INDOCO REMEDIES LTD. Packaging Development Department

Item:	**Leaflet**
Item Code:	2008567
Open Size:	110 x 260 mm
Folding Size:	H:Unfolded: 260 mm Folded: 130 mm
	W:Unfolded: 110 mm Folded: 27.5 mm
GSM/ Paper:	40 gsm ITC Superfine paper
Colour:	Black
Pharmacode:	257 std
Layout No.:	9919934-002

Reason for Preparation/ Revision:
1) Text Change

Prepared by	Checked by	Approved by

Path: Y:\A\Arian\Arian 10\malaysia\Current 23\Arian 10 mg\Arian mg Leaflet 2008567.cdr **R1**

Date: 16.01.23/ 18.01.23

27.5 mm
5 mm
5 mm
5 mm
260 mm
16 mm
130 mm
260 mm
110 mm
110 mm

ARIAN 10 mg Tablets (Aripiprazole 10 mg Tablets USP)
ARIAN 15 mg Tablets (Aripiprazole 15 mg Tablets USP)
ARIAN 20 mg Tablets (Aripiprazole 20 mg Tablets USP)

DESCRIPTION AND COMPOSITION:
ARIAN 10 mg Tablets: White, uncoated, oval shaped bevelled edge tablets. Each uncoated tablet contains 10 mg of Aripiprazole USP.
ARIAN 15 mg Tablets: White, uncoated, round, biconvex, bevelled edge tablets. Each uncoated tablet contains 15 mg of Aripiprazole USP.
ARIAN 20 mg Tablets: White, uncoated, round, biconvex tablets. Each uncoated tablet contains 20 mg of Aripiprazole USP.

PHARMACODYNAMICS
Aripiprazole is a psychotropic drug intended for the treatment of schizophrenia and related manic disorders.
Aripiprazole exhibits high affinity for dopamine D2 and D3, serotonin 5.HT1A and 5.HT2A receptors, moderate affinity for dopamine D4, serotonin 5.HT2C and 5.HT7, alpha 1. adrenergic and histamine HI receptors and moderate affinity for the serotonin reuptake site. Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors.
The exact mechanism of action of aripiprazole is unknown. However, it has been proposed that the efficacy of aripiprazole is medicated through a combination of partial agonist activity at D2 and 5.HT1A receptors and antagonist activity at 5-HT2A receptors.

PHARMACOKINETICS
Aripiprazole is well absorbed after administration of the tablet, with peak plasma concentrations occurring within 3 hours to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. ARIAN tablets can be administered with or without food. At therapeutic concentrations, Aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 mg/day to 30 mg/day Aripiprazole for 14 days, there was dose-dependent D2 receptor occupancy indicating brain penetration of Aripiprazole in humans.
Aripiprazole is metabolized 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 drug moiety in the systemic circulation. At steady-state, dehydroaripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

INDICATION
ARIAN is indicated for the treatment of schizophrenia and for maintenance of clinical improvement. ARIAN is indicated for the treatment of acute maniac episodes associated with Bipolar 1 Disorder.

RECOMMENDED DOSE
Schizophrenia: 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.
Bipolar mania: Aripiprazole should be administered on a once-a-day schedule without regard to meals, generally starting at a dose of 15 to 30 mg/day. Dosage adjustments, if any, should occur at not before 24 hours interval. Antimanic efficacy (3-12 weeks) has been demonstrated in a dose ranging from 15 to 30 mg/day. The safety of doses above 30 mg 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 ARIAN 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.
Dosage adjustment for patients taking aripiprazole concomitantly with potent CYP3A4 or CYP2D6 inhibitors: 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.

ROUTE OF ADMINISTRATION
Oral

CONTRAINDICATION
Known hypersensitivity reaction to Aripiprazole tablets. Reactions have ranged from pruritus/ urticarial to anaphylaxis.

WARNING AND PRECAUTIONS
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.

Hyperglycemia and Diabetes Mellitus:
Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus. Given this confounder, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood.
However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia- related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.
Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS
General
Orthostatic Hypotension
Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α1-adrenergic 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
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 advance 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 judgement, 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.
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.
Pathological gambling and impulse-control problems
Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours.
It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, or other urges, while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases urges were reported to have stopped when the dose was reduced or the medication was discontinued. Patients who are at higher risk for impulse-control problems (e.g. personal or family history of obsessive-compulsive disorder, impulse-control disorder, bipolar disorder, impulsive personality, alcoholism, drug abuse or other addictive behaviours) would require closer monitoring for new or worsening of uncontrollable urges. Impulse-control problems may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole.

INTERACTION WITH OTHER MEDICAMENTS
Drug Interaction:
Due to its alpha-adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.
Potential for other drugs to affect Arian:
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.
As with most psychoactive medications, patients should be advised to avoid alcohol while taking Arian.

PREGNANCY AND LACTATION
It is not indicated in pregnancy and in lactating mothers since its safety is not established in this population.
Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation.
ARIAN should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

SIDE EFFECTS
Psychiatric disorders – insomnia, restlessness
Nervous System disorders – headache, dizziness, akathisia, somnolence / sedation, tremor, Restless leg syndrome.
Eye disorders – blurred vision
Cardiac disorders – tachycardia
Vascular disorders – orthostatic hypotension
Gastrointestinal disorders – nausea, vomiting, constipation, dyspepsia
General disorders and administration site conditions – asthenia / fatigue
Digestive system disorder – Weight gain, Increased appetite
Musculoskeletal System Disorder – Dystonia.

Others
Undesirable effects known to be associated with antipsychotic therapy and also reported during treatment with aripiprazole include neuroleptic malignant syndrome, tardive dyskinesia, seizure, cerebrovascular adverse events and increased mortality in elderly demented patients, hyperglycaemia and diabetes mellitus.
The following adverse events have also been reported very rarely:
Immune system disorders – allergic reaction (e.g., anaphylactic reaction, angioedema, pruritis or urticaria)
Psychiatric disorders – nervousness, agitation
Nervous System Disorders – speech disorder
Vascular disorders – syncope
Gastrointestinal disorders – increased salivation, pancreatitis
Musculoskeletal, connective tissue and bone disorders – stiffness, myalgia, rhabdomyolysis, Cogwheel rigidity, rigidity of limbs.
Reproductive system and breast disorders – priapism
General disorders and administration site conditions – chest pain, temperature regulation disorder (e.g., hypothermia, pyrexia)
Investigations – increased creatine phosphokinase, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased gamma glutamyl transferase (GGT)
Psychiatric Disorders – Pathological gambling, hypersexuality, impulse-control problems (See warning and precautions).
Respiratory, Thoracic and Mediastinal Disorders:
Sleep apnoea*
*Atypical antipsychotic drugs, such as, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, ARIAN should be prescribed with caution.

Renal and Urinary Disorders: Urinary retention

SYMPTOMS AND TREATMENT OF OVERDOSE
Accidental or intentional acute overdosage of aripiprazole alone was identified in patients with estimated doses up to 1260mg with no fatalities.
The potentially medically important signs and symptoms observed included lethargy, blood pressure increased, somnolence, tachycardia and vomiting. In addition, accidental overdose with aripiprazole alone (up to 210mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms include somnolence and transient loss of consciousness.
Overdose Management: Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple drug involvement should be considered. Therefore, cardiovascular monitoring should commence 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, suggesting that charcoal may be effective for overdose management. 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 not eliminated unchanged by the kidneys and is highly bound to plasma proteins.
Effect on Ability to Drive and Use Machine:
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, and diplopia.

STORAGE CONDITION: Do not store above 30°C.

SHELF LIFE
Arian 10 mg, 15 mg & 20 mg Tablets: 36 months

PRESENTATION
For Arian 10 mg, 15 mg & 20 mg Tablets:
I) 10 blisters of 10 tablets each are packed in a printed carton along with a package insert.
II) 3 blisters of 10 tablets each are packed in a printed carton along with a package insert.

MAL NO.: MAL15095025AZ
MAL NO.: MAL15095024AZ
MAL NO.: MAL15105033AZ

MANUFACTURED BY:
INDOCO REMEDIES LIMITED
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PRODUCT REGISTRATION HOLDER:
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