Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

SCHIZORAL-15
Aripiprazole Tablets USP 15 mg

2. Qualitative and quantitative composition

Each uncoated tablet contains aripiprazole USP 15 mg.
Excipient with known effect: this medicinal product contains lactose.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

4. Clinical particulars

4.1 Therapeutic indications

Apiprazole is indicated for the treatment of schizophrenia in adults and in adolescents aged 15byears and older
Apiprazole is indicated for the treatment of moderate to severe manic episodes in Bipolar 1 disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to ariprazole treatment.Ariprazole is 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

4.2 Posology and method of administration

Schizophrenia in adults
The recommended starting dose is 10 or 15 mg/day, with a maintenance dose of 15 mg/day administered once daily, without regard to meals. Aripiprazole is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than 15 mg daily has not been demonstrated, although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.
Manic episodes in Bipolar I Disorder
The recommended starting dose is 15 mg administered once daily, without regard to meals, as monotherapy or combination therapy. 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, therapy should be continued at the same dose. Adjustments of daily dosage, including dose reduction, should be considered on the basis of clinical status.
Schizophrenia in adolescents aged 15 years and older
The recommended dose is 10 mg/day administered once daily, without regard to meals. Treatment should be initiated at 2 mg (using

aripiprazole oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 additional days, to reach the recommended daily dose of 10 mg. Where appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg. Enhanced efficacy at doses higher than 10 mg daily has not been demonstrated, although individual patients may benefit from a higher dose. Aripiprazole is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy.

Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older

Treatment should be initiated at 2 mg (using aripiprazole oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 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 10 mg daily has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant adverse reactions including extrapyramidal events, somnolence, fatigue and weight gain (see section 4.8). 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; aripiprazole is therefore not recommended for use in patients below 13 years of age.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Cardiovascular

Aripiprazole should be used with caution in patients with known cardiovascular disease.

Venous thromboembolism

Cases of venous thromboembolism have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for venous thromboembolism, all possible risk factors should be identified before and during treatment and preventive measures undertaken.

QT prolongation

In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. Aripiprazole should be used with caution in patients with a family history of QT prolongation.

Concomitant use with stimulants

Despite the high frequency of comorbidity of Bipolar I Disorder and attention deficit hyperactivity disorder, very limited safety data are available on the concomitant use of aripiprazole and stimulants.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with the use of antipsychotics, including aripiprazole. Aripiprazole should be used cautiously in patients at risk of aspiration pneumonia.

Excipients

Aripiprazole tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Quinidine and other CYP2D6 inhibitors

The aripiprazole dose should be reduced to approximately one-half of the prescribed dose when concomitant administration with quinidine occurs. Other strong 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

In a clinical trial in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and Cmax by 63% and 37% respectively; the AUC and Cmax of dehydro-aripiprazole increased by 77% and 43% respectively. In CYP2D6 poor metabolisers, concomitant use of strong CYP3A4 inhibitors may result in higher plasma concentrations of aripiprazole than in CYP2D6 extensive metabolisers. When considering concomitant administration of ketoconazole or other strong CYP3A4 inhibitors, the potential benefits should outweigh the potential risks; where such administration occurs, the aripiprazole dose should be reduced to approximately one-half of the prescribed dose. Other strong 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 (see section 4.2). Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage should be increased to the level prior to initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g. diltiazem) or CYP2D6 (e.g. escitalopram) are used concomitantly, modest increases in plasma aripiprazole concentrations may be expected.

Carbamazepine and other CYP3A4 inducers

Following concomitant administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizoaffective disorder, the geometric means of Cmax and AUC for aripiprazole were 68% and 73% lower respectively than when aripiprazole was administered alone. The aripiprazole dose should be doubled when concomitant administration with carbamazepine occurs. Concomitant administration of aripiprazole with other 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 strong CYP3A4 inducers, the dosage should be reduced to the recommended dose.

4.6 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 (see section 5.3). Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment. 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 clearly 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 and feeding disorder. Newborn infants should consequently be monitored carefully.

Breast-feeding

Aripiprazole and its metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue or abstain from aripiprazole therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

[Not addressed in the submitted document. To be completed by the applicant.]

4.7 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, blurred vision and diplopia.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in placebo-controlled trials were akathisia and nausea, each occurring in more than 3% of patients treated with oral aripiprazole.

Tabulated list of adverse reactions

All adverse drug reactions are listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency of adverse reactions reported during post-marketing use cannot be determined, as they are derived from spontaneous reports; the frequency of these events is qualified as “not known”.

System Organ Class	Frequency	MedDRA terms
Blood and lymphatic system disorders	Not known	Leukopenia, neutropenia, thrombocytopenia
Immune system disorders	Not known	Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, allergic pruritus or urticaria)
Endocrine disorders	Uncommon	Diabetic hyperosmolar coma, diabetic ketoacidosis
Metabolism and nutrition disorders	Uncommon	Diabetes mellitus, hyperglycaemia
Psychiatric disorders	Common	Insomnia, anxiety, restlessness
	Uncommon	Depression, hypersexuality
Nervous system disorders	Common	Akathisia, extrapyramidal disorder, tremor, headache, sedation, somnolence, dizziness
	Uncommon	Tardive dyskinesia, dystonia
Eye disorders	Common	Vision blurred
	Uncommon	Diplopia, photophobia
Cardiac disorders	Uncommon	Tachycardia
Vascular disorders	Uncommon	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Hiccups
Gastrointestinal disorders	Common	Constipation, dyspepsia, nausea, salivary hypersecretion, vomiting
General disorders and administration site conditions	Common	Fatigue

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS): https://pv.pharmacyboardkenya.org

4.9 Overdose

Signs and symptoms

Deliberate or accidental overdose with aripiprazole alone has been reported at 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

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. Cardiovascular monitoring should therefore be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

Following any confirmed or suspected overdose, 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

ATC code: N05AX12.

Mechanism of action

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 and serotonin 5-HT1A and 5-HT2A receptors, and moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, 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.

Pharmacodynamic effects

Aripiprazole doses ranging from 0.5 to 30 mg administered once daily to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, to the caudate and putamen, detected by positron emission tomography.

5.2 Pharmacokinetic properties

Biotransformation

Aripiprazole is extensively metabolised by the liver, in part 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.

6. Pharmaceutical Particulars

6.1 List of Excipients

Starch
Microcrystalline cellulose
Povidone K-30
Croscarmellose sodium
Colloidal silicon dioxide
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

3 years.

6.4 Special Precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and Content of container

10 tablets packed in each Alu-PVC blister. One blister is packed in one carton, and 10 cartons are packed in one outer carton.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Hiral Labs Ltd
265, Sisona, Near Bhagwanpur, Roorkee, Uttarakhand – 247661, India.
Telephone: +91-9897890650 Email: Export@hirallabs.com Website: www.hirallabs.com

8. Marketing Authorization Number

H2022/CTD8775/18784

9. Date of first authorization/renewal of the authorization

2022 November 08

10. Date of revision of the text

2022 November 08