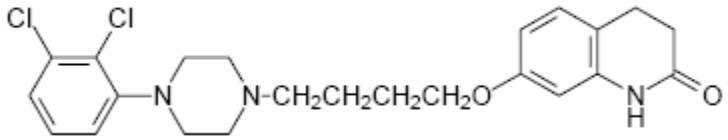
APO-ARIPIPRAZOLE TABLETS

NAME OF THE MEDICINE

Aripiprazole.

Chemical Name: 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone

Structural Formula:



Molecular Formula: $C_{23}H_{27}Cl_2N_3O_2$

Molecular Weight: 448.39 g/mol

CAS Registry Number: 129722-12-9

DESCRIPTION

Aripiprazole is an off-white to white powder. Aripiprazole melts between 139.0 and 139.5°C. It is practically insoluble in water and its solubility is pH dependent.

Each tablet contains 2mg, 5mg, 10mg, 15mg, 20mg and 30mg aripiprazole as the active ingredient. In addition, each tablet contains the following inactive ingredients: cellulose - microcrystalline, tartaric acid, magnesium stearate, and croscarmellose sodium. In addition, the following colouring agents are added: 2mg tablets- indigo carmine, iron oxide yellow; 5 mg tablets – indigo carmine; 10 mg and 30mg tablets - iron oxide red, 15 mg tablets - iron oxide yellow; 20mg tablets – no colouring.

PHARMACOLOGY

Pharmacological Actions

Aripiprazole's mechanism of action is not known, as is the case with other drugs having efficacy in schizophrenia. Nonetheless, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at dopamine D_2 and serotonin $5HT_{1A}$ receptors and antagonist activity at serotonin $5HT_{2A}$ receptors.

Aripiprazole demonstrated higher affinity binding *in vitro* for dopamine D_2 and D_3, serotonin $5HT_{1A}$ and $5HT_{2A}$ receptors (K_i values of 0.3, 0.8, 1.7, and 3.4nM, respectively), than for dopamine D_4, serotonin $5HT_{2C}$ and $5HT_7$, $alpha_1$-adrenergic and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61nM, respectively) and the serotonin reuptake site (K_i value of 98nM). Aripiprazole did not exhibit any appreciable affinity for muscarinic receptors (IC_{50} >1000nM).

It has been demonstrated that the predominant metabolite in human plasma, dehydro-aripiprazole, has a similar affinity for dopamine D_2 and D_3 receptors (K_i values 0.4 and 0.5nM, respectively) as the parent compound and a reduced affinity for the other receptor subtypes.

In animal models of dopaminergic hypoactivity, aripiprazole exhibited agonist properties and it was shown to have antagonist properties in animal models of dopaminergic hyperactivity

Some of the other clinical effects of aripiprazole may be explained by interaction with receptors other than dopamine and serotonin subtypes.

Pharmacokinetics

Absorption

After oral administration, aripiprazole is absorbed with peak plasma concentrations occurring within 3-5 hours after dosing. The absolute oral bioavailability of the tablet formulation of aripiprazole tablets is 87%. Aripiprazole tablets can be taken without regard to meals. After administration of a 15 mg aripiprazole tablet with a standard high-fat meal, the C_{max} of aripiprazole and its active metabolite, dehydro-aripiprazole, increased by 11%. The AUC of aripiprazole was increased by 18% and that of the active metabolite by 14%. Food delayed T_{max} by 3 hours for aripiprazole and 12 hours for the active metabolite. Aripiprazole accumulation is predictable from single dose pharmacokinetics. The pharmacokinetics of aripiprazole is dose-proportional at steady state. There is no diurnal variation in the disposition of aripiprazole and its active metabolite, dehydro-aripiprazole.

Distribution

The apparent volume of distribution of aripiprazole throughout the body is 4.9 L/kg. In vitro, aripiprazole is highly bound to serum proteins (primarily albumin) at therapeutic concentrations (88 – 97% to > 99%, as determined by polydimethylsiloxane-glass bead and equilibrium dialysis assays, respectively) Aripiprazole did not change the pharmacokinetics and pharmacodynamics of highly protein-bound warfarin, which indicates that protein displacement of warfarin did not occur.

Metabolism

There is minimal pre-systemic metabolism of aripiprazole. In the liver, aripiprazole is extensively metabolized. Principally, this occurs by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. The enzymes principally responsible for dehydrogenation and hydroxylation of aripiprazole are CYP3A4 and CYP2D6, while N-dealkylation is primarily catalysed by CYP3A4, according to the results of *in vitro* studies. Aripiprazole is the predominant drug moiety in systemic circulation. The active metabolite, dehydro-aripiprazole, represented about 39% of aripiprazole AUC in plasma at steady state. Approximately 8% of Caucasians are unable to metabolise CYP2D6 substrates and are classified as poor metabolisers (PM), while the remainder are extensive metabolisers (EM). Compared to EMs, PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite. This results in PMs having about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. The safety profile reflects experience in both EMs and PMs as subjectswere entered into clinical studies without knowledge of their metaboliser status.

Excretion

After a single, oral dose of [^{14}C]-labelled aripiprazole, recovery of the administered radioactivityin the urine and faeces was approximately 27% and 60%, respectively. In the urine, less than 1% of the oral dose was excreted unchanged and in the faeces, approximately 18% of the oral dose was recovered unchanged. The total body clearance of aripiprazole is mainly hepatic and is 0.7mL/min/kg.

A bioavailability study comparing fasted and fed subjects at a dose of 15 mg, showed that the elimination half-life of aripiprazole from human plasma was 75 hours mean, range 32–146 hours, n=58, in fasted subjects and 84 hours mean, range 32-157 hours, n=57 in subjects taking a high-fat meal immediately prior to drug administration. Within 14 days of dosing, steady-state concentrations are reached. The plasma elimination half-life of dehydro-aripiprazole, the chief metabolite, from human plasma was found to be approx. 100 hours.

Elderly

There were no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects. There was also no detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients. In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), compared to younger adult subjects (18-64 years), aripiprazole clearance was 20% lower in elderly (≥ 65 years) subjects. However, in the population pharmacokinetic analysis in schizophrenia patients no age effect was evident. In addition, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that seen in young healthy subjects. Dosage adjustment is not recommended for elderly patients (see **PRECAUTIONS, Increased Mortality in Elderly Patients with Dementia- Related Psychosis** and **Use in the Elderly**).

Gender

Between healthy male and female subjects, there were no differences in the pharmacokinetics of aripiprazole. There was also no detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients. C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than in men, and accordingly, the apparent oral clearance of aripiprazole is lower in women. However, these differences are explained, for the most part, by differences in body weight (25%) between men and women. Dosage adjustment based on gender is not recommended.

Race

Population pharmacokinetic evaluation has not revealed any evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole.

Smoking

Population pharmacokinetic evaluation has not revealed any evidence of clinically significant effects of smoking on the pharmacokinetics of aripiprazole. In studies utilizing human liver enzymes *in vitro*, it was demonstrated that aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. It follows that smoking should not have an effect on the pharmacokinetics of aripiprazole. Further, population pharmacokinetic evaluation did not show any significant pharmacokinetic differences between smokers and nonsmokers which is consistent with these *in vitro* results. Dosage adjustment is not recommended based on smoking status.

Renal Impairment

In patients with severe renal disease, the pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar to that in young healthy subjects. In patients with severe renal impairment (creatinine clearance < 30 mL/min), given in a single dose of 15 mg, the C_{max} of aripiprazole 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. Dosage adjustment is not required in subjects with renal impairment.

Hepatic Impairment

The pharmacokinetics of aripiprazole and dehydro-aripiprazole are not significantly affected by hepatic impairment, as demonstrated by a study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C). 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. These differences do not require dose adjustment.

CLINICAL TRIALS

Schizophrenia

Six short-term (4- and 6-week), placebo-controlled trials of inpatients were performed to assess the efficacy of aripiprazole in the treatment of schizophrenia, four of which also included an active control group consisting of either risperidone (one trial) or haloperidol (three trials). The design of the studies did not allow for a comparison of aripiprazole and the active comparators. Efficacy was also assessed in two long-term trials, one of 52 weeks duration, which compared aripiprazole to haloperidol and one of 26 weeks duration, which compared aripiprazole to placebo. The patients in these trials met DSM-III/IV criteria for schizophrenia or schizo-affective disorder.

Psychiatric signs and symptoms were evaluated using a variety of instruments. 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. The Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) are both multi-item inventories of general psychopathology used to assess the effects of drug treatment in schizophrenia. The BPRS Psychosis Cluster (Core Score), a subset of the BPRS that can also be derived from the PANSS, is used to evaluate actively psychotic patients.
Four short-term, fixed-dose trials were well controlled and powered to statistically demonstrate the efficacy of aripiprazole over placebo. The results of these trials are described below.

Trial 1 was a 4-week, placebo-controlled trial (n=414) involving administration of 2 fixed doses of aripiprazole (15 or 30 mg/day) and haloperidol (10 mg/day) in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia or schizo-affective disorder. In this trial, aripiprazole at 15 mg/day was superior to placebo with clinically meaningful changes in PANSS total, PANSS positive and negative subscales, CGI-severity, CGI-improvement, and PANSS-derived BPRS-core scores. The 30 mg dose was superior to placebo for all parameters except PANSS negative subscale.

Trial 2 was a 4-week, placebo controlled trial (n=404) involving administration of 2 fixed doses of aripiprazole (20 or 30 mg/day) and risperidone (6 mg/day) in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia or schizo-affective disorder. In this trial, both doses of aripiprazole were superior to placebo with clinically meaningful changes in the PANSS total, PANSS positive and negative subscales, CGI-severity, CGI-improvement and PANSS-derived BPRS-core scores.

Trial 3 was a 6-week, placebo-controlled trial (n=420) involving administration of 3 fixed doses of aripiprazole (10, 15, or 20 mg/day) in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia. In this trial, all aripiprazole dose groups were superior to placebo with clinically meaningful changes in the PANSS total score, the PANSS positive and negative subscales, the CGI severity and improvement scales, and the PANSS-derived BPRS core score.

Trial 4, was a 6-week trial (n=367) comparing three fixed doses of aripiprazole (2, 5 or 10 mg/day) to placebo, in acutely relapsed patients with a DSM-IV diagnosis of schizophrenia. The results of this trial demonstrated that the 10 mg dose of aripiprazole was superior to placebo in the PANSS total score, the primary outcome measure of the study. In addition, the 10mg dose was also superior to placebo in the PANSS positive subscale and the CGI severity score. Although the 5-mg dose of aripiprazole did not reach significance in the PANSS total score or the PANSS positive subscale, it was superior to placebo in the PANSS negative subscale and the CGI severity scale. The 2-mg dose did not reach significance in any of these outcome measures.

The efficacy of aripiprazole was investigated in two initial placebo-controlled trials. The first trial (Trial 5) was a placebo-controlled, 4-week ascending dose trial of aripiprazole (5 to 30 mg/day) in 103 patients diagnosed with schizophrenia according to the DSM-III-R criteria with acute schizophrenic relapse and a history of response to antipsychotic drugs. In this trial, aripiprazole differentiated from placebo in the PANSS total score, the PANSS positive subscale, and the CGI severity scale. The second trial (Trial 6) was a placebo-controlled, 4-week, fixed-dose trial of aripiprazole (2, 10, or 30 mg/day) in 272 patients diagnosed with schizophrenia according to the DSM-IV criteria with acute schizophrenic relapse and a history of response to antipsychotic drugs. Statistical significance was reached only for the 30 mg dose on the PANSS total score, the PANSS positive subscale, and the CGI severity and improvement scales.

Accordingly, the efficacy of 10 mg, 15 mg, 20 mg and 30 mg was established in two studies for each dose. There was no evidence that the higher dose groups offered any advantage over the lowest dose group. Broad efficacy was established across a variety of endpoints with an onset of action as early as Week 1 for positive symptoms at doses of 15 mg and higher.

Table 1 summarises the results across all six trials.

Table 1: Key Efficacy Results in Short-Term, Placebo-Controlled Trials

	CGI Severity Score	CGI Improvement Score	PANSS Positive Subscale Score	PANSS Negative Subscale Score	PANSS Total Score	PANSS Derived BPRS Core Score
Trial/Treatment	Mean Change	Mean Change	Mean Change	Mean Change	Mean Change	Mean Change
Trial 1						
Placebo	-0.1	4.3	-0.6	-1.2	-2.9	-1.1
Ari 15 mg	-0.6**	3.5**	-4.2**	-3.6**	-15.5**	-3.1**
Ari 30 mg	-0.4**	3.8*	-3.8**	-2.3	-11.4**	-3.0**
Trial 2						
Placebo	-0.2	4.0	-1.8	-0.8	-5.0	-1.7
Ari 20 mg	-0.5*	3.4**	-4.9**	-3.4**	-14.5**	-3.5**
Ari 30 mg	-0.6**	3.3**	-3.9*	-3.4**	-13.9**	-3.3*
Trial 3						
Placebo	-0.2	4.0	-1.1	0.1	-2.3	-1.4
Ari 10 mg	-0.7**	3.3**	-5.0**	-3.5**	-15.0**	-3.9**
Ari 15 mg	-0.5*	3.4**	-3.8**	-2.6**	-11.7**	-2.9*
Ari 20 mg	-0.6**	3.3**	-4.5**	-3.3**	-14.4**	-3.6**
Trial 4						
Placebo	-0.3	3.6	-2.3	-1.3	-5.3	-2.3
Ari 2 mg	-0.3	3.6	-2.4	-2.0	-8.2	-2.3
Ari 5 mg	-0.6*	3.2	-3.4	-2.9*	-10.6	-3.2
Ari 10 mg	-0.6*	3.2	-4.2*	-2.7	-11.3*	-3.4
Trial 5						
Placebo	0.0	4.0	-0.1	-0.9	-1.5	-2.4
Ari 5-30 mg	-0.6**	3.5*	-3.0*	-3.6	-13.5**	-8.6*
Trial 6						
Placebo	-2.8	3.9	-0.97	-1.31	-3.0	-1.48
Ari 2 mg	-0.30	3.7	-1.96	-2.05	-8.0	-1.95
Ari 10 mg	-0.30	3.5	-2.10	-2.48	-8.6	-1.79
Ari 30 mg	-0.60*	3.1**	-3.89*	-3.11	-13.7**	-2.97

** (P≤ 0.01), * (0.01<P≤0.05) significantly different from placebo. NOTE:

Results in boxes indicate the protocol-specified primary efficacy measures.

Ari = aripiprazole

A 52-week, haloperidol-controlled, long-term, maintenance trial (n=1294) was performed in patients with acute relapse of chronic schizophrenia. The trial involved the administration of aripiprazole 30mg/day and haloperidol 10mg/day, with a one time option to decrease aripiprazole to 20mg/day and haloperidol to 7mg/day, aripiprazole was at least comparable to haloperidol in time-to-failure to maintain response in responders. Based on patients who responded at any time during the 52-week study (610/853, 72% in the aripiprazole group and 298/430, 69% in the haloperidol group), there was a 12% lower risk of subsequent failure with aripiprazole relative to haloperidol (relative risk: 0.881, 95% CI: 0.645 - 1.204). In all randomised patients, aripiprazole was comparable to haloperidol in time-to-failure to maintain response. Patients in the aripiprazole group had a 14% lower risk of failure compared with the haloperidol group (relative risk: 0.858, 95% CI: 0.721, 1.021). Aripiprazole was statistically superior to haloperidol in the analysis of the proportion of patients on treatment and in response at Weeks 8, 26, and 52 (prespecified key time points). At Week 52, 40% of aripiprazole patients were still on-study and in response compared to 27% of haloperidol patients (p<0.001). Aripiprazole-treated patients had a statistically significant lower risk (31%) of discontinuations due to lack of efficacy or adverse event relative to haloperidol treated patients (relative risk 0.692; 95% CI: 0.573 - 0.837). In terms of change from baseline PANSS total scores, PANSS positive

subscores, CGI-severity or improvement scores. , there were no significant differences between aripiprazole and haloperidol groups. However, aripiprazole treatment resulted in a significantly greater improvement in the PANSS negative subscores at weeks 26 & 52 and the MADRS total score at Weeks 8, 26, and 52. [Mean change PANSS negative subscale score (week 26: p=0.029; 95% CI: -1.52, -0.08) (week 52: p=0.011; 95% CI: -1.73, -0.23). Mean change MADRS total score (week 8: p=0.027; 95% CI: -1.74, -0.11) (week 26: p=0.22; 95% CI:-1.95, -0.15) (week 52: p= 0.031; 95% CI: -1.97, -0.09).]

The maintenance effects of aripiprazole were also shown by a double-blind study which was performed in chronic, symptomatically stable schizophrenic patients (n=310) randomised to aripiprazole 15mg or placebo and followed for 26 weeks. Patients were observed for "impending psychotic relapse", defined as CGI-improvement score ≥ 5 (minimally worse) or scores ≥ 5 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days or ≥ 20% increase in the PANSS Total Score. Patients in the placebo group experienced a higher relapse rate and/or relapsed sooner than those in the aripiprazole group. Beyond 4 weeks, there were markedly more relapses in the placebo group than the aripiprazole group. Kaplan Meier estimates showed that the estimated probability of not experiencing relapse prior to week 26 was 39% in the placebo group versus 63% in aripiprazole group [relative risk aripiprazole: placebo = 0.50 (95% CI=0.35, 0.71, p≤0.01)]. Compared to placebo, the number of relapses was significantly lower in the aripiprazole group (34% vs. 57%, RR=0.59, 95% CI: 0.45, 0.75, p≤0.01).

Trials using APO- APOTEX- Chemmart Terry White chemists Aripiprazole tablets have not been conducted in patients with first episode schizophrenia or treatment-resistant schizophrenia to adequately establish the efficacy of aripiprazole in these groups of patients.

INDICATIONS

Aripiprazole is indicated for the treatment of schizophrenia including maintenance of clinical improvement during continuation therapy.

Although this document refers to the results of studies of aripiprazole in conditions other than schizophrenia, the APO- Aripiprazole tablets are not indicated for use in the treatment of conditions other than schizophrenia.

CONTRAINDICATIONS

Aripiprazole is contraindicated in patients who are hypersensitive to aripiprazole or any of the excipients (see **DESCRIPTION**).

For specific information about the contraindications of mood stabilisers refer to the **CONTRAINIDICATIONS** section of the prescribing information for those aripiprazole products indicated for use in combination with lithium or valproate.

PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Compared to placebo, elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the length of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. The causes of death varied, but most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g. pneumonia) in nature.

In three placebo-controlled trials of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, cerebrovascular adverse events (e.g. stroke, transient ischaemic attack), including fatalities, occurred in 1.3% (8/595) of aripiprazole-treated patients compared with 0.6% (2/343) of placebo-treated patients during the 10-week double-blind period or within 30 days of the last dose for those who discontinued the study during the double-blind phase. The all cause mortality rate in the same trials over the same period was 3.5% (21/595) in aripiprazole-treated patients and 1.7% (6/343) in the placebo group.

Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.

General

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

Suicide

The chance of attempted suicide is inherent in psychotic illnesses and drug therapy should be accompanied by close supervision of high-risk patients. To reduce the risk of overdose, prescriptions for aripiprazole should be written for the smallest quantity consistent with good patient management

Tardive Dyskinesia

The risk of tardive dyskinesia is increased with long-term exposure to antipsychotic treatment. If signs and symptoms of tardive dyskinesia develop in a patient on aripiprazole, a decrease in dosage or drug discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs including aripiprazole. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. Clinical manifestations of NMS are altered mental status, muscle rigidity, hyperpyrexia, and evidence of autonomic instability (irregular pulse or blood pressure, diaphoresis, tachycardia, and cardiac dysrhythmia). Further signs may include elevated creatine kinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If signs and symptoms indicative of NMS appear in a patient, or a patient presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic drugs, including aripiprazole must be discontinued.

Seizure

In short-term, placebo controlled trials, seizures occurred in 0.1% (3/2467) of adult patients treated with aripiprazole.

As with other antipsychotic drugs, aripiprazole should be used cautiously in patients who have a history of seizure disorder or have conditions associated with seizures.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled clinical studies (2 flexible dose and 1 fixed dose study) of dementia-related psychosis, there was an increased occurrence of cerebrovascular adverse events (e.g. transient ischemic attack, stroke), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis (see also **PRECAUTIONS, Increased Mortality in Elderly Patients with Dementia-Related Psychosis** and **Use in Patients with Concomitant Illness***: Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease*).

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients with atypical antipsychotics including aripiprazole. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increase 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 hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during

treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

In patients with significant treatment-emergent hyperglycaemia, discontinuation of aripiprazole should be considered.

Cardiovascular Adverse Events

Potentially due to its $\alpha_1$1-adrenergic receptor antagonism, aripiprazole may be associated with orthostatic hypotension.

The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral aripiprazole (n=2467) included (aripiprazole incidence, placebo incidence): orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%).

Orthostatic hypotension occurred in 0.8% (112/13543) of oral aripiprazole-treated patients during clinical trials.
As with other atypical antipsychotics, aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medications).

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

Body Temperature Regulation

Antipsychotic agents, including aripiprazole have been attributed with interfering with the body's ability to increase or decrease core body temperature. Appropriate care should be taken when prescribing aripiprazole for patients who will be experiencing conditions that may contribute to an increase in core body temperature, for example, receiving concomitant medication with anticholinergic activity being subject to dehydration, exposure to extreme heat, or exercising strenuously.

Advice should be provided to patients in relation to appropriate care in avoiding overheating and dehydration.

Dysphagia

Oesophageal dysmotility and aspiration have been linked with antipsychotic drug use. Aripiprazole and other antipsychotic drugs should be used with caution in patients at risk of aspiration pneumonia (e.g. elderly patients).

Akathisia

Class effect: The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Leukopenia, Neutropenia and Agranulocytosis

Class Effect: In clinical trial and/or postmarketing experience, events of leucopenia/neutropenia have been reported temporally related to antipsychotic agents, including aripiprazole. Agranulocytosis has also been reported.

Possible risk factors for leucopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leucopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leucopenia/neutropenia should have their complete blood cell (CBC) monitored frequently during the first few months of therapy and discontinuation of 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 < 1000/mm3) should discontinue aripiprazole and have their WBC followed until recovery.

Potential for Cognitive and Motor Impairment

Aripiprazole, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. In short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (n=2467) treated with oral aripiprazole (11%, 6%). Somnolence (including sedation) led to discontinuation in
0.3% (8/2467) of adult patients on oral aripiprazole in short-term, placebo-controlled trials.

Despite the relatively modest increased incidence of these events compared to placebo, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with aripiprazole does not affect them adversely.

Pathological gambling and impulse-control disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported include: increased sexual urges, compulsive spending, binge or compulsive eating, and other impulsive and compulsive behaviours. 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 urges were reported to have stopped when the dose was reduced or the medication was discontinued. Impulse control disorders may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole. (see ADVERSE EFFECTS,)

Use in Patients with Concomitant Illness

Clinical experience with aripiprazole in patients with certain concomitant systemic illnesses is limited (see **PHARMACOLOGY**, **Renal Impairment** and **Hepatic Impairment**).

Patients with a recent history of myocardial infarction or unstable heart disease were excluded from premarketing clinical studies. because aripiprazole has not been evaluated or used to any appreciable extent in these patients.

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease

In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the treatment-emergent adverse effects that were reported at an incidence of ≥ 5% and aripiprazole incidence at least twice that for placebo wereincontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole 5%]. , lethargy [placebo 2%, aripiprazole 5%] and somnolence (including sedation) [placebo 3%, aripiprazole 8%].

The safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with dementia have not been established. Aripiprazole is not indicated for the treatment of psychosis associated with Alzheimer's disease. (see also **PRECAUTIONS, Increased Mortality in Elderly Patients with Dementia-Related Psychosis** and **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis**).

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. (See **PRECAUTIONS, INTERACTIONS** and **DOSAGE AND ADMINISTRATION – Concomitant Medication**)

Carcinogenicity

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and Fischer (F344) rats. For 2 years Aripiprazole was administered 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 maximum recommended human dose [MRHD] based on mg/m^2, respectively). SD rats were dosed orally by gavage for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 18 times the MRHD based on mg/m^2). In male mice and rats, there was no evidence of tumorigenesis. 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 MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (< 0.1 times MRHD based on AUC and 3 times the MRHD based on mg/m^2) and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral gavage dose of 60 mg/kg/day (10 times the MRHD based on AUC and 18 times MRHD based on mg/m^2). In male rats, the incidence of benign and combined benign/malignant phaeochromocytomas were also increased at an oral gavage dose of 60 mg/kg/day (10 times the MRHD based on AUC and 18 times the MRHD based on mg/m^2).

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. Hyperprolactinaemia was observed in female mice in a 13-week dietary study at doses associated with mammary gland and pituitary tumours, but not in female rats in 4- and 13-week dietary studies at doses associated with mammary gland tumours. Hyperprolactinaemia was observed in female rats after 5 and 13 weeks of oral administration at doses up to that associated with adrenocortical tumours, but serum prolactin was decreased at this dose in male rats. The relationship between tumourigenic findings with aripiprazole and prolactin is unclear and the relevance for human risk of prolactin-mediated endocrine tumours is unknown. The adrenocortical response in female rats is considered a consequence of increased adrenocortical cell proliferation secondary to chronic drug-related adrenocortical cytotoxicity; the no-effect exposure (plasma AUC) was about fold 7 clinical exposure at the MRHD.

Genotoxicity

Aripiprazole was tested using a standard range of assays for chromosomal damage, gene mutation, and DNA damage and repair. Aripiprazole was non-genotoxic in the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* bacterial reverse-mutation assay, and the unscheduled DNA synthesis assay in rat hepatocytes. However, aripiprazole and its minor metabolite 2,3-DCPP were clastogenic in the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells in both the presence and absence of metabolic activation. A positive response for aripiprazole in 1 of 6 *in vivo* mouse micronucleus tests was attributed to drug-induced hypothermia.

Effects on Fertility

Aripiprazole did not have an effect on fertility in female rats treated orally with 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the MRHD based on mg/m^2) for 2 weeks prior to mating through to gestation day 7. It was considered that drug-related effects (corpora lutea, persistent dioestrus and increased mating time pre-implantation losses) seen at all doses were the result of perturbed oestrous cyclicity secondary to drug-mediated hyperprolactinaemia.

Aripiprazole did not have an effect on fertility in male rats treated with PO doses of 20, 40, and 60 mg/kg/day (6, 12, and 18 times the MRHD based on mg/m2) for 9 weeks prior to mating through mating. Disturbances of spermatogenesis were observed at 60 mg/kg/day and prostatic atrophy was observed at 40 and 60 mg/kg/day.

Use in Pregnancy (Category C)

Congenital anomalies have been reported; however, a causal relationship with aripiprazole could not be established in animal studies in rats and rabbits aripiprazole demonstrated developmental toxicity, including possible teratogenic effects.

During the period of organogenesis, pregnant rats were treated with oral doses of aripiprazole of 3, 10, and 30 mg/kg/day (1, 3, and 9 times the MRHD on an mg/m^2 basis). At 30 mg/kg, treatment was associated with slightly prolonged gestation, and a slight delay in foetal development as evidenced by undescended testes, reduced foetal weight, and delayed skeletal ossification. There were no adverse effects on embryo foetal or pup survival. There were increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia in delivered offspring at 30 mg/kg (the other doses not being examined for these findings). (A low occurrence of diaphragmatic hernia was also seen in the foetuses exposed to 30 mg/kg). Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg, and decreased pup weight (persisting

into adulthood) and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live foetuses, and increased post-implantation loss, likely mediated through effects on female offspring) were observed at 30 mg/kg. Maternal toxicity was observed at 30 mg/kg, which was similar to doses eliciting embryotoxicity.

During the period of organogenesis, pregnant rabbits were treated with oral doses of aripiprazole of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 8, 24, and 81 times the MRHD based on mg/m^2). Increased abortions and decreased maternal food consumption were seen at 100 mg/kg. Treatment caused increased incidence of a skeletal abnormality (fused sternebrae at 100 mg/kg), increased foetal mortality (100 mg/kg), minor skeletal variations (100 mg/kg) and decreased foetal weight (30 mg and 100 mg/kg).

From late gestation through weaning, rats were treated with oral doses of aripiprazole of 3, 10, and 30 mg/kg/day (1, 3, and 9 times the MRHD on a mg/m^2 basis) At 30 mg/kg, an increase in stillbirths, maternal toxicity, poor postnatal care/nursing slightly prolonged gestation, and decreases in pup weight (persisting into adulthood) and survival were seen.

Non-teratogenic class effect
Neonates exposed to antipsychotics drugs including ariprazole during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market 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 additional medical treatment or monitoring.

Aripiprazole should be used during pregnancy only if the anticipated benefit outweighs the risk, and the administered dose and duration of treatment should be as low and short as possible.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant.

Use in Lactation

Aripiprazole and/or its metabolites have been found in the milk of lactating rats. Aripiprazole is excreted in breast milk. Therefore, patients should be advised not to breast-feed if they are taking aripiprazole.

Use in Labor and Delivery

The effect of aripiprazole on labor and delivery has not been studied.

Animal Toxicology

Choleliths (gallsand and/or gallstones) were observed in the bile of monkeys given aripiprazole orally for 4-52 weeks at doses of 25-125 mg/kg/day (1- 3 times the MRHD based on plasma AUC and 15-76 times the MRHD based on mg/m^2) and were attributed to precipitation of sulfate conjugates of hydroxy metabolites, which exceeded their solubility limits in bile. After repeated daily administration of the MRHD, human biliary concentrations of these sulfate conjugates are substantially lower (0.2-14% of their *in vitro* solubility limits).

Bilateral retinal degeneration was observed in albino rats given oral aripiprazole for 6 months or two years at exposures of 6-13 times the clinical exposure at the MRHD (based on plasma AUC). The exposure at the NOEL dose was 3 times that at the MRHD. A subsequent 18-month study reported this finding in albino but not pigmented rats, possibly due to lack of photoprotective ocular melanin in the albino rats, although it is unknown whether pigmentation prevented or merely delayed retinal degeneration in the pigmented rats. The clinical relevance of this finding is uncertain.

Use in Children

Safety and effectiveness in patients under 18 years of age have not been established.

Use in the Elderly

Placebo-controlled studies of aripiprazole in schizophrenia or Bipolar Mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Of the 13,543 patients treated with oral aripiprazole in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. The majority (81%) of the 1073 patients were diagnosed with

Dementia of the Alzheimer's Type.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia (see **PRECAUTIONS**, **Increased Mortality in Elderly Patients with Dementia-Related Psychosis** and **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis** and **Use in Patients with Concomitant Illness**). The safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with Alzheimer's disease has not beendetermined. Aripiprazole is not indicated for the treatment of psychosis associated with Alzheimer's disease.

Of the 749 patients treated with aripiprazole injection in clinical trials, 99 (13%) were ≥65 years old and 78 (10%) were ≥75 years old. Almost all of the use in the elderly was in clinical trials for an indication for which registration has not been requested. Placebo-controlled studies of aripiprazole injection in patients with agitation associated with schizophrenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single, 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects (≥65 years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients.

Effects on Ability to Drive and to Use Machines

As with other antipsychotics, patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that they are not affected adversely. by aripiprazole.

INTERACTIONS WITH OTHER MEDICINES

CNS Drugs (including Alcohol)

Caution should be used when aripiprazole is administered in combination with other centrally acting drugs and alcohol because of the primary CNS effects of aripiprazole.

Patients should be advised to avoid alcohol while taking aripiprazole.

Co-administration of lithium titrated upwards from a starting dose of 900 mg until serum lithium concentrations near the upper end of the lithium therapeutic concentration range (1.0 – 1.4 mmol/L) were achieved and maintained for at least 5 days or until dose-limiting adverse events were observed and valproate (divalproex sodium) titrated upwards from a starting dose of 250 mg twice daily to achieve serum concentrations within the therapeutic range of 50 – 125 µg/mL for at least 14 days, with 30 mg aripiprazole once daily . This co-administration had no clinically significant effects on the pharmacokinetics of aripiprazole. Nor was there any clinically significant change in valproate or lithium pharmacokinetics when aripiprazole 30 mg once daily was administered concomitantly for 7 days with either divalproex sodium 500 mg every 12 hours or controlled release lithium 450 mg every 12 hours.

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

Antihypertensive Agents

Aripiprazole can potentially enhance the effect of certain antihypertensive agents because of its α_1-adrenergic receptor antagonist activity.

Medicines which cause QT prolongation or electrolyte imbalance

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

Inhibitors and Inducers of CYP2D6 & CYP3A4

Aripiprazole is metabolised by multiple pathways primarily involving the CYP3A4 and CYP2D6 enzymes. Clinical studies with healthy subjects demonstrated that potent inhibitors of 3A4 (***ketoconazole***) and CYP2D6 (***quinidine***) decreased oral clearance of aripiprazole by 38% and 52%, respectively. Other potent inhibitors of CYP3A4 and CYP2D6 could be expected to have similar effects. The aripiprazole dose should be halved when concomitant administration of quinidine or ketoconazole with aripiprazole occurs.The aripiprazole dose should be increased when the inhibitor is withdrawn from the combination therapy (see

DOSAGE AND ADMINISTRATION, **Concomitant Medication**).

No data are available for use of aripiprazole with other inhibitors of CYP3A4 or CYP2D6. Examples of medicines or substances that have the potential to inhibit CYP3A4 or CYP2D6 include, but are not limited to, amiodarone, cimetidine, clarithromycin, cyclosporin, erythromycin, fluconazole, fluoxetine, grapefruit juice, indinavir, itraconazole, nefazodone, paroxetine, and ritonavir

Dose reduction of aripiprazole should be applied with concomitant administration of potent CYP3A4 inhibitors such as itraconazole, clarithromycin and HIV protease inhibitors, as similar effects to that seen in the clinical studies with ketaconazole may be expected. Dose reduction of aripiprazole should be applied with concomitant administration of potent CYP2D6 inhibitors such as fluoxetine and paroxetine as similar effects to that seen in the clinical studies with quinidine may be expected **(see DOSAGE & ADMINISTRATION – Concomitant Medication)**.

In a clinical study in patients with schizophrenia or schizo-affective disorder, co-administration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, with aripiprazole (30 mg daily) resulted in an approximate 70% decrease in AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. Other potent inducers of CYP3A4 and CYP2D6 may be expected to have similar effects. When a potent inducer like carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be increased. Other potent inducers of CYP3A4 include, but are not limited to, St Johns Wort, phenytoin, rifampicin, efavirenz, and nevirapine. Additional dose increases should be based on clinical evaluation. When the inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced. (See **DOSAGE & ADMINISTRATION - Dosage adjustment for patients taking CYP3A4 inducers**)

Inhibitors and Inducers of CYP1A1, CYP1A2, CYP2C9, and CYP2C19
Aripiprazole is not metabolised by CYP1A1, CYP1A2, CYP2C9, and CYP2C19 *in vitro,* suggesting that interactions with medications or other factors (e.g., smoking), which are inhibitors or inducers of these enzymes, are unlikely.

Effects of aripiprazole on Substrates for CYP2D6, CYP2C9, CYP2C19, CYP3A4, & CYP1A2

Aripiprazole and dehydro-aripiprazole were weak inhibitors of CYP2C9, CYP2C19, CYP2D6, and CYP3A4-mediated metabolism *in vitro* (IC_{50} values 2.4 – 25 µM). Neither aripiprazole nor dehydro-aripiprazole inhibited CYP1A2 -mediated metabolism *in vitro* (IC_{50} value >50 – 66 µM).

In clinical studies, 10-30 mg/day doses of aripiprazole had no significant effect on metabolism of substrates of CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan). Therefore, aripiprazole is unlikely to cause clinically important drug interactions mediated by these enzymes.

Famotidine

The pharmacokinetics of aripiprazole was not significantly affected by the H_2 antagonist famotidine, a potent gastric acid blocker.

Food

Aripiprazole can be administered without regard to meals. Following administration of a 15-mg aripiprazole tablet with a standard high-fat meal, the Cmax of aripiprazole and its active metabolite, dehydro-aripiprazole, increased by 11%. The AUC of aripiprazole was increased by 18% and that of the active metabolite by 14%. Food delayed Tmax by 3 hours for aripiprazole and 12 hours for the active metabolite.

ADVERSE EFFECTS

Although this document reports the adverse effects associated with the use of aripiprazole in conditions other than schizophrenia, the APO- Aripiprazole tablets are not indicated for use in the treatment of conditions other than schizophrenia.

Aripiprazole has been evaluated for safety in 13543 patients who participated in multiple-dose clinical trials in Schizophrenia (including schizo-affective disorder), Bipolar I Disorder, Major Depressive Disorder, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7619

patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole injection. A total of 3390 patients were treated with oral aripiprazole for at least 180 days and 1933 patients treated with oral aripiprazole had at least 1 year of exposure.

The conditions and duration of treatment with aripiprazole (monotherapy and in combination treatment with lithium or valproate) 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.

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

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

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

Oral Administration

Adult Patients with Schizophrenia

Adverse Effects Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Patients with Schizophrenia

Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which aripiprazole was taken by acutely relapsed patients with schizophrenia in doses ranging from 2 to 30 mg/day, there was no difference in the incidence of discontinuation due to adverse events between placebo-treated (9%) and aripiprazole-treated (7%)patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

Adult Patients with Bipolar I Disorder

Monotherapy

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

Adverse Reactions Associated with Discontinuation of Treatment

Overall, in patients with Bipolar I Disorder, there was little difference in the incidence of discontinuation due to adverse reactions between aripiprazole-treated (11%) and placebo-treated (10%) patients. The types of adverse reactions that led to discontinuation were similar between aripiprazole-treated and placebo-treated patients.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of aripiprazole in patients with Bipolar I Disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 2:

Table 2: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patients with Bipolar I Disorder Treated with Oral Aripiprazole Monotherapy

	Percentage of Patients Reporting Reaction	
Preferred Term	Aripiprazole (n=917)	Placebo (n=753)
Akathisia	13	4
Sedation	8	3
Restlessness	6	3
Tremor	6	3
Extrapyramidal Disorder	5	2

Less Common Adverse Reactions in Adults

Adverse Events Occurring at an Incidence of at Least 2% Among Aripiprazole- Treated Patients in Short-Term Placebo-Controlled Trials

Table 3 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in Schizophrenia and up to 3 weeks in Bipolar Mania), 2 or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

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

	Percentage of patients Reporting Reaction[a]	
System Organ Class Preferred Term	Aripiprazole (n=1843)	Placebo (n=1166)
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasm	2	1

Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyradimal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2
[a] Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.		

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

Adult Patients with Adjunctive Therapy with Bipolar I Disorder

The following findings are based on a placebo-controlled trial of adult patients with Bipolar I Disorder in which aripiprazole was administered at doses of 15mg/day or 30mg/day in combination with lithium or valproate.

Adverse Reactions Associated with Discontinuation of Treatment

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

1%, respectively).

Commonly Observed Adverse Reactions

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

Less Common Adverse Reactions in Adults with Adjunctive Therapy in Bipolar I Disorder

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

Table 4: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of combination therapy with lithium or valproate in Patients with Bipolar I Disorder.

	Percentage of Patients Reporting Reaction [a]	
System Organ Class	**Aripiprazole + Lithium or Valproate**	**Placebo + Lithium or Valproate**
Preferred Term	**(n=253)**	**(n=130)**
Gastrointestinal Disorders		
Nausea	8	5
Vomiting	4	0
Salivary Hypersecretion	4	2
Dry Mouth	2	1
Infections and Infestations		
Nasopharyngitis	3	2
Investigations		
Weight increased	2	1
Nervous System Disorders		
Akathisia	19	5
Tremor	9	6
Extrapyramidal Disorder	5	1
Dizziness	4	1
Sedation	4	2
Psychiatric Disorders		
Insomnia	8	4
Anxiety	4	1
Restlessness	2	1

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

Dose-Related Adverse Effects in Short-Term, Placebo-Controlled Trials in Schizophrenia

In four trials that compared fixed doses (2, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo, dose response relationships for the incidence of treatment-emergent adverse events were evaluated This analysis, stratified by study, demonstrated that the only adverse event to have a potential dose response relationship, and then most prominent only with 30 mg, was somnolence (including sedation) [placebo, 7.1%; 10mg, 8.5%, 15 mg, 8.7 %; 20 mg, 7.5%; 30 mg, 12.6%].

Adverse Effects Occurring in Long-Term Controlled Trials

A 26-week, double-blind trial comparing aripiprazole and placebo in patients with schizophrenia, the adverse events reported were largely consistent with those reported in the short-term, placebo-controlled trials, apart from an increased 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. Furthermore, in a long-term (52-week), active-controlled study, the incidence of tremor for aripiprazole was 5% (40/859).

Weight Gain

In placebo-controlled trials, there was a slight difference in mean weight change between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively, in short-term studies; p≤0.01, and -1.3 kg vs. -0.9 kg, respectively, in 26 week study; p = n.s.) and also a difference in the proportion of patients meeting the significant weight gain criterion of ≥7% of body weight (aripiprazole 8% compared to placebo 3% in short-term studies; p ≤ 0.01; and aripiprazole 6% compared to placebo 4% in long-term studies; p = n.s.).

In 3-week trials in adults with Bipolar I Disorder with monotherapy aripiprazole, the mean weight gain for aripiprazole and placebo patients was 0.1kg versus 0.0kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (2%) compared to placebo (3%). In the 6-week trial in Bipoar I Disorder with aripiprazole as adjunctive therapy with either lithium or valproate, the mean weight gain for aripiprazole and placebo patients was 0.6kg versus 0.2kg, respectively. The proportion of patients meeting weight gain criterion of ≥7% of body weight with adjunctive aripiprazole was 3% compared to adjunctive placebo 4%.

In long-term, double-blind, active-comparator trials in schizophrenia, aripiprazole was linked to an increased incidence of significant weight gain (≥ 7% above baseline) compared with haloperidol (20% vs. 13%, respectively; p ≤ 0.01; 1.1 kg vs. 0.4 kg, respectively; p=n.s.) but a reduced incidence of significant weight gain compared to olanzapine (aripiprazole 13% vs. olanzapine 33%; p < 0.001; -0.9 kg vs. 3.4 kg; p < 0.001 in a double-blind study).

Weight change results (see Table 5) from long-term, double-blind, controlled trials in schizophrenia demonstrated that patients with high body mass index (BMI) (> 27) were less likely to have significant weight gain on aripiprazole compared to those with low BMI (< 23).

Table 5
Weight Change Results Categorised by BMI at Baseline in Double-Blind, Controlled Trials in Schizophrenia

Study		BMI <23	BMI 23-27	BMI >27
26-week Placebo Controlled	Mean Change from Baseline (kg)	-0.5	-1.3	-2.1
	% Patients with ≥7% increase of body weight relative to baseline	7%	5%	6%
26-week Olanzapine Controlled	Mean Change from Baseline (kg)	1.2	-0.4	-1.4
	% Patients with ≥7% increase of body weight relative to baseline	21%	7%	11%
52-week Haloperidol Controlled	Mean Change from Baseline (kg)	2.6	1.4	-1.2
	% Patients with ≥7% increase of body weight relative to baseline	30%	19%	8%

Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 13% vs. 12 % for placebo. The incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 5% for placebo-treated patients.

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

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

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

In a long-term, double-blind, haloperidol-controlled study in schizophrenia, the incidence of haloperidol-treated patients showing at least one EPS-related adverse event including dystonia was significantly greater than that of the aripiprazole group (57% vs. 26%; p<0.001). In a long-term, double-blind, olanzapine-controlled study, the incidence of olanzapine-treated patients showing at least one EPS-related adverse event was comparable to aripiprazole-treated patients (15% vs. 15%, respectively; p = n.s.).

Dystonia

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

ECG Changes

Between group comparisons for pooled, acute, placebo-controlled trials in patients with schizophrenia, did not show significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. Furthermore, within the dose range of 10 to 30 mg/day, aripiprazole tended to slightly shorten the QTc interval. Aripiprazole was associated with a median increase in heart rate of 4 beats per minute compared to a 1 beat per minute increase in placebo patients.

In a 26-week, placebo-controlled trial in schizophrenia, there were no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters.

Laboratory Test Abnormalities

A between group comparison for acute, 3 to 6-week, placebo-controlled trials did not show any medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, urinalysis parameters or haematology. Also, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, urinalysis or haematology.

In a long-term (26-week), placebo-controlled trial, there were no statistically significant differences between the aripiprazole and placebo patients in the mean change from baseline in fasting glucose, LDL, triglyceride, and total cholesterol measurements.

Adverse Reactions Observed During Premarketing Evaluation of Oral Aripiprazole

The following is a list of MedRA terms that reflect adverse reactions reported by adult patients treated with oral aripiprazole at multiple doses ≥ 2mg/day during any phase of a trial within a database of 13,543 adult patients. The listing does not show adverse events mentioned in Table 2, 3, and 4 or in other sections of this prescribing information. It is important to emphasise that although the events reported occurred with treatment they are not necessarily caused by it. The adverse reactions are classified by system organ class and are according to the following definitions: common adverse reactions are those occurring in at least 1/100 patients; uncommon adverse reactions are those occurring in at least 1/1000, but less than 1/100 patients; rare adverse reactions are those occurring in less than 1/1000 patients.

<u>Blood and Lymphatic System Disorders:</u>

Uncommon: leukopenia, neutropenia, thrombocytopenia;
Rare: lymphadenopathy, eosinophilia.

<u>Cardiac Disorders:</u>

Uncommon: cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, sinus tachycardia, atrial fibrillation, angina pectoris, myocardial ischaemia, palpitations, bradycardia.
Rare: atrial flutter, supraventricular tachycardia, ventricular tachycardia.

Ear and Labyrinth Disorders:

Rare: tinnitus, hypoacusis, ear canal erythemavertigo positional,

Endocrine Disorders:

Rare: early menarche.

Eye Disorders:

Uncommon: dry eye, photophobia, diplopia, eyelid oedema, photopsia.
Rare: lacrimation increased, eye disorder, eye redness, chromotopsia, eye movement disorder, gaze palsy, conjunctivitis.

Gastrointestinal Disorders:

Uncommon: gastroesophageal reflux disease, dysphagia, gastritis, hypoaesthesia oral, diarrhoea, swollen tongue, oesophagitis.
Rare: pruritus ani, abnormal faeces, parotid gland enlargement, faeces discoloured, constipation, lip dry, tongue discolouration, gastrointestinal disorder, abdominal distension, gastrointestinal pain, glossitis, eructation, pancreatitis.

General Disorders and Administration Site Conditions:

Common: asthenia, peripheral oedema, irritability, chest pain.
Uncommon: face oedema, angiodema, chills, gait disturbance, mobility decreased, discomfort, adverse event, feeling abnormal.
Rare: swelling, generalised oedema, difficulty in walking, sluggishness, malaise, thirst, chest discomfort, energy increased, facial pain, feeling cold, local swelling, oedema, tenderness, xerosis, cyst, hypothermia.

Hepatobiliary Disorders:

Rare: hepatitis, jaundice.

Immune System Disorders:

Rare: decreased immune responsiveness, hypersensitivity.

Infections and Infestations:

Rare: parotitis, body tinea, sinusitis, lower respiratory tract infection, gastroenteritis viral, localised infection, herpes simplex, oral candidiasis, gastroenteritis, urinary tract infection.

Injury, Poisoning, and Procedural Complications:

Common: fall.
Uncommon: self mutilation.
Rare: mouth injury, injury, hip fracture, muscle strain, femoral neck fracture, humerus fracture, open wound, clavicle fracture, heat stroke.

Investigations:

Common: weight decreased, creatinine phosphokinase increased.
Uncommon: blood creatinine increased, pyrexia, blood prolactin increased, blood urea increased, electrocardiogram QT prolonged, blood bilirubin increased, hepatic enzyme increased, weight increased, heart rate increased, blood glucose increased.
Rare: orthostatic hypotension, blood lactate dehydrogenase increased, glycosylated haemoglobin increased, gamma-glutamyl transferase increased, physical examination, electrocardiogram T wave inversion, electrocardiogram abnormal, blood urine present, urine output increased, blood creatine phosphokinase abnormal, electrocardiogram PR prolongation, eosinophil count increased, head lag abnormal, urine ketone body present, white blood cell count increased, heart rate irregular.

Metabolism and Nutrition Disorders:

Uncommon: hyperlipidaemia, anorexia, diabetes mellitus (including blood insulin increased, carbohydrate tolerance decreased, diabetes mellitus non-insulin-dependent, glucose

tolerance impaired, glycosuria, glucose urine, glucose urine present), hyperglycaemia, hypokalaemia, hypoglycaemia, polydipsia, dehydration, increased appetite, hyponatraemia.

Rare: diabetic ketoacidosis, hyperuricaemia.

Musculoskeletal and Connective Tissue Disorders:

Uncommon: musculoskeletal rigidity, mobility decreased, muscle tightness, muscle rigidity, muscle spasms, muscular weakness.

Rare: rhabdomyolysis, flank pain, nuchal rigidity, jaw disorder, kyphosis, sensation of heaviness, bone pain, osteoarthritis.

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps):

Rare: skin papilloma, oral neoplasm.

Nervous System Disorders:

Common: coordination abnormal.

Uncommon: memory impairment, cerebrovascular accident, hypokinesia, hypotonia, myoclonus, hypertonia, akinesia, bradykinesia, speech disorder, dystonia, drooling, parkinsonism, dizziness postural, cogwheel rigidity, paraesthesia, disturbance in attention, psychomotor hyperactivity, dysarthria, hypoaesthesia, tardive dyskinesia.

Rare: Grand Mal convulsion, choreoathetosis, burning sensation, convulsion, depressed level of consciousness, dysgeusia, akinaesthesia, ataxia, coma, dysphasia, facial palsy, judgement impaired, loss of consciousness, migraine, neuroleptic malignant syndrome, paraesthesia circumoral, sleep phase rhythm disturbance, unresponsive to verbal stimuli.

Psychiatric Disorders:

Common: suicidal ideation.

Uncommon: aggression, loss of libido, suicide attempt, libido increased, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation, nightmare, mania, hallucination auditory, nervousness, abnormal dreams, apathy, anger, depression, bruxism, confusional state, hallucination, hostility, thinking abnormal.

Rare: catatonia, sleep walking, delirium, depressed mood, euphoric mood, insomnia, eating disorder, asthenia, mood swings, bradyphrenia, cognitive deterioration, mental status changes, disorientation, euphoric mood, logorrhea, mood altered, panic attack, blunted affect, delusional perception, impulsive behaviour, psychomotor retardation, emotional distress, somatoform disorder, sleep disorder.

Renal and Urinary Disorders:

Uncommon: nocturia, polyuria, pollakiuria, incontinence, urinary retention.

Rare: bladder discomfort, proteinuria, oliguria, chromaturia, micturition urgency, urethral discharge, urinary hesitation, enuresis.

Reproductive System and Breast Disorders:

Uncommon: erectile dysfunction, amenorrhea[f], breast pain, menstruation irregular[f].

Rare: gynaecomastia, priapism, pelvic pain, genital pruritus female[f], vulvovaginal discomfort[f], breast discharge, sexual dysfunction.

Respiratory, Thoracic and Mediastinal Disorders:

Common: nasal congestion, dyspnoea, pneumonia aspiration.

Uncommon: hiccups, epistaxis.

Rare: paranasal sinus hypersecretion, sinus congestion, dry throat, rhinorrhoea, hoarseness, painful respiration, nasal dryness.

Skin and Subcutaneous Tissue Disorders:

Common: rash (including erythematous, exfoliative, generalised, macular, maculopapular, popular rash, acneiform, allergic contact, exfoliative seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis.

Uncommon: pruritus, photosensitivity reaction, alopecia, urticaria.

Rare: decubitus ulcer, face oedema, psoriasis, pemphigus, dry skin.

Social Circumstances:

Rare: smoker.

Vascular Disorders:

Common: hypertension.
Uncommon: hot flush, hypotension.
Rare: flushing, hyperaemia.

[f] (female) indicates incidence based on gender total

Post marketing Experience

The following adverse reactions have been identified during postapproval use of aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angiodema, laryngospasm, pruritis/urticaria, or oropharyngeal spasm), and blood glucose fluctuation. Very rare occurrences of increased AST,increased ALT and hiccups have been reported.

Psychiatric Disorders

Uncommon: hypersexuality
Unknown: pathological gambling, impulse-control disorders, obsessive-compulsive disorders, eating disorders

Drug Abuse and Dependence

The potential for abuse, tolerance, or physical dependence of aripiprazole has not been systematically studied in humans. Aripiprazole demonstrated marginal to no abuse potential in self-administration studies in rats and monkeys. In physical dependence studies in rats and monkeys, modest withdrawal symptoms were seen upon abrupt cessation of dosing. Although the clinical trials did not demonstrate any tendency for any drug-seeking behaviour, 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 diverted, misused, and/or abused once marketed. As a result, patients should be carefully evaluated for a history of drug abuse and such patients should be observed closely for signs of aripiprazole misuse or abuse (e.g. drug-seeking behaviour, development of tolerance, increases in dose).

DOSAGE AND ADMINISTRATION

Adults

Recommended Dosage - Schizophrenia

The recommended starting dose for aripiprazole is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. In clinical trial, doses in the range of 10 to 30 mg/day have been effective. Daily dosage may be adjusted with regard to individual clinical status within the range of 10-30 mg daily. Dosage increases should not be made prior to the time needed to achieve steady state, 2 weeks. There is no evidence that doses higher than 15 mg/day are more effective than the recommended starting dose of 10-15mg.

The maintenance dose for aripiprazole is 15 mg/day.

Renal Impairment

Dosage adjustment is not required in adult patients with renal impairment.

Hepatic impairment

Dosage adjustment is not required for adult patients with hepatic impairment (Child-Pugh Class A, B or C).

Elderly

Dosage adjustment is not required for patients ≥ 65 years of age.

Gender

Dosage adjustment is not required for female adult patients relative to male adult patients.

Concomitant Medications

Dosage Adjustment for Patients Taking Aripiprazole Concomitantly with Potential CYP3A4 Inhibitors

The aripiprazole dose should be reduced when concomitant administration of a potent CYP3A4 inhibitor with aripiprazole occurs. When the CYP3A4 inhibitor is removed from the combination therapy, the aripiprazole dose should then be increased.

Dosage Adjustment for Patients Taking Aripiprazole Concomitantly with Potential CYP2D6 Inhibitors

The aripiprazole dose should be halved when concomitant administration of potential CYP2D6 inhibitors such as paroxetine, fluoxetine, or quinidine with aripiprazole occurs. When the CYP2D6 inhibitor is removed from the combination therapy, the aripiprazole dose should then be increased.

Dosage Adjustment for Patients Taking Aripiprazole Concomitantly with Multiple Medications that Inhibit CYP3A4 and CYP2D6

Even though no clinical studies have been conducted in which aripiprazole was taken concomitantly with multiple drugs that inhibit CYP3A4 and CYP2D6, consideration should be given to decreasing the daily dose of aripiprazole in individual circumstances.

Dosage Adjustment for Patients Taking Aripiprazole Concomitantly with Potential CYP3A4 Inducers

The aripiprazole dose should be increased when a potent CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy. Additional dose increases should be based on clinical evaluation. When the CYP3A4 inducer is removed from the combination therapy, the aripiprazole dose should then be decreased.

Smoking Status

Dosage adjustment is not required for smoking patients relative to non-smoking patients.

Switching from Other Antipsychotics

Data was prospectively and systematically collected to address the safety of switching from other antipsychotics to aripiprazole (30mg/day). These data indicate that any of the following methods can be used safely for switching patients to aripiprazole from another antipsychotic monotherapy:

- immediate discontinuation of the patient's current antipsychotic regimen and immediate initiation of aripiprazole;
- immediate initiation of aripiprazole while tapering off the current antipsychotic regimen over a 2-week period.
- upward titration of aripiprazole over a 2-week period and simultaneous tapering off of the patient's current antipsychotic regimen over the same 2-week period;

OVERDOSAGE

Symptoms

In clinical studies and postmarketing experience, accidental or intentional acute overdosage of aripiprazole alone was identified in adult patients with estimated doses up to 1260 mg with no fatalities. The potentially medically important signs and symptoms seen in adult patients who overdosed with aripiprazole alone at doses up to 1260 mg included somnolence, lethargy, tachycardia, blood pressure increased, and vomiting. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been established. The potentially medically serious signs and symptoms reported include transient loss of consciousness and somnolence. There were no reported observations indicating a clinically significant adverse change in vital signs, laboratory assessments, or ECG in patients who were evaluated in hospital settings.

Treatment

No specific information is available on the treatment of overdose with aripiprazole. The chance of multiple drug involvement should be considered. Accordingly, cardiovascular monitoring should begin immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Otherwise, management of overdose should focus on supportive therapy, oxygenation and ventilation, maintaining an

adequate airway, and management of symptoms. Close medical supervision and monitoring should continue until recovery.

Charcoal

In the event of an overdose of aripiprazole, the early administration of charcoal may assist in partially preventing the absorption of aripiprazole. In a single-dose study in which 15 mg of aripiprazole was administered to fully compliant, fully conscious, healthy, male volunteers and followed by activated charcoal (50 g), administered one hour after aripiprazole, aripiprazole AUC and C_{max} was decreased by 51 and 41%, respectively, compared to historic controls, suggesting that charcoal may be effective for overdose management.

Haemodialysis

Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is not likely to be of assistance in overdose management, since aripiprazole is not eliminated unchanged by the kidneys and is highly bound to plasma proteins.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

APO-Aripiprazole tablets are intended for oral administration.

Each tablet contains 2mg, 5mg, 10mg, 15mg, 20mg or 30mg aripiprazole as the active ingredient.

2 mg tablets
Green, rectangular, slightly biconvex tablets, engraved “2” on one side, “A” on the other side.

Blister pack (Al/Al) of 30 tablets (AUST R 152903).
Bottle (HDPE) of 30 or 100 tablets (AUST R 152917).

5 mg tablets
Blue, rectangular, slightly biconvex tablets, engraved “5” on one side, “A” on the other side.

Blister pack (Al/Al) of 30 tablets (AUST R 152904).
Bottle (HDPE) of 30 or 100 tablets (AUST R 152911).

10 mg tablets
Pink, rectangular, slightly biconvex tablets, engraved “10” on one side, “A” on the other side.

Blister pack (Al/Al) of 30 tablets (AUST R 152908).
Bottle (HDPE) of 30 or 100 tablets (AUST R 152920).

15 mg tablets
Yellow, round, slightly biconvex tablets, engraved “ARI” over “15” on one side, “APO” on the other side.

Blister pack (Al/Al) of 30 tablets (AUST R 152924).
Bottle (HDPE) of 30 or 100 tablets (AUST R 152898).

20 mg tablets
White to off-white, round, slightly biconvex tablets, engraved “ARI” over “20” on one side, “APO” on the other side.

Blister pack (Al/Al) of 30 tablets (AUST R 152899).
Bottle (HDPE) of 30 or 100 tablets (AUST R 152932).

30 mg tablets
Pink, round, slightly biconvex tablets, engraved “ARI” over “30” on one side, “APO” on the other side.

Blister pack (Al/Al) of 30 tablets (AUST R 152905).

Bottle (HDPE) of 30 or 100 tablets (AUST R 152929).

* Not all strengths, pack types and/or pack sizes may be available.

Storage
Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd

16 Giffnock Avenue
Macquarie Park NSW 2113

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POISONS SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

26 June 2009

DATE OF MOST RECENT AMENDMENT:

09 February 2017