8050634-8883

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

ARIP MT

(Aripiprazole Tablets, 5 mg/10 mg/15 mg/20 mg/30mg)

COMPOSITION

ARIP MT 5 : Each uncoated tablet contains Aripiprazole.....5 mg
ARIP MT 10 : Each uncoated tablet contains Aripiprazole.....10 mg
ARIP MT 15 : Each uncoated tablet contains Aripiprazole.....15 mg
ARIP MT 20 : Each uncoated tablet contains Aripiprazole.....20 mg
ARIP MT 30 : Each uncoated tablet contains Aripiprazole.....30 mg

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 $C_{23}H_{27}Cl_2N_3O_2$ 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.

Dose : As directed by the Physician

WARNINGS

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.

PRECAUTIONS

General

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α 1adrenergic 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 1adrenergic receptor antagonism, Aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Potential for Other Drugs to Affect Aripiprazole

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 metabolite 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

Pregnancy Category C

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

There are no adequate and well-controlled studies in pregnant women. It is not known whether Aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

ADVERSE EVENTS

Dose-related Adverse Events

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from clinical trial. The most prominent was somnolence, Insomnia, rigidity and headache.

Extrapyramidal Symptoms

Various clinical trials reported EPS for aripiprazole-treated patients was similar to 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) also did not show a difference between aripiprazole and placebo.

Laboratory parameters

Various clinical trial revealed that patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis.

Weight Gain

Effect of Aripiprazole on weight is minimal, in short-term trials; there was a slight difference in mean weight gain between aripiprazole and placebo patients, which was not statistically significant.

ECG Changes

Between group comparisons for pooled, placebo-controlled trials revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters; in fact, within the dose range of 10 to 15 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 among placebo patients.

Cardiovascular System: Frequent-hypertension, tachycardia, hypotension, bradycardia; Infrequent-palpitation, hemorrhage, myocardial infarction, prolonged QT interval, cardiac arrest, atrial fibrillation, heart failure, AV block, myocardial ischemia, phlebitis, deep vein thrombosis, angina pectoris, extrasystoles; Rare-vasovagal reaction, cardiomegaly, atrial flutter, thrombophlebitis.

Digestive System: Frequent-anorexia, nausea and vomiting; Infrequent -increased appetite, gastroenteritis, dysphagia, flatulence, gastritis, tooth caries, gingivitis, hemorrhoids, gastroesophageal reflux, gastrointestinal hemorrhage, periodontal, tongue edema, fecal incontinence, colitis, rectal hemorrhage, stomatitis, mouth ulcer, cholecystitis, fecal impaction, oral moniliasis, cholelithiasis, eructation, intestinal obstruction; Rare- esophagitis, gum hemorrhage, glossitis, hematemesis, melena, duodenal ulcer, cheilitis, hepatitis, hepatomegaly, pancreatitis, intestinal perforation.

Endocrine System: Infrequent-hypothroidism; Rare -goiter, hyperthyroidism.

Hemic/Lymphatic System: Frequent-ecchymosis, anemia; Infrequent -hypochromic anemia, leukopenia, leukocytosis, lymphadenopathy, thrombocytopenia; Rare- eosinophilia, thrombocythemia, macrocytic anemia.

Metabolic and Nutritional Disorders: Frequent-weight loss, creatine phosphokinase increased; Infrequent-dehydration, edema, hypercholesteremia, hyperglycemia, hypokalemia, diabetes mellitus, SGPT increased, hyperlipemia, hypogycemia, thirst, BUN increased, hyponatremia, SGOT increased, alkaline phosphatase increased, iron deficiency anemia, creatinine increased, bilirubinemia, lactic dehydrogenase increased, obesity; Rare-hyperkalemia, gout, hypernatremia, cyanosis, hyperuricemia, hypoglycemic reaction.

Musculoskeletal System: Frequent-muscle cramp; Infrequent-arthralgia, bone pain, myasthenia, arthritis, arthrosis, muscle weakness, spasm, bursitis; Rare-rhabdomyolysis, tendonitis, tenosynovitis, rheumatoid arthritis, myopathy.

Nervous System: Frequent -depression, nervousness, increased salivation, hostility, suicidal thought, manic reaction, abnormal gait, confusion, cogwheel rigidity; Infrequent-dystonia, twitch, impaired concentration, paresthesia, vasodilation, hypesthesia, extremity tremor, impotence, bradykinesia, decreased libido, panic attack, apathy, dyskinesia, hypersomnia, vertigo, dysarthia, tardive dyskinesia, ataxia, impaired memory, stupor, increased libido, amnesia, cerebrovascular accident, hyperactivity, depersonalization, hypokinesia, restless leg, myoclonus, dysphoria, neuropathy, increased reflexes, slowed thinking, hyperkinesia, hyperesthesia, hypotonia, oculogyric crisis; Rare-delirium, euphoria, buccoglossal syndrome, akinesia, blunted affect, decreased consciousness, incoordination, cerebral ischemia, decreased reflexes, obsessive thought, intracranial hemmorage.

Respiratory System: Frequent-dyspnea, pneumonia; Infrequent -asthma, epistaxis, hiccup, laryngitis; Rare-hemoptysis, aspiration pneumonia, increased sputum, dry nasal passages, pulmonary edema, pulmonary embolism, hypoxia, respiratory failure, apnea.

Skin and Appendages: Frequent - dry skin, pruritis, sweating, skin ulcer; Infrequent -acne, vesiculobullous rash, eczema, alopecia, psoriasis, seborrhea; Rare- maculopapular rash, exfoliative dermatitis, urticaria.

Special Senses: Frequent - conjunctivitis, ear pain; Infrequent – dry eye, eye pain, tinnitus, otitis media, cataract, altered taste, blepharitis; Rare – increased lacrimation, frequent blinking, otitis externa, amblyopia, deafness, diplopia, eye hemorrhage, photophobia.

Urogenital System: Frequent-urinary incontinence; Infrequent-cystitis, urinary frequency, leukorrhea, urinary retention, hematuria, dysuria, amenorrhea, abnormal ejaculation, vaginal hemorrhage, vaginal moniliasis, kidney failure, uterus hemorrhage, menorrhagia, albuminuria, kidney calculus, nocturia, polyuria, urinary urgency; Rare-breast pain, cervicitis, female lactation, anorgasmy, urinary burning, glycosuria, gynecomastia, urolithiasis, priapism.

DOSAGE AND ADMINISTRATION

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.

Dosage in Special Populations

Dosage adjustment for patients taking **ARIP MT** concomitantly with potential CYP3A4 inhibitors: When concomitant administration of ketoconazole with **ARIP MT** occurs, **ARIP MT** dose should be reduced to one-half of the usual dose.

When concomitant administration of quinidine, fluoxetine, or paroxetine with **ARIP MT** occurs, **ARIP MT** dose should be reduced at least to one-half of its normal dose.

When a potential CYP3A4 inducer such as carbamazepine is added to **ARIP MT** therapy, the **ARIP MT** dose should be doubled (to 20 to 30 mg). Additional dose increases should be based on clinical evaluation.

Maintenance therapy

There is no body of evidence available from controlled trials to answer the question of how long a patient treated with aripiprazole should remain on it. It is generally agreed, however, that pharmacological treatment for episodes of acute schizophrenia should continue for up to 6 months or longer. Patients should be periodically reassessed to determine the need for maintenance treatment.

Switching to ARIP MT from other antipsychotics

Switching schizophrenic patients to new antipsychotic **ARIP MT** from both conventional and atypical antipsychotics appears to be both safe and well tolerated. Switching strategy consist of a switch to a full dose of **ARIP MT** without titration from prior antipsychotic treatment, switching to a full dose of **ARIP MT** along with tapering of the previous treatment for one/two weeks, or switching to **ARIP MT** with titration up along with titration down of the previous medication over one/two weeks.

OVERDOSAGE

Overdosage of Aripiprazole was identified in seven patients. In the two patients taking the largest identified amount, 180 mg, the only symptoms reported were somnolence and vomiting in one of the two patients.

STORAGE

Srore below 30^{o}C, Protected form moistrure

EXPIRY DATE

Do not use later than the date of expiry.

PRESENTATION

ARIP MT 5 : It is available as Light orange colored, round, flat, beveled edged, uncoated tablets, plain on both side, in strip of 10 tablets.

ARIP MT 10 : It is available as Light yellow colored, round, flat, beveled edged, uncoated tablets, in strip of 10 tablets.

ARIP MT 15 : It is available as Light yellow colored, round, flat, beveled edged, uncoated tablets, in strip of 10 tablets.

ARIP MT 20 : It is available as Light yellow colored, round, flat, beveled edged, uncoated tablets, in strip of 10 tablets.

ARIP MT 30 : It is available as Light yellow colored, round, flat, beveled edged, uncoated tablets, in strip of 10 tablets.

torrent PHARMA

Manufactured by :
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