SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Aripiprazole 5 mg tablets
ARIP MT 5

Aripiprazole 10 mg tablets
ARIP MT 10

Aripiprazole 15 mg tablets
ARIP MT 15

Aripiprazole 20 mg tablets
ARIP MT 20

2. Qualitative and quantitative composition

ARIP MT 5
Each tablet contains 5 mg of aripiprazole.

ARIP MT 10
Each tablet contains 10 mg of aripiprazole.

ARIP MT 15
Each tablet contains 15 mg of aripiprazole.

ARIP MT 20
Each tablet contains 20 mg of aripiprazole.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

ARIP MT 5
White to off-white, round, uncoated tablets, debossed with “5” on one side and “17” on the other side.

ARIP MT 10
White to off-white, round, uncoated tablets debossed with “10” on one side and “18” on the other side.

ARIP MT 15
White to off-white, round, uncoated tablets debossed with “15” on one side and “19” on the other side.

ARIP MT 20
White to off-white, round, uncoated tablets debossed with “20” on both sides.

4. Clinical particulars

4.1 Therapeutic indications

Aripiprazole is indicated for the treatment of acute episodes of schizophrenia and maintenance of clinical improvement during continuation therapy. Aripiprazole is also indicated for the treatment of acute manic episodes associated with Bipolar I Disorder.

4.2 Posology and method of administration

Posology

Schizophrenia
The recommended starting dose for aripiprazole is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. The maintenance dose for aripiprazole is 15 mg/day. Doses in the range of 10 to 30 mg/day have been established as effective in clinical trials.

Bipolar mania
The recommended starting and target dose for aripiprazole is 15 mg given once a day, without regard to meals. The dose can be increased to 30 mg/day based on clinical response. Dose adjustments, if indicated, should occur at intervals of not less than 24 hours. Antimanic efficacy (3-12 weeks) was demonstrated in doses of 15 or 30 mg/day in clinical trials. The safety of doses above 30 mg/day 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).

Paediatric
The safety and efficacy of aripiprazole 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.

<u>Dosage adjustment for patients taking aripiprazole concomitantly with potent CYP3A4 or CYP2D6 inhibitors:</u>
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.

Method of administration
Oral administration.

4.3 Contraindications
Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored throughout this period.

Suicidality
The occurrence of suicidal behaviors is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole. Close supervision of high-risk patients should accompany antipsychotic therapy.

Cardiovascular disorders
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, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant. Cases of venous thromboembolism (VTE) has 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 and during treatment with aripiprazole and preventive measures undertaken.

Conduction abnormalities
As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

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

deteriorate or can even arise after discontinuation of treatment.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including aripiprazole, must be discontinued.

Seizure
Aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Cerebrovascular adverse reactions
Aripiprazole is not indicated for the treatment of dementia-related psychosis.

Hyperglycaemia and diabetes mellitus
Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotic agents, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and a family history of diabetes.

Patients treated with any antipsychotic agents, including aripiprazole, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening glucose control.

Hypersensitivity
As with other medicinal products, hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole.

Weight gain
Weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed lifestyle, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma.

Dysphagia
Oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including aripiprazole. Aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling
Post-marketing reports of pathological gambling have been reported among patients prescribed aripiprazole, regardless of whether these patients had a prior history of gambling.

Patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully.

Patients with ADHD comorbidity
Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these drugs are co-administered.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Due to its α 1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as sedation.

If aripiprazole is administered concomitantly 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's rate of absorption but this effect is deemed not clinically relevant.

Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

Quinidine and other CYP2D6 inhibitors
Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

Ketoconazole and other CYP3A4 inhibitors
Concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to approximately one-half of its prescribed dose. Other potent inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors, may be expected to have similar effects and similar dose reductions should therefore be applied.

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of aripiprazole should be increased to the level before the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g., diltiazem or escitalopram) or CYP2D6 are used concomitantly with aripiprazole, modest increases in aripiprazole concentrations might be expected.

Carbamazepine and other CYP3A4 inducers
Aripiprazole dose should be doubled when concomitant administration of aripiprazole occurs with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon

discontinuation of potent CYP3A4 inducers, the dosage of aripiprazole should be reduced to the recommended dose.

Valproate and lithium
When either valproate or lithium was administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations.

Serotonin syndrome
Cases of serotonin syndrome have been reported in patients taking aripiprazole, and possible signs and symptoms for this condition can occur especially in cases of concomitant use with other serotonergic drugs, such as SSRI/SNRI, or drugs that are known to increase aripiprazole concentrations.

Potential for aripiprazole to affect other medicinal products
Aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (dextromethorphan). Additionally, aripiprazole and dehydroaripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Therefore, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, a causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit justifies the potential risk to the foetus.

Newborn infants exposed to antipsychotics (including aripiprazole) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborn infants should be monitored carefully.

Breastfeeding
Aripiprazole is excreted in human breast milk. Patients should be advised not to breastfeed if they are taking aripiprazole.

4.7 Effects on the ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely. Some paediatric patients with Bipolar I Disorder have an increased incidence of somnolence and fatigue.

4.8 Undesirable effects

The adverse reactions reported for aripiprazole are as follows: -

Endocrine disorders Uncommon: hyperprolactinaemia
Psychiatric disorders *Common:* restlessness, insomnia, anxiety *Uncommon:* depression*, hypersexuality
Nervous system disorders *Common:* extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache
Eye disorders *Common:* blurred vision *Uncommon:* diplopia
Cardiac disorders *Uncommon:* tachycardia*
Vascular disorders *Uncommon:* orthostatic hypotension*
Gastrointestinal disorders *Common:* dyspepsia, vomiting, nausea, constipation, salivary hypersecretion
General disorders and administration site conditions *Common:* fatigue

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on Google Play or Apple App Store.

4.9 Overdose

Accidental or intentional acute overdose of aripiprazole was identified in adult patients with reported estimated doses up to 1,260 mg with no fatalities. The potentially medically important signs and symptoms observed included lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting and diarrhoea. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence, transient loss of consciousness and extrapyramidal symptoms.

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple medicinal product involvement should be considered. Therefore, cardiovascular monitoring should be started 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 Cmax by about 41 % and AUC by about 51 %, suggesting that charcoal may be effective in the treatment of overdose.

Haemodialysis
Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacological classification: 13.2.3 Psychotherapeutic medicines: Antipsychotics.

Mechanism of action
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.

5.2 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.

Biotransformation
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 the 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 [14C]-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.

Pharmacokinetics in special patient groups

Pediatric population
The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weight.

Elderly
There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender
There are no differences in the pharmacokinetics of aripiprazole between healthy males and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking and Race
Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal and Hepatic impairment
The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

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.

6. Pharmaceutical particulars

6.1 List of excipients
Mannitol
Microcrystalline cellulose
Colloidal silicon dioxide
Hydroxypropyl cellulose
Crospovidone
Magnesium stearate
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of the container
The tablets are packed in Alu-Alu blister packs.

Pack size: 3 x 10 tablets.

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. APPLICANT
Torrent Pharmaceuticals Ltd
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Ahmedabad - 380 009
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8. MANUFACTURER
Torrent Pharmaceuticals Limited
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Indrand, Dst. Mehsana
Gujarat state
India

9. REGISTRATION DETAILS
ARIP MT 5
Zimbabwe registration number: 2023/13.2.3/6514
Zimbabwe category for distribution: Prescription Preparations (P.P.)

ARIP MT 10
Zimbabwe registration number: 2023/13.2.3/6515
Zimbabwe category for distribution: Prescription Preparations (P.P.)

ARIP MT 15
Zimbabwe registration number: 2023/13.2.3/6516
Zimbabwe category for distribution: Prescription Preparations (P.P.)

ARIP MT 20
Zimbabwe registration number: 2023/13.2.3/6517
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF TEXT
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