Arian 10 mg Tablets (Aripiprazole 10 mg Tablets)

Arian 15 mg Tablets (Aripiprazole 15 mg Tablets)

Arian 20 mg Tablets (Aripiprazole 20 mg Tablets)

DESCRIPTION AND COMPOSITION:

Arian 10 mg Tablets:

White, uncoated, oval shaped beveled edged tablets. Each uncoated tablet contains 10 mg of Aripiprazole.

Arian 15 mg Tablets:

White, uncoated, round, biconvex, beveled edged tablets. Each uncoated tablet contains 15 mg of Aripiprazole.

Arian 20 mg Tablets:

White, uncoated, round, biconvex tablets.

Each uncoated tablet contains 20 mg Aripiprazole.

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 biotrasformation 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 catalyzed 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 maintainence 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).

Pediatric

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 confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood.

However, epidemiological studies suggests 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 Hypotensions

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.

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.

SIDE EFFECTS

Psychiatric disorders – insomnia, restlessness

Nervous System disorders – headache, dizziness, akathisia, somnolence / sedation, tremor

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

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

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)

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.

STORAGE CONDITION

Store below 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.

MANUFACTURED BY:

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