10844

1. NAME OF THE MEDICINAL PRODUCT

ARILIFT 10 mg tablets
ARILIFT 15 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARILIFT 10 mg tablets
Each Uncoated Tablet contains:
Aripiprazole 10 mg
Excipients q.s.

ARILIFT 15 mg tablets
Each Uncoated Tablet contains:
Aripiprazole 15 mg
Excipients q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

ARILIFT 10 mg tablets
Pink color, modified rectangular shaped, uncoated mottled tablets debossed with '252' on one side and plain on other side.

ARILIFT 15 mg tablets
Yellow color, round shaped, beveled edge, uncoated mottled tablets debossed with'253' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

I. For the treatment of acute episodes of schizophrenia and for maintenance of clinical improvement during continuation therapy
II. For the treatment of acute manic episodes associated with Bipolar I Disorder.

4.2 Posology and method of administration

Mode of administration
Oral

Instructions for Use
May be taken with or without food.

Posology

Adults

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 15mg/day. Doses in the range of 10 to 30 mg/day have been established as effective.

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. Anti-manic efficacy (3-12 weeks) was demonstrated in doses of 15 or 30 mg/day. The safety of doses above 30 mg/day has not been evaluated.

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 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 CYP3A4

- 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed below.

Lactose monohydrate (Flowlac 100)
Microcrystalline cellulose (Avicel PH 102)
Hydroxy propyl cellulose (Klucel EXF)
Maize Starch
Crospovidone (Polyplasdone XL)
Colloidal silicon dioxide (Aerosil 200)
Magnesium stearate
Pigment Blend PB-24880 Pink (Lactose monohydrate & Iron oxide Red)
Pigment Blend PB-52290 Yellow (Iron oxide Yellow & Lactose monohydrate)

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) have 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 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 in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-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 hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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 co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, 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 and other impulse control disorders

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.

Lactose

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

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

Due to its α1-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 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 ketoconozole 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 prior to 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.

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 dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism in vitro. Thus, 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.

400 mm
150 mm
Front Side

Product: Arilift Tablets
Size : 150 x 400 mm (Packinsert)
Color : Black
Date : 07-03-2025

Note: Actual pharma code number is for reference & should not be printed.

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 with drugs that are known to increase aripiprazole concentrations.

Other medicines not listed above maly also interact with Aripiprazole Tablets.

4.6 Fertility, pregnancy and lactation

Pregnancy
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole.
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.
ARILIFT should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation
Aripiprazole is excreted in human breast milk. Patients should be advised not to breast feed if they are taking Aripiprazole.

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, diplopia.

4.8 Adverse(Side) Effects / Undesirable effects

The most commonly reported adverse reactions (ADRs) are akathisia and nausea in patients treated with oral aripiprazole.

Following adverse(side) effects are associated with Aripiprazole Tablets though not everybody gets them.

- *Neuroleptic malignant syndrome (NMS):*
  High fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure. These may be symptoms of a rare and serious condition that can lead to death.
- *Increased risk of death in elderly patients with dementia-related psychosis:*
  Elderly patients with dementia- related psychosis treated with antipsychotic drugs are at an increased risk of death. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.
- *High blood sugar (hyperglycemia):* Increases in blood sugar can happen in some people who take Aripiprazole Tablet. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start Aripiprazole Tablet and during therapy.
- *Difficulty swallowing:*
  It may lead to aspiration and choking.
- *Tardive dyskinesia:*
  Patient cannot control in your face, tongue, or other body parts. These may be signs of a serious condition. Tardive dyskinesia may not go away, even if you stop taking *Aripiprazole* Tablet. Tardive dyskinesia may also start after you stop taking *Aripiprazole* Tablet.
- *Orthostatic hypotension (decreased blood pressure):*
  Light-headedness or fainting when rising too quickly from a sitting or lying position.
- Nausea, vomiting, constipation, headache, insomnia (inability to fall asleep), dizziness, restlessness, inflammation of the pancreas.
- Chest pain, sudden increase in body temperature, sweating, fast heartbeat, muscle stiffness, seizures (convulsions).
- Allergic reaction (rash, itching or hives on the skin; shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue, throat or other parts of the body).
- Increases in blood sugar level and/or symptoms of high blood sugar (e.g. increased thirst, increased hunger and frequent urination).
- Unpleasant leg sensations and an intense urge to move the legs (restless legs syndrome).
- Trouble breathing during sleep (sleep apnoea).
- Difficulty or inability to pass urine (urinary retention)
- Excessive gambling or other unusual urges, such as increased sexual urges, binge or compulsive eating and compulsive shopping. If you or your family members notice that you are having unusual urges or behaviors, talk to your doctor or pharmacist.

- Please note the following specific labelling requirement as per DRGD as below:

Psychiatric Disorders
Pathological gambling, hypersexuality, impulse-control problems (See Section Warnings and Precautions).
Nervous System Disorders
Restless legs syndrome
Respiratory, Thoracic and Mediastinal Disorders
Sleep apnoea*
*Atypical antipsychotic drugs, such as aripiprazole, 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, ARILIFT should be prescribed with caution.
Renal and Urinary Disorder:
Urinary retention

4.9 Overdose
- Accidental or intentional acute overdose of aripiprazole alone was identified in adult patients with reported estimated doses up to 1260 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 and AUC, suggesting that charcoal may be effective in the treatment of overdose.
- 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

Pharmacotherapeutic group: Psycholeptics, other antipsychotics,

ATC code: N05AX12

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 D_2 and serotonin 5-HT_{1A} receptors and antagonism of serotonin 5-HT_{2A} 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 D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic and histamine H_1 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 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 [^{14}C]-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

Paediatric population
The pharmacokinetics of Aripiprazole and dehydro-Aripiprazole in paediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

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 male 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 effects from smoking on 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (Flowlac 100)
Microcrystalline cellulose (Avicel PH 102)
Hydroxy propyl cellulose (Klucel EXF)
Maize Starch
Crospovidone (Polyplasdone XL)
Colloidal silicon dioxide (Aerosil 200)
Magnesium stearate
Pigment Blend PB-24880 Pink (Lactose monohydrate & Iron oxide Red) (for 10mg strength)
Pigment Blend PB-52290 Yellow (Iron oxide Yellow & Lactose monohydrate) (for 15mg strength)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C. Store in the original package.

6.5 Dosage form and packaging available

Blisters of Aluminium foil and cold form blister foil.
Such 3 blisters are in a carton. (i.e. A carton of 3 x 10 tablets).

6.6 Special precautions for disposal

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

7. Product Registration Holder in MY:

GENPHARMA SDN. BHD.
Lot 5016, Jalan Teratai,
5 ½ Mile Off Jalan Meru,
41050 Klang, Selangor, Malaysia.

Manufactured by:
Alembic Pharmaceuticals Limited (Formulation Division)
Panelav, P.O. – Tajpura,
Taluka – Halol, District – Panchmahal,
Gujarat 389350,
India.

8. DATE OF REVISION OF THE TEXT

20/04/2020

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Back Side