xxxxxxxx-5253

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

ARIP MT

(Aripiprazole Tablets, 10 mg/15 mg)

COMPOSITION

ARIP MT 10 : Each uncoated tablet contains Aripiprazole 10mg
ARIP MT 15 : Each uncoated tablet contains Aripiprazole 15mg

Not all strengths available in all countries.

CHEMISTRY

Aripiprazole is a psychotropic drug that is available as tablets for oral administration. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4- dihydrocarbostyril. The empirical formula is $C_{23}H_{27}C_{12}N_3O_2$ and its molecular weight is 448.38

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors, moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha1-adrenergic and histamine H_1 receptors and moderate affinity for the serotonin reuptake site (K_i = 98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors. Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor.

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia and schizophrenic disorder is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} 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.

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 been shown to have affinities for D_2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. Steady-state concentrations are attained within 14 days of dosing for both active moieties. The mean elimination half-lives are about 75 hours and 95 hours for aripiprazole and dehydro-aripiprazole, respectively.

Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole is dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

Absorption

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. Absorption of Aripiprazole is not affected by food.

Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin.

Metabolism and Elimination

Primarily three biotransformation pathways metabolize Aripiprazole: 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.

Poor metabolizers have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to Extensive metabolizers, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to Extensive Metabolisers. The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in Extensive Metabolisers and Poor Metabolisers, respectively. 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

Patient's age, gender, race, smoking status, hepatic function, or renal functions do not significantly affect the pharmacokinetics of the drug and do not require dose adjustment.

The pharmacokinetics of aripiprazole in special populations is described below.

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 Hepatic Impairment, increased 8% in moderate Hepatic Impairment, and decreased 20% in severe Hepatic Impairment. None of these differences would require dose adjustment.

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.

Elderly

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).

INDICATIONS

ARIP MT is indicated for the treatment of schizophrenia and for maintenance of clinical improvement.

ARIP MT is indicated for the treatment of acute manic episodes associated with Bipolar 1 Disorder.

CONTRAINDICATION

Aripiprazole is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Metabolic Changes

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

Hyperglycemia and Diabetes Mellitus

Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycemiarelated adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment- emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including Aripiprazole. The management of NMS should include:

1) Immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy;
2) Intensive symptomatic treatment and medical monitoring; and
3) Treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia

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

Phenylketonurics

Unsuitable for phenylketonurics

PRECAUTIONS

General

Use in Elderly Patients with Dementia-Related Psychosis Increased Mortality

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidences of orthostatic hypotension associated events are very rare. Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities).

Seizure

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients in short-term, placebo-controlled trials. As with other antipsychotic drugs, Aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing Aripiprazole for patients.

Dysphagia

Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy.

Interference with Cognitive and Motor Performance

Because Aripiprazole may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Aripiprazole therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with Aripiprazole.

Nursing

Patients should be advised not to breast-feed an infant if they are taking Aripiprazole.

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.

Alcohol

Patients should be advised to avoid alcohol while taking Aripiprazole.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Drug-Drug Interactions

Due to its α_1-adrenergic receptor antagonism, Aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Potential for Other Drugs to Affect ARIP MT

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. 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.

Ketoconazole : Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabo-lite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied.

Quinidine: Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when concomitant administration of quinidine with aripiprazole occurs.

Carbamazepine: Coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70% decrease in Cmax and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled.

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

ANIMAL TOXICOLOGY

Carcinogenesis

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/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 human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2

Mutagenesis

Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the in vitro chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the in vitro assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the in vivo micronucleus assay in mice, however, the response was shown to be due to a mechanism not considered relevant to humans.

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 maximum recommended human dose [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.

Pregnancy & Lactation

Neonates exposed to antipsychotic drugs 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 hospitalisation.

Arip MT should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

ADVERSE EVENTS

Psychiatric disorders – insomnia, restlessness
Nervous System disorders – headache, dizziness, akathisia, somnolence / sedation, tremor
Eye disorders – blurred vision
Cardiac disorders – tachycardia
Vascular disorders – orthostatic hypotension
Gastrointestinal disorders – nausea, vomiting, constipation, dyspepsia
General disorders and administration site conditions – asthenia/fatigue
Others

Undesirable effects known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse events and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus.

The following adverse events have also been reported very rarely :

Immune system disorders – allergic reaction (e.g. anaphylactic reaction, angioedema, pruritis or urticaria)
Psychiatric disorders – nervousness, agitation
Nervous System disorders – speech disorder
Vascular disorders – syncope
Gastrointestinal disorders – increased salivation. pancreatitis
Musculoskeletal, connective tissue and bone disorders – stiffness, myalgia, rhabdomyolysis
Reproductive system and breast disorders – priapism
General disorders and administration site conditions – chest pain, temperature regulation disorder (e.g. hypothermia, pyrexia)
Investigations – increased creatine phosphokinase, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased gamma glutamyl transferase (GGT)

DOSAGE AND ADMINISTRATION

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

Bipolar Mania : Aripiprazole should be administrated on a once-a-day schedule without regard to meals, generally starting at a dose of 15 to 30 mg/day. Dosage adjustments, if any, should occur at not before 24 hours interval. Antimanic efficacy (3-12 weeks) has been demonstrated in a dose ranging from 15 to 30 mg/day. The safety of doses above 30mg has not been evaluated in clinical trials.

Special Populations

Renal impairment
No dosage adjustment is required in patients with renal impairment.
Hepatic impairment
No dosage adjustment is required for patients with hepatic impairment (Child-Pugh Class A, B, or C).
Pediatric
The safety and efficacy of ARIP MT in patients under 18 years of age have not been established.
Elderly
No dosage adjustment is required for patients 65 years of age. However, experience with this patient population is limited.
Gender
No dosage adjustment is required for female patients relative to male patients.
Patients Taking Medications metabolized by CYP2D6 or 3A4.
Dosage adjustment for patients taking aripiprazole concomitantly with potent CYP3A4 or CYP2D6 inhibitors : When concomitant administration of a potent CYP3A4 or CYP2D6 inhibitor with aripiprazole occurs, the aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should then be increased.
Dosage adjustment for patients taking potent CYP3A4 inducers: When a potent CYP3A4 inducer is added to aripiprazole therapy, the aripiprazole dose should be doubled. Additional dose increases of aripiprazole should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should be reduced.
Consideration should be given to reducing the daily dose in individual patients who are on multiple concomitant medications that inhibit CYP3A4 and CYP2D6 enzymes.
Smoking Status
No dosage adjustment is required for smoking patients relative to non-smoking patients.

ROUTE OF ADMINISTRATION

For oral use

OVERDOSAGE

Human Experience in clinical studies and postmarketing experience, accidental or intentional acute overdosage of aripiprazole alone was identified in patients with estimated doses up to 1260mg with no fatalities. The potentially medically important signs and symptoms observed included lethargy, blood pressure increased, somnolence, tachycardia and vomiting. In addition, reports of accidental overdose with aripiprazole alone (up to 210mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported include somnolence and transient loss of consciousness. In the patients who were evaluated in hospital settings, there were no reported observations indicating clinically significant adverse change in vital signs, laboratory assessments, or ECG. Overdose Management 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. Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole AUC and Cmax by 51 and 41%, respectively, suggesting that charcoal may be effective for overdose management. 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 not eliminated unchanged by the kidneys and is highly bound to plasma proteins.

STORAGE

Store below 30^{o}C. Protected from moisture.

PRESENTATION

ARIP MT 10: It is available as light yellow colored, round, flat, beveled edge, uncoated tablets, in strips of 10 tablets, 3 x 10 tablets, 10 x 10 tablets packed in aluminum foil.

ARIP MT 15: It is available as light yellow colored, round, flat, beveled edge, uncoated tablets, in strips of 10 tablets, 3 x 10 tablets, 10 x 10 tablets packed in aluminum foil.

Not all pack sizes may be marketed.

DATE OF REVISION OF PACKAGE INSERT

18/08/2014

torrent PHARMA

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TORRENT PHARMACEUTICALS LTD.
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