures to aripiprazole and its pharmacologically-active metabolite, dehydro-aripiprazole, were slightly higher in female rats than in male rats; there were no gender-related differences in mice or monkeys. Systemic accumulation of aripiprazole and its metabolites was seen at toxicologically-relevant doses after once-daily chronic administration in both rats and monkeys.

In rats, concentrations of unchanged aripiprazole in the brain were up to 5-times higher than plasma concentrations. Following [^{14}C]-aripiprazole administration to pregnant rats, radioactivity in the fetus was low and only a trace amount was detected in the amniotic fluid.
After [^{14}C]-aripiprazole administration to lactating rats, milk vs. blood concentration ratios were greater than one for up to 24 hours. *In vitro*, aripiprazole bound extensively (99.4 to 99.8%) to proteins in mouse, rat, rabbit, dog, monkey, and human sera.

Parent drug was undetectable in rat and monkey urine, indicating that renal clearance is not an important mechanism of elimination. Aripiprazole was mainly eliminated via metabolic clearance and aripiprazole metabolites were eliminated by both renal and biliary routes in monkeys and predominantly by the biliary route in rats. After oral administration of [^{14}C]-aripiprazole to rats and monkeys, drug-derived radioactivity was recovered primarily in the feces (~90 and 62% of dose, respectively). The metabolism of aripiprazole in rats and monkeys was qualitatively similar to that in humans, though the rate of elimination through metabolism in humans was slower compared to animals. The metabolism of aripiprazole was primarily by dehydrogenation, hydroxylation, and N-dealkylation. Formation of the pharmacologically-active dehydro-aripiprazole was a major route metabolism. This and other Phase 1 metabolites were subject to further metabolism, including conjugation reactions. In rats, as in humans, unchanged drug was the major drug-related component in plasma, while in monkeys, aripiprazole accounted for only 13% of the drug-related material in plasma. All of the major metabolites in human plasma were present in the plasma rats and monkeys, the principle species used for nonclinical toxicity testing, indicating that these species were appropriate for safety assessment of aripiprazole and its metabolites.

In vitro studies indicated that cytochrome P450 (CYP) isoforms, CYP3A4 and CYP2D6 were responsible for the dehydrogenation and hydroxylation of aripiprazole, while its N-dealkylation was catalyzed by CYP3A4 only. Clinical studies were conducted to evaluate the potential for drug-drug interactions *in vivo*. While co-administration of CYP3A4 or CYP2D6 inhibitors decreased the oral clearance of aripiprazole by approximately 40-50% and co-administration of an inducer of CYP3A4 increased the oral clearance of aripiprazole, these changes were not regarded as clinically meaningful. *In vitro* studies also indicated that neither aripiprazole nor it's dehydro metabolite should meaningfully inhibit the *in vivo* activity of CYP isozymes at clinically-relevant concentrations. This was confirmed in clinical studies in which no clinically-meaningful effect of

aripiprazole on the clearance of substrates for CYP3A4, CYP2D6, CYP2C9, and CYP2C19 was found.

TOXICOLOGY

Acute Toxicity

The acute oral toxicity of aripiprazole was determined in rats and monkeys. The estimated median lethal oral dose in male and female rats was 953 and 705 mg/kg, respectively, and in monkeys was greater than 2000 mg/kg for both sexes. Clinical signs consistent with pharmacologically mediated central nervous (CNS) depression and extrapyramidal side effects were noted in both species. In rats, clinical signs included decreased spontaneous motor activity, crouching, prone position, ataxia, tremors, convulsions, straub tail, catalepsy, ptosis, and coldness to touch. In monkeys, principal drug-related effects included impaired motor activity, hyporeactivity to external stimuli, tremors, catalepsy, closed eyes, crouching, and prone and/or lateral position.

Short- and Long-Term Toxicity

The short- and long-term toxicity of aripiprazole was determined in 4- to 52-week oral toxicity studies in rats and monkeys. The results from these studies are summarized in the following table.

Short- and Long-Term Toxicity

Species/ Strain	Route of Administration	Duration of Dosing	Dose (mg/kg)	Number/Sex	Noteworthy Findings
Rat/SD	Oral gavage	4 weeks	0, 60, 100	10 or 15 M 10 or 15 F	60 and 100 mg/kg/day: Sedation (primarily in Week 1) and dose-related decreases in body weight, body weight gain, and food consumption; dose-related minimal or mild increases in serum glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, and γ-glutamyltranspeptidase; and microscopically, dose-related minimal to moderate adrenocortical hypertrophy, mild atrophy of the pars intermedia in the pituitary gland, minimal to mild bone marrow hypocellularity, increased incidence and severity of pulmonary alveolar foam cell accumulation in the lung, minimal salivary gland acinar cell hypertrophy, minimal mammary gland lobular hyperplasia with minimal to mild milk secretion, minimally decreased numbers of ovarian corpora lutea, and low incidences of minimal uterine atrophy. 100 mg/kg/day: Emaciation, transient hypothermia, lacrimation, tremors, and unkempt appearance and microscopically, minimal mucification of the vaginal epithelium. All mammary gland and reproductive tract changes in females were considered to be secondary to aripiprazole-related increases in serum prolactin. Additionally, all changes were reversible or partially reversible after a 4-week post-dose period for the 100 mg/kg/day animals.
Rat/SD	Oral gavage	13 weeks	0, 2, 6, 20	10 or 16 M 10 or 16 F	2 and 6 (M) mg/kg/day: No drug-related changes. 6 (F) and 20 mg/kg/day: In females, minimal increases in body weight gain and food consumption (6 mg/kg/day only) and microscopically, mucification of vaginal epithelium and lobular hyperplasia of the mammary glands. 20 mg/kg/day: Minimal decreases in body weight gain and food consumption in males; decreased liver and uterus weights; and microscopically, mammary milk secretion in females. Anatomic changes in the mammary gland and reproductive tract of females were considered to be secondary to aripiprazole-related increases in serum prolactin. At the end of the 4-week post-dose period, all findings were reversible except for minimal decreases in body weight gain and food consumption.

Species/ Strain	Route of Administration	Duration of Dosing	Dose (mg/kg)	Number/Sex	Noteworthy Findings
Rat/SD	Oral gavage	26 weeks	0, 10, 30, 60	20 or 25 M 20 or 25 F	10 mg/kg/day: Minimal or mild increases in body weight and food consumption in females. 10, 30, and 60 mg/kg/day: Dose-related minimal to moderate decreases in body weight (10 mg/kg/day only in males), including initial weight loss at 60 mg/kg/day; minimal or mild decreases in serum total protein and albumin; pale discoloration of the lungs; and microscopically, dose-related minimal to moderate atrophy of pituitary pars intermedia, increased incidence of minimal to moderate pulmonary histiocytosis, and changes in the mammary gland (atrophy in males ≥ 30 mg/kg/day; hyperplasia in females) and female reproductive tract (i.e., persistent diestrus) that were considered secondary to drug-related hyperprolactinemia. 30 and 60 mg/kg/day: Dose-related increased incidences of transient post-dose hypoactivity and ptosis and predose hyperactivity; minimal to moderate decreases in food consumption; and microscopically, minimally increased adrenocortical lipofuscin pigment and minimal to mild adrenocortical hypertrophy in females. 60 mg/kg/day: Minimal decreases in hematocrit, reticulocytes, and hemoglobin (females); increased adrenal (females) and lung weights; decreased testicular size and weight; dark discoloration of the adrenals and ovaries; and, microscopically, minimal to moderate bilateral testicular atrophy and minimally increased ovarian lipofuscin pigment. Except for remnants of the adrenal and ovarian pigment, all aripiprazole-related effects were reversible or partially reversible (hyperactivity and pulmonary histiocytosis with associated increases in lung weight) after a 13-week post-dose period.
Rat/SD	Oral gavage	52 weeks	0, 1, 3, 10	20 M 20 F	1, 3, and 10 mg/kg/day: Mild to moderate uterine atrophy and slight increase in corpora lutea. 3 and 10 mg/kg/day: Minimal to mild increases (transient at 10 mg/kg/day) in body weights; minimal, sporadic increases in food consumption; decreases in adrenal, liver, kidney, and uterus weights and increases in ovarian weights; and microscopically, increased severity of lobular hyperplasia of mammary gland and increased incidence and severity of vaginal epithelial mucification in females (changes considered secondary to aripiprazole-related increases in prolactin). 10 mg/kg/day: Decreased liver weight; macroscopic evidence of mammary gland development in females; and microscopically, karyomegaly of hepatocytes, renal proximal tubular epithelium, and Harderian gland acinar cells.

Species/ Strain	Route of Administration	Duration of Dosing	Dose (mg/kg)	Number/Sex	Noteworthy Findings
Monkey/ Cynomolgus	Oral gavage	4 weeks	1, 5, 25, 125	1 M 1 F	1, 5, 25, and 125 mg/kg/day: Impairment of motor activity characterized by ataxic gait, reduced motor activity, and/or absence of motion (1 mg/kg/day only in Week 1). 5, 25, and 125 mg/kg/day: Closed eyes, catalepsy, tremors, and slight decreases in food consumption (Weeks 1 and 2). 25 and 125 mg/kg/day: Abnormal posture (crouching, lateral, or prone position) and hyporeactivity; minimal dose-related body weight loss (Weeks 1 and 2); and at necropsy, retention of gallsand (granular material) in the gallbladder. 125 mg/kg/day: At necropsy, a stone (calculus) in the gallbladder of 1 animal.
Monkey/ Cynomolgus	Oral gavage	13 weeks	0, 0.5, 1, 5, 25	3 to 5 M 3 to 5 F	0.5 and 1 mg/kg/day: No drug-related findings. 5 and 25 mg/kg/day: Dose-related impairment of motor activity, hyporeactivity, tremors, catalepsy, and abnormal posture. These clinical signs generally were mild at 5 mg/kg/day and severe at 25 mg/kg/day early in the study, but improved with continued dosing at 25 mg/kg/day. 25 mg/kg/day: Minimal decreases in body weight, moderate decreases in food consumption, and sporadic absence of feces in Weeks 1 and 2 and moderate to severe muddy substance in the bile at necropsy. All drug-related alterations disappeared or improved during the 4-week post-dose period.

Species/ Strain	Route of Administration	Duration of Dosing	Dose (mg/kg)	Number/Sex	Noteworthy Findings
Monkey/ Cynomolgus	Oral gavage	39 weeks	0, 25, 50, 75/100	4 M 4 F	Due to pronounced clinical signs at 100 mg/kg/day on Day 1, high-dose animals were not treated on Days 2 to 4. Starting on Day 5 through remainder of the study, high-dose animals were treated at 75 mg/kg/day. 25 mg/kg/day: Low incidence of impaired motor activity in 1 male. 25, 50, and 75 mg/kg/day: Dose-related tremors and mild to moderate hypoactivity (transient at 25 mg/kg/day), vomitus (emesis), qualitatively reduced food consumption, low incidences of hunched or unusual posture, and mucus-like and granular (gallsand) materials in the gallbladder. 50 and 75 mg/kg/day: Low incidences of excessive salivation, sternal recumbency, and gallbladder calculi (gallstones); and, microscopically, low incidence of generally minimal liver alterations consistent with hepatolithiasis in the subcapsular parenchyma of the right median lobe proximal to the gallbladder. 75 mg/kg/day: One female euthanatized moribund in Week 3 due to severe clinical toxicity characterized by mild to severe hypoactivity, tremors, excessive salivation, lateral or sternal recumbency, hunched or unusual posture, impaired motor activity, and reduced food consumption (low or none). This female was the only high-dose animal that had not recovered when dosing resumed at 75 mg/kg/day on Day 5. Minimal decreases in body weight in males and low incidence of ataxia in 1 female. Analyses of gallsand and gallstones indicated that sulfate conjugates of hydroxy metabolites of aripiprazole were the major drug-related constituents; and bile acids, principally taurodeoxycholic acid, were the primary nondrug-related constituents. Analyses of intrahepatic concretions (hepatoliths) demonstrated morphologic features and elemental composition that were similar to gallsand and gallstones.
Monkey/ Cynomolgus	Oral gavage	52 weeks	0, 0.5, 5, 25	4 M 4 F	0.5 mg/kg/day: No drug-related changes. 5 and 25 mg/kg/day: Dose-related incidences and/or severity of impaired motor activity, hyporeactivity, tremors, catalepsy, and abnormal posture (crouching, lateral, and/or prone position) that were most evident during Weeks 1 and 2. At 25 mg/kg/day, impaired motor activity was severe in Week 1 and generally mild during the remainder of the study. Hyporeactivity disappeared by Week 3 and catalepsy and abnormal posture were observed sporadically throughout the dosing period. 25 mg/kg/day: Minimal decreases in body weight and mild to moderate decreases in food consumption during Weeks 1 and 2. At necropsy, slight to generally moderate gallsand in 3 animals and gallstones in 1 animal. In comparison, slight gallsand noted in 2 controls.

Juvenile Toxicity
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.

Mutagenesis
The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole was clastogenic in the *in vitro* chromosomal aberration assay in CHL cells with and without metabolic activation. A positive response was obtained in the *in vivo* micronucleus assay in mice; however, the response was due to a mechanism considered not relevant to humans.

Reproductive Toxicity
In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats receiving aripiprazole injection intravenously (3, 9, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose, which also caused maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 30 and 100 mg/kg), and minor skeletal variations (100 mg/kg).

In pregnant rabbits receiving aripiprazole injection intravenously (3, 10, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal

toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which produced 5 times the human exposure at the MRHD based on AUC.

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/ m^2 basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose.

In rats receiving aripiprazole injection intravenously (3, 8, and 20 mg/kg/day) from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8 and 20 mg/kg, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg. These doses produced some maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

Impairment of fertility
Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the MRHD on a mg/ m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/ m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

Carcinogenicity
Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the MRHD based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/ m^2). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (10 times human exposure at MRHD based on AUC).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies.

However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Other Toxicity Studies

Adrenocortical Changes in Rats

A series of investigative studies were conducted in rats to determine the mechanism for the aripiprazole-related adrenocortical changes after subchronic and chronic dosing. The data from these studies supported the conclusion that the female rat-specific adrenocortical tumorigenic response at 60 mg/kg/day in the oral carcinogenicity study was secondary to aripiprazole-related adrenocortical cytotoxicity and consequent increased cell proliferation. The female specificity of the adrenocortical tumorigenic response was considered a consequence of the earlier onset and greater severity of the adrenocortical cytotoxic changes. The adrenocortical cytotoxic and tumorigenic effects have no established clinical relevance since they occurred at a dose 10 times human exposure at the MRHD based on AUC.

Retinal Degeneration in Rats

Aripiprazole produced retinal degeneration in albino Sprague-Dawley (SD) rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40 and 60 mg/kg doses are 7 to 10 times human exposure at the MRHD based on AUC. In a subsequent 18-month investigative study in albino SD and pigmented Long-Evans (LE) rats administered 60 mg/kg/day aripiprazole, pharmacologically mediated hyperactivity occurred in both rat strains early in the study predisposing the animals to increased light exposure. Time-dependent retinal degeneration with electroretinographic and morphologic features consistent with spontaneous light-induced retinal degeneration was observed in albino SD rats, whereas there was no evidence of light-induced retinal injury in pigmented LE rats at any timepoint despite comparable systemic exposures to aripiprazole. This was due to the photoprotective effect of ocular melanin pigment in LE rats. Therefore, the retinal degeneration observed in albino SD rats after chronic dosing at high doses of aripiprazole was considered to be a consequence of drug-related, pharmacologically mediated hyperactivity during the animal room light phase, resulting in increased light exposure rather than a direct drug effect on the retina. Light-induced retinal degeneration in albino SD rats has no established clinical relevance.

Dermal Sensitization and Dermal and Ocular Irritation

Aripiprazole was not a dermal sensitizer in mice and was nonirritating to rabbit skin and eye.

Phototoxicity

Aripiprazole was nonphototoxic in Balb/c 3T3 mouse fibroblast cultures.

Antigenicity

Aripiprazole produced no evidence of active systemic anaphylaxis or passive cutaneous reactions in guinea pigs.

Immunotoxicity

Aripiprazole did not adversely affect the T-cell-dependent humoral immune response to sheep red blood cells in rats.

Dependence

In a battery of studies conducted to evaluate physical dependence and abuse potential, aripiprazole demonstrated no abuse liability in rats; mild, transient physical dependence in monkeys (rebound arousal) considered to be of little clinical significance; and no positive reinforcing effects in monkeys. Overall, the results support that aripiprazole has no abuse liability.

Metabolites

In single-dose intravenous studies in rats, OPC-14857 produced clinical effects similar to those observed at high single oral doses of parent drug, whereas OPC-3373 produced no drug-related toxicity. In a 28-day oral toxicity study in rats, 2,3-DCPP produced CNS-related clinical signs with deaths at the high dose (30 mg/kg/day) but no evidence of target organ toxicity. All 3 metabolites were not mutagenic in bacterial reverse-mutation tests. In an *in vitro* cytogenetics assay in CHL cells, 2,3-DCPP increased chromosome aberrations in the presence and absence of metabolic activation; however, the increases were considered secondary to excessive cytotoxicity rather than direct DNA reactivity.

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PART III: CONSUMER INFORMATION

[Pr]pms-ARIPIPRAZOLE
Aripiprazole Tablets, House Standard
2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg

This leaflet is part III of a three-part "Product Monograph" published when pms-ARIPIPRAZOLE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-ARIPIPRAZOLE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

pms-ARIPIPRAZOLE is used to treat symptoms of schizophrenia in adults and in adolescents (15-17 years of age). Schizophrenia is characterised by symptoms such as:

- hearing, seeing or sensing things that are not there,
- suspiciousness, mistaken beliefs,
- incoherent speech and behaviour and emotional flatness.

People with this condition may also feel depressed, guilty, anxious or tense.

It is important to discuss your depressive symptoms and possible side effects of pms-ARIPIPRAZOLE with your doctor.

pms-ARIPIPRAZOLE is not a cure for your condition, but it can help manage your symptoms and in adult patients may reduce the risk of relapse.

Your doctor may have prescribed pms-ARIPIPRAZOLE for another reason. Ask your doctor if you have any questions about why pms-ARIPIPRAZOLE has been prescribed for you.

What it does:

pms-ARIPIPRAZOLE belongs to a group of medicines called atypical antipsychotic drugs.
Antipsychotic medications affect the chemicals that allow communication between nerve cells (neurotransmitters). Illnesses that affect the brain may be due to certain chemicals in the brain being out of balance. These imbalances may cause some of the symptoms you may be experiencing. Doctors and scientists are not sure what causes these imbalances to occur. Exactly how pms-ARIPIPRAZOLE works is unknown. However, it seems to adjust the balance of chemicals called dopamine and serotonin.

When it should not be used:

Do not take pms-ARIPIPRAZOLE if you have had an allergic reaction to pms-ARIPIPRAZOLE or any of the ingredients listed in the "What the nonmedicinal ingredients are" section of this leaflet. Signs of allergic reaction may include a rash, itching, shortness of breath or swelling of the face, lips or tongue.

What the medicinal ingredient is:

Aripiprazole.

What the nonmedicinal ingredients are:

Croscarmellose Sodium, Hydroxypropyl-Cellulose, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. In addition, the following strengths contain:

- 2 mg: indigo carmine, iron oxide yellow.
- 5 mg: indigo carmine.
- 10 mg: iron oxide red.
- 15 mg: iron oxide yellow.
- 30 mg: iron oxide red.

What dosage forms it comes in:

Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Various medicines of the group to which pms-ARIPIPRAZOLE belongs, including pms-ARIPIPRAZOLE, have been associated with an increased rate of death when used in elderly patients with dementia. pms-ARIPIPRAZOLE is not indicated in elderly patients with dementia.

pms-ARIPIPRAZOLE is not for use in children with schizophrenia under the age of 15.

BEFORE you use pms-ARIPIPRAZOLE talk to your doctor or pharmacist if you:

- are taking any other medicines (prescriptions or over the counter medicines).
- are pregnant, think you are pregnant or plan to become pregnant. You should not take pms-ARIPIPRAZOLE if you are pregnant unless you have discussed this with your doctor.
- are breast-feeding or plan to breast-feed. Breast-feeding mothers should not take pms-ARIPIPRAZOLE.
- have high blood sugar or a family history of diabetes.
- have a low white blood cell count.
- have ever had blackouts or seizures.
- have involuntary, irregular muscle movements, especially in the face.
- suffer from heart disease or have a family history of heart disease, stroke or "mini" stroke.
- have a history of any problems with the way your heart beats or if you are taking any medicines that may have an impact on the way your heart beats.
- suffer from abnormal (high) blood pressure or have rapid heartbeat and a drop in blood pressure when getting up.
- are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

- have risk factors for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity, recent major surgery (such as hip or knee replacement), immobility due to air travel or other reason, take oral contraceptives ("The Pill").
- exercise vigorously or work in hot, sunny places.
- drink alcoholic beverages or use recreational drugs.
- have ever abused drugs.
- have a history of gambling or impulse control disorders (urge to gamble, spend money, eat or other urges).
- have a history of or are at risk of sleep apnea (a sleep disorder where your breathing is interrupted during sleep).
- suffer from lactose intolerance or have hereditary galactose intolerance or glucose-galactose malabsorption, because pms-ARIPIPRAZOLE tablets contain lactose.

Thoughts of suicide and worsening of your depression or other mental illnesses:

If you are depressed and/or have other mental illnesses you may sometimes have thoughts of harming or killing yourself. These may be increased when first starting treatment, since these medicines all take time to work, usually about two weeks but sometimes longer.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed or have other mental illnesses, and ask them to read this leaflet. You might ask them to tell you if they think your depression or mental illness is getting worse, or if they are worried about changes in your behaviour.

Effects on newborns
In some cases, babies born to a mother taking aripiprazole during pregnancy have experienced symptoms that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek emergency medical attention for your newborn, if he/she has difficulty breathing, is overly sleepy, has muscle stiffness or floppy muscles (like a rag doll), is shaking or is having difficulty feeding.

INTERACTIONS WITH THIS MEDICATION

Tell all doctors, dentists and pharmacists who are treating you that you are taking pms-ARIPIPRAZOLE.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

- If you are taking other medicines, your doctor may need to change your dose of pms-ARIPIPRAZOLE. You should tell your doctor if you are taking ketoconazole (antifungal), quinidine (antiarrythmic), paroxetine (antidepressant) or fluoxetine (antidepressant). These medicines may lead to higher concentrations of aripiprazole in your blood.
- You should also tell your doctor if you are taking carbamazepine as it may lead to lower concentrations of aripiprazole in your blood, making pms-ARIPIPRAZOLE less effective.

pms-ARIPIPRAZOLE may increase the effect of medicines used to lower the blood pressure. Be sure to tell your doctor if you take a medicine to keep your blood pressure under control.

The effects of alcohol could be made worse while taking pms-ARIPIPRAZOLE. It is recommended that you **do not** drink alcohol while taking pms-ARIPIPRAZOLE.

Only take other medicines while you are on pms-ARIPIPRAZOLE if your doctor tells you to.

PROPER USE OF THIS MEDICATION

The most important thing about taking pms-ARIPIPRAZOLE is to take it exactly the way your doctor has prescribed it, every day. You should check with your doctor or pharmacist if you are not sure. Your doctor has decided on the best dosage for you based on individual situation. Your doctor may increase or decrease your dose depending on your response.

Schizophrenia

Usual adult dose
The usual dose is 10 mg or 15 mg once a day, without regard to meals. However, your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Usual adolescent (15-17 years of age) dose
The usual dose is 10 mg once a day, without regard to meals. At the start of treatment, your doctor will prescribe a lower daily dose (2 mg) and will increase the dose to 5 mg once a day after 2 days and to the target dose of 10 mg once a day after 2 additional days. Depending on how well you respond and tolerate the 10 mg dose, your doctor may prescribe a lower or higher dose, to a maximum of 30 mg once a day.

The maximum dose should not exceed 30 mg once a day.

Try to take pms-ARIPIPRAZOLE at the same time each day. It does not matter whether you take it with or without food. Always take the tablet with water and swallow it whole.

If you have the impression that the effect of pms-ARIPIPRAZOLE is too strong or too weak, talk to your doctor or pharmacist.

Even if you feel better, do not change or discontinue the daily dose of pms-ARIPIPRAZOLE without first consulting your doctor. Although pms-ARIPIPRAZOLE cannot cure your condition, it can help relieve your symptoms. If your symptoms improve or disappear, it is probably because your treatment is working. pms-ARIPIPRAZOLE should be taken for as long as you and your doctor believe it is helping you.

Do not give pms-ARIPIPRAZOLE to anyone else. Your doctor has prescribed it for you and your condition.

pms-ARIPIPRAZOLE is not for use in children under the age of 15 years for the treatment of schizophrenia.

Overdose:

If you have taken more pms-ARIPIPRAZOLE tablets than your doctor has prescribed (or if someone else has taken some of your pms-ARIPIPRAZOLE tablets), contact your regional Poison Control Centre and talk to your doctor right away or go to your nearest hospital emergency department. Take the medication package with you.

Missed Dose:

If you miss a dose, take the missed dose as soon as you remember but **do not take two doses in one day**.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medicines, pms-ARIPIPRAZOLE can cause some side effects. These side effects are most likely to be minor and temporary. However, some may be serious and need medical attention.

Certain side effects occur more frequently in adolescent compared to adult patients, including abnormal movements, drowsiness and weight gain.

The most common side effects of pms-ARIPIPRAZOLE are:

- feeling of restlessness (akathisia)
- drowsiness
- shaking (tremors)
- abnormal movements
- nausea, vomiting, upset stomach
- dizziness
- constipation
- headaches
- insomnia
- anxiety
- sleep apnea (a sleep disorder where your breathing is interrupted during sleep)
- sleep walking and eating while asleep (sleep-related eating disorders)

The following other side effects may also happen in some people who take pms-ARIPIPRAZOLE:

- weight gain
- increase in the amount of sugar (glucose) in the blood (hyperglycemia). Symptoms of high blood sugar can include feeling very thirsty and/or hungry, needing to urinate more than usual, feeling weak or tired, feeling sick to your stomach, feeling confused, fruity smelling breath.
- decrease in the amount of white blood cells.
- difficulty swallowing, which may lead to aspiration and choking.
- decreased blood pressure. Symptoms of decreased blood pressure can include lightheadedness or fainting when rising too quickly from a sitting or lying position.
- hypersexuality (uncontrollable and/or inappropriate sexual behaviour of severity or duration that causes distress).
- an urge to gamble, to spend money, to eat (binge eating) or other urges (development of a new or increased urge).

Because some people experience sleepiness, you should avoid driving a car or operating machinery until you know how pms-ARIPIPRAZOLE affects you.

Your doctor should check your body weight before starting pms-ARIPIPRAZOLE and continue to monitor it for as long as you are being treated.

Your doctor should take blood tests before starting pms-ARIPIPRAZOLE. These tests will monitor blood sugar, cholesterol, triglycerides and the number of infection fighting white blood cells. Your doctor should continue to monitor your blood for as long as you are being treated.

You should tell your doctor if you notice any symptoms that worry you, even if you think the problems are not connected with the medicine or are not listed here.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
Common			
Skin Rash on its own	✓		
Constipation	✓		
Uncommon			
Tardive Dyskinesia: Muscle twitching or abnormal movement of your face or tongue		✓	
Stroke and Transient Ischemic Attacks: Sudden weakness or numbness of the face, arms, or legs and speech or vision problems			✓
Allergic Reaction: Symptoms include swelling in the mouth, tongue, face and throat, itching, rash			✓
Seizure: Loss of consciousness with uncontrollable shaking			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical attention**
	Only if severe	**In all cases**	
Neuroleptic Malignant Syndrome: Pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness			✓
Priapism: Long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
Blood Clots: Swelling, pain and redness in an arm or leg that is warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations		✓	

This is not a complete list of side effects. For any unexpected effects while taking pms-ARIPIPRAZOLE, contact your doctor or pharmacist.

HOW TO STORE IT

pms-ARIPIPRAZOLE should be stored at room temperature (15ºC - 30ºC).

Do not use pms-ARIPIPRAZOLE after the expiry date which is stated on the label after EXP. Keep out of the reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about pms-ARIPIPRAZOLE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), or by contacting Pharmascience Inc. at 1-888-550-6060.

This leaflet was prepared by
Pharmascience Inc.
Montréal, Canada
H4P 2T4

www.pharmascience.com

Last revised: February 14, 2018