ARIPITAS-10 & 15

(Aripiprazole Tablets 10 mg & 15 mg)

1. Name of the medicinal product
ARIPITAS-10 (Aripiprazole Tablets 10 mg)
ARIPITAS-15 (Aripiprazole Tablets 15 mg)
2. Qualitative and quantitative composition
For 10 mg:
Each uncoated tablet contains:
Aripiprazole USP 10 mg
For 15 mg:
Each uncoated tablet contains:
Aripiprazole USP 15 mg
For the full list of excipients, see excipient list section.

3. Pharmaceutical form
Uncoated tablet

4. Clinical particulars

4.1 Therapeutic indications
Aripiprazole is indicated for the treatment of schizophrenia.

4.2 Posology and method of administration

Usual Dose
The recommended starting and target dose for Aripiprazole is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. Aripiprazole has been systematically evaluated and shown to be effective in a dose range of 10-30 mg/day, however, doses higher than 10 or 15 mg/day, the lowest doses in these trials, were not more effective than 10 or 15 mg/day.

Dosing in Special Populations
Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status.
Dosage adjustment for patients taking Aripiprazole concomitantly with potential CYP3A4 inhibitors: When concomitant administration of ketoconazole with Aripiprazole occurs, Aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, Aripiprazole dose should then be increased.
Dosage adjustment for patients taking Aripiprazole concomitantly with potential CYP2D6 inhibitors: When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with Aripiprazole occurs, Aripiprazole dose should be reduced at least to one-half of its normal dose. When the CYP206 inhibitor is withdrawn from the combination therapy, Aripiprazole dose should then be increased.
Dosage adjustment for patients taking potential CYP3A4 inducers: When potential CYP3A4 inducer such as carbamazepine is added to Aripiprazole therapy, Aripiprazole dose should be doubled (to 20 or 30 mg). Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, Aripiprazole dose should be reduced to 10-15 mg.

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 upto 6 months or longer. Patients should be periodically reassessed to determine the need for maintenance treatment

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

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

4.4 Special warnings and precautions for use
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. Two possible cases of NMS occurred during Aripiprazole treatment in the premarketing worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular-pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.
Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.
General
Orthostatic Hypotension
Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α 1-adrenergic receptor antagonism. 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), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).
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. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.
Potential for Cognitive and Motor Impairment
In short-term, placebo-controlled trials, somnolence was reported in 11% of patients on Aripiprazole compared to 8% of patients on placebo: somnolence led to discontinuation in 0.1% (11926) of patients on Aripiprazole in short-term, placebo-controlled trials.
Body Temperature Regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents.
Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drug use.
Suicide
The possibility of a suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy.
Use in Patients with Concomitant Illness
Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's disease
In a flexible dose (2-15 mg/day). 10 week placebo-controlled study of Aripiprazole in elderly patients (mean age. 81.5 years; range: 56-95) with psychosis associated with Alzheimer's dementia, 4 of 105 patients (3.8%) who received Aripiprazole died compared to no deaths among 102 patients who received placebo during or within 30 days after termination of the double-blind portion of the study.

4.5 Interaction with other medicinal products and other forms of interaction
Drug Interaction
Potential of other drugs to affect Aripiprazole
Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYPX19, or CYP2EI enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of Aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely. Both CYP3A4 and CYP2D6 are responsible or Aripiprazole metabolism. Agents that induce CYP3A4 (eg. 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.
Potential for Aripiprazole to affect other drugs
Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10-30 mg/day doses of Aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, Aripiprazole and dehydroaripiprazole did not show potential for altering CYPIA2-mediated metabolism *in vitro*. Aripiprazole had no clinically important interactions with the following drugs.
Famotidine:
Co administration of Aripiprazole (given in a single dose of 15 mg) with a 40 mg single dose of the H2 antagonist Famotidine, a potent gastric acid blocker, decreased the solubility of Aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the Cmax of Aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of Aripiprazole is required when administered concomitantly with Famotidine.
Valproate:
When valproate (500-1500 mg/day) and Aripiprazole (30 mg/day) were co administered at steady state, the Cmax and AUC of Aripiprazole were decreased by 25%. No dosage adjustment % Aripiprazole is required when administered concomitantly with valproate.
Lithium:
A pharmacokinetic interaction of Aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins. It is not metabolized, it is almost entirely excreted unchanged in urine. Co administration of therapeutic dose of lithium (1200-1800 mg/day) for 21 days with Aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of Aripiprazole or its active metabolite, dehydro-aripiprazole (C and AUC increased by less than 20%). No dosage adjustment of Aripiprazole required when administered concomitantly with lithium.
Dextromethorphan:
Aripiprazole at doses of 10-30 mg/day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite. Dextrorphan, a pathway known to be dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methyoxymorphan, a pathway known to be dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with Aripiprazole.
Warfarin:
Aripiprazole 10 mg/day for 14 days has no effect on the pharmacokinetics of R- and S-warfarin or on the pharmacodynamic endpoint of International Normalized Ratio, indicating the lack of a clinical relevant effect of Aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with Aripiprazole.
Omeprazole:
Aripiprazole 10 mg/day for 15 days had no effect on the pharmacokinetics of a single 20 mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with Aripiprazole.

4.6 Fertility, pregnancy and lactation
Pregnancy
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.
Nursing Mothers
Aripiprazole was excreted in milk of rats during lactation. It is not known whether Aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving Aripiprazole should not breast-feed.

4.7 Undesirable effects
The conditions and duration of treatment with Aripiprazole included (in overlapping categories) double-blind and comparative and non-comparative open-label studies, inpatient and outpatient studies, fixed and flexible-dose studies, and short- and longer-term exposure.
The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; i.e., all reported events are included.
Body as a Whole*: Frequent:* Flu syndrome, peripheral edema, chest pain, neck pain, neck rigidity; *Infrequent:* Pelvic pain, suicide attempt, face edema, malaise, photosensitivity, a rigidity, jaw pain, chills, bloating, jaw tightness, enlarged abdomen, chest tightness; *Rare*: Throat pain, back tightness, head heaviness, moniliasis, throat tightness, leg rigidity, neck tightness, Mendelson's syndrome, heat stroke.

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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, thrombophlehtis.
Digestive System: *Frequent* Anorexia, nausea and vomiting; *Infrequent* Increased appetite, gastroenteritis, dysphagia, flatulence, gastritis, tooth canes, gingivitis, hemorrhoids, gastroesophageal reflux, gastrointestinal hemorrhage, periodontal abscess, tongue edema, fecal incontinence, colitis, rectal hemorrhage, stomatitis, mouth ulcer, cholecystitis, fecal Impaction, oral monliasis, cholelithiasis, eructation, intestinal obstruction, peptic ulcer; *Rare*. Esophagitis, gum hemorrhage, glossitis, hematemesis, melena, duodenal ulcer, cheilitis, hepatitis, hepatomegaly, pancreatitis, intestinal perforation.
Endocrine System: *Infrequent* Hypothyroidism; *Rare:* Goiter, hyperthyroidism.
Hemic/Lymphatic System: *Frequent:* Ecchymosis, anemia; *Infrequent:* Hypochromic anemia, leukopenia, leulcocytosis, 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, hypoglycemia, 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, dysarthria, tardive dyskinesia, ataxia, impaired memory, stupor, increased libido, amnesia, cerebrovascular accident, hyperactivity, depersonalization, hypokinesia, restless leg, myoclonus. dysphoria, neuropathy, increased reflexes, slowed thinking, hyperkinesias, hyperesthesia, hypotonia, oculogyric crisis; *Rare:* Delirium, euphoria, buccoglossal syndrome, akinesia, blunted affect, decreased consciousness. Incoordination, cerebral ischemia, decreased reflexes, obsessive thought, intracranial hemorrhage.
Respiratory System: *Frequent*: Dyspnea, pneumonia; *Infrequent:* Asthma, epistaxis, hiccup, laryngitis. *Rare:* Hemophtysis, aspiration pneumonia, increased sputum, dry nasal passages, pulmonary edema, 'pulmonary embolism, hypoxia, respiratory failure, apnea.
Skin and Appendages: *Frequent:* Dry skin, pruritus, sweating, skin ulcer; *Infrequent*: Acne, vesiculobullous rash, eczema, alopecia, psoriasis, seborrhea: *Rare*: Maculopapular rash, exfoliative dermatitis, urticaria.
Special Senses: *Frequent:* Conjunctivitis, pain , *Infrequent:* Dry eye, eye pain, tinnitus, otitis media, cataract, altered taste, blespharitis, *Rare:* Increased lacrimation, frequent blinking, otitis ecterna, 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.

4.9 Overdose

In premarketing clinical studies, involving more than 5500 patients, accidental or intentional acute overdosage of Aripiprazole was identified in 7 patients. In the 2 patients taking the largest identified amount, 180 mg, the only symptoms reported were somnolence and vomiting in 1 of the 2 patients. In the patients who were evaluated in hospital settings including the 2 patients taking 180 mg, there was no observations indicating adverse change in vital signs.-laboratory assessments or ECG. An uneventful, accidental overdose (15 mg) occurred in a non-patient, an 18-month-old child, with concomitant ingestion of Ativan (2 mg).

Management of Overdose

No specific information is available on the treatment of overdose with Aripiprazole. An electrocardiogram should be obtained in case of overdosage and, if QTc interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.
Charcoal: In the event of an overdose of Aripiprazole, an early charcoal administration may be useful in partially preventing the absorption of Aripiprazole. Administration of 50 g of activated charcoal, 1 hour after a single 15 mg oral dose of Aripiprazole, decreased the mean AUC and Cmax of Aripiprazole by 50%.
Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with Aripiprazole, hemodialysis is unlikely to be useful in overdose management since Aripiprazole is highly bound to plasma proteins.

5. Pharmacological properties

Pharmacodynamic properties:
Pharmacotherapeutic group: other antipsychotics, ATC code: N05AX12
It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.
Aripiprazole doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}Craclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.
Pharmacokinetic properties
Absorption:
Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of Aripiprazole.
Distribution:
Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 l/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99% bound to serum proteins, binding primarily to albumin.
Metabolism:
Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.
Elimination:
The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.
The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.
Following a single oral dose of [^{14}C]labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose
Microcrystalline Cellulose
Hydroxy Propyl Cellulose
Croscarmellose Sodium
Magnesium Stearate
Colloidal Anhydrous Silica
Colorants:
For 10 mg and 15 mg:
Ferric Oxide Red

6.2 Shelf life

3 years

6.3 Storage

Do not store above 30°C.

6.4 Nature and contents of container

Aripiprazole Tablets 10 mg are packed in Alu - PVC blister pack of 10 tablets and 3 such blisters are packed in 1 carton.
Aripiprazole Tablets 15 mg are packed in Alu - PVC blister pack of 10 tablets and 3 such blisters are packed in 1 carton.

7. Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.
Selaqui, Dehradun – 248 197, INDIA

8. Date of revision of the text

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