SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal Product

Aripiprazole Tablets USP 10 mg

2. Qualitative and Quantitative Composition

Qualitative declaration

Aripiprazole USP

Quantitative declaration

Each tablet contains 68.350 mg of Lactose Monohydrate.
For full list of Excipients, see section 6.1.

3. Pharmaceutical Form

Oral Tablet
Off white to pink colour with small specks, round shaped, biconvex, plain on both sides of Uncoated tablets.
The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. Clinical Particulars

1. Therapeutic Indications

It is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years, older, and moderate to severe manic episodes in bipolar I disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment. It is also indicated for the treatment up to 12 weeks of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 years and older.

2. **Posology and Method of Administration**

Adults

- ***Schizophrenia:*** starting recommended dose is 10-15 mg/day with a maintenance dose of 15 mg/day. Improved efficacy at doses higher than a daily dose has not been proved although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg. It is effective in a dose range of 10 mg/day to 30 mg/day
- **Manic episodes in Bipolar I Disorder:** Initially starting dose 15 mg once daily, some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.
- **Recurrence prevention of manic episodes in Bipolar I Disorder:** for preventing recurrence of manic episodes in patients, who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered because of clinical status.

Special populations

- **Hepatic impairment:** No dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. The dosing should be managed cautiously in patients with severe hepatic impairment. However, the max., daily dose of 30 mg.
- **Renal impairment:** No dosage adjustment is required.
- **Elderly:** The safety and efficacy has not been established in elderly aged 65 years and older.
- **Gender:** No dosage adjustment is required for female patients as compared to male patients.
- **Smoking status:** No dosage adjustment is required for smokers (conferring to the metabolic pathway).

- **Dose adjustments due to interactions:** By using concomitantly aripiprazole with Strong CYP3A4 or CYP2D6 inhibitors, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased. By using concomitantly aripiprazole with strong CYP3A4 inducers, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose.

Paediatric population:

Schizophrenia in adolescents aged 15 years and older:

- **Schizophrenia:** initial recommended dose is 10 mg/day. Treatment should be initiated at 2 mg (using oral solution 1 mg/mL) for 2 days, titrated to 5 mg for two additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg. The effective in a dose range of 10 mg/day to 30 mg/day.
- Improved efficacy at doses higher than a daily dose of 10 mg has not been proved although individual patients may benefit from a higher dose.

Schizophrenia in patients below 15 years of age:

- **Schizophrenia:** Not recommended for use, the safety and efficacy have not been established.
- **Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older:** Suggested dose is 10 mg/day. Treatment should be initiated at 2 mg (using oral solution 1 mg/mL) for 2 days, titrated to 5 mg for two additional days to reach the recommended daily dose of 10 mg. The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been proved, and a daily dose of 30 mg is associated with a substantially higher incidence of significant adverse reactions including EPS related events, somnolence, fatigue and weight gain.
- Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring. Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, it not used in patients below 13 years of age.
- **Irritability associated with autistic disorder:** The safety and efficacy have not been established children and adolescents in (age below 18 years).
- **Tics associated with Tourette's disorder:** The safety and efficacy have not been established children and adolescents in (age of 6 to 18 years).

Route of administration: Oral, it can be administered on a once-a-day schedule without regard to meals or as directed by physician.

3. Contraindications

It is contraindicated in patients with a history of a known hypersensitivity reactions, pruritus/ urticaria to anaphylaxis.

4. Special warnings and precautions for use

During treatment with aripiprazole tablets, progress in the patient's clinical situation may take several days to some weeks. Patients should be closely monitored throughout this period.

Suicidality: The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder. Supervision of high-risk patients should accompany aripiprazole treatment.

Cardiovascular disorders: Orthostatic hypotension: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease adjust dose of aripiprazole accordingly.

QT prolongation: It should be used with caution in patients. Blood clots, as antipsychotics may be associated antipsychotic with formation of blood clots.

Tardive dyskinesia: If signs and symptoms of tardive dyskinesia appear in a patient on aripiprazole, dose reduction or discontinuation should be considered.

Other extrapyramidal symptoms: In paediatric, akathisia and parkinsonism observed. If signs and symptoms of appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex associated with antipsychotics.

Seizure: It should be use cautiously in patients with a history of seizures, involuntary, irregular muscle movements, especially in the face and when operating machinery.

Elderly patients with dementia-related psychosis: Increased mortality, cerebrovascular adverse reactions. It is not indicated for the treatment of patients with dementia-related psychosis.

Hyperglycemia and diabetes mellitus: Patients glucose level should be monitored regularly. Hypersensitivity reactions, characterized by allergic symptoms, may occur with aripiprazole.

Weight gain: Patient's body weight should be monitored regularly. Dysphagia: Oesophageal dysmotility and aspiration have been associated with the use of aripiprazole. It should be used cautiously in patients at risk for aspiration pneumonia.
Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole, it is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse control disorders might 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.
Patients with attention deficit hyperactivity disorder (ADHD) comorbidity: very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these medicinal products are co-administered.
Pregnancy: It should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.
Lactation: It is present in human breast milk, it should not be used in during in lactation, taking into account the importance of the drug to the mother.
Caution for use: Excipients known effect; it contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

5. Interaction with other medicinal products and other forms of interaction

Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents. Monitor blood pressure and adjust dose accordingly. When use of aripiprazole with alcohol or other CNS medicinal products with overlapping adverse reactions such as sedation (primary CNS effects). If concomitantly use of aripiprazole with medicinal products known to cause QT prolongation or electrolyte imbalance, caution should be used. Potential for other medicinal products to affect aripiprazole: A gastric acid blocker, the H2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect deemed not clinically relevant. Quinidine and other CYP2D6 inhibitors: (i.e. quinidine, fluoxetine and paroxetine) increased aripiprazole dose should be

reduced to approximately one-half of its prescribed dose. Ketoconazole and other CYP3A4 inhibitors: concomitant use of ketoconazole or other strong CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. The dose should be reduced to approx., one-half of its prescribed dose. Other strong inhibitors of CYP3A4, (itraconazole, HIV protease inhibitors) upon withdrawal of the CYP2D6 or CYP3A4 inhibitor, the dosage of aripiprazole should be increased to the level prior to the initiation of the concomitant therapy. Weak inhibitors of CYP3A4 (e.g. Diltiazem) or CYP2D6 (e.g. escitalopram) are used concomitantly with aripiprazole, modest increases in plasma aripiprazole concentrations may be expected. Carbamazepine and other CYP3A4 inducers: concomitant use of aripiprazole with CYP3A4 (e.g. carbamazepine, rifampin, phenytoin) by increasing the dosage of aripiprazole clinically recommended. Upon withdrawal of strong CYP3A4 inducers, the dosage of aripiprazole should be reduced to the recommended dose. Valproate and lithium: Use of valproate or lithium by concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations no dosage adjustment is required. Potential for aripiprazole to affect other medicinal products: 10 mg/day to 30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6, CYP2C9, CYP2C19, and CYP3A4, CYP1A2, concomitantly use of aripiprazole with either valproate, lithium or lamotrigine, there was no clinically important change in valproate, lithium or lamotrigine concentrations. Serotonin syndrome: Cases of serotonin syndrome reported in patients, such as selective serotonin reuptake inhibitor/selective serotonin noradrenaline reuptake inhibitor (SSRI/SNRI), or with medicinal products that are known to increase aripiprazole concentrations.

6. Pregnancy and Lactation

Pregnancy

Aripiprazole Tablets Should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

Lactation

Aripiprazole Tablets is present in human breast milk it should not be recommended in during in lactation, taking into account the importance of the drug to the mother.

7. **Effects on ability to Drive and use Machines**

Aripiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia

8. Undesirable effect

Common: Diabetes mellitus, insomnia, anxiety, restlessness, akathisia, extrapyramidal disorder tremor, headache, sedation, somnolence, dizziness, vision blurred, constipation, dyspepsia, nausea, salivary, hypersecretion, vomiting, fatigue.

Uncommon: Hyperprolactinaemia, hyperglycaemia, depression hypersexuality, tardive dyskinesia, dystonia, restless legs syndrome, diplopia, photophobia, tachycardia, orthostatic hypotension, hiccups.

Not known: Leukopenia, neutropenia, thrombocytopenia, allergic reaction, diabetic hyperosmolar coma, diabetic ketoacidosis, hyponatremia, anorexia, suicidal ideation and completed suicide, pathological gambling impulse-control disorder, binge eating, compulsive shopping, poriomania, aggression, agitation, nervousness, neuroleptic malignant syndrome, grand mal convulsion, serotonin syndrome, speech disorder, oculogyric crisis, torsades de pointes, ventricular arrhythmia, cardiac arrest, venous thromboembolism, hypertension, syncope, aspiration pneumonia, laryngospasm, oropharyngeal spasm, pancreatitis, dysphagia, diarrhoea, abdominal and stomach discomfort, hepatitis, jaundice, rash, photosensitivity reaction, alopecia, hyperhidrosis, drug reaction with eosinophilia and systemic symptoms (dress) rhabdomyolysis, myalgia, stiffness, urinary incontinence, drug withdrawal syndrome neonatal, priapism, hypothermia, pyrexia, chest pain, peripheral oedema, weight decreased, weight gain, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, alkaline phosphatase

increased, QT prolonged, glycosylated haemoglobin increased, blood glucose fluctuation, creatine phosphokinase increased.

9. **Overdose**

Symptoms and signs: side effect may occur vomiting, somnolence, and tremor, include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine, phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia with overdose consistent with for aripiprazole use.
Treatment: In the event of overdosage, no specific information is available on the treatment of overdose with aripiprazole,. If QT interval prolongation is present in electrocardiogram, cardiac monitoring should be instituted. Supportive measures and management of symptoms should be employed, maintaining an adequate airway, oxygenation and ventilation, close medical supervision and monitoring should continue until the patient recovers. Activated charcoal may be given if considered appropriate and hemodialysis, is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

Pharmacotherapeutic Group: Psycholeptics, other Antipsychotics
ATC Code: N05AX12
The antipsychotic action of aripiprazole exhibits high affinity for dopamine D2 and D3, serotonin 5-HT1A and 5-HT2A receptors though the exact mechanism not known. Moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, alpha1-adrenergic and histamine H1 receptors and moderate affinity for the serotonin reuptake site. Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors.

5.2 Pharmacokinetic Properties

Absorption: Aripiprazole tablets is well absorbed after oral administration with peak plasma concentrations occurring within 3-5 hours; the absolute oral bioavailability formulation is 87% can be administered with or without food.
Distribution: The aripiprazole tablets at in plasma and steady-state volume of distribution is high 4.9L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins primarily albumin.
Metabolism: It is the predominant drug moiety in the systemic circulation, metabolized primarily by three biotransformation pathways: dehydrogenation dehydroaripiprazole, the active metabolite, represents about 40% of aripiprazole AUC, hydroxylation, and N-dealkylation. CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4.
Excretion: Elimination of aripiprazole is mainly through hepatic metabolism involving CYP2D6 and CYP3A4 (P450) isozymes. The mean elimination half-lives 75 hours aripiprazole and 94 hours dehydro-aripiprazole, steady-state concentrations are achieved within 14 days of dosing for both active moieties, poor CYP2D6 metabolizers, mean elimination half-life of aripiprazole is 146 hours and these should be treated with half the normal dose. Single oral dose in the urine 1% and 18% feces, unchanged form respectively.

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects

were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 mg/kg/day to 60 mg/kg/day (3 to 10 times the mean steady-state AUC at the maximum recommended human dose) and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 7 times the human exposure at the recommended dose.

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 mg/kg/day to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m^2). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6 % of the bile concentrations found in the monkeys in the 39-week study and are well below (6 %) their limits of in vitro solubility.

In repeat-dose studies in juvenile rats and dogs, the toxicity profile of aripiprazole was comparable to that observed in adult animals, and there was no evidence of neurotoxicity or adverse reactions on development.

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose Monohydrate (Super Tab 11SD, Spray-dried) USP-NF (C)
Microcrystalline Cellulose (PH 102) BP
Colloidal Anhydrous Silica (Aerosil) BP
Hydroxy propyl cellulose (Klucel HXF) USP-NF
Maize starch BP
Colour Iron Oxide Red IHS
Magnesium Stearate BP

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Do not store above 30°C. Protect from light and moisture.

6.5 Nature and contents of container

1 x 10 Tablets in Alu-Alu blister pack.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder and Manufacturing Site Addresses

7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

7.2 Name and Address of Manufacturing Site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

8 Marketing Authorization Number

TAN 22 HM 0182

9 Date of First <Registration> / Renewal of The <Registration>

04th May, 2022

10 Date of Revision of the Text