1. NAME OF THE MEDICINAL PRODUCT

ARIPIPEPRAZOLE MOUTH DISSOLVING TABLETS (AQUED)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EACH UN-COATED MOUTH DISSOLVING TABLET CONTAINS:

ARIPIPRAZOLE USP ……..……10 MG.

EXCIPIENTS ……Q.S.

COLOUR : TARTRAZINE YELLOW

Sr. No	*Ingredients*	Specification	Std.Quantity / Tablet (mg)	Reason for Inclusion
1.	Aripiprazole (A)	USP	10.00	Antipsychotic
2.	Lactose	BP	48.00	Diluent
3.	Mannitol	BP	48.00	Diluent
4.	Colour Tartrazine Yellow Supra	IHS	0.30	Colouring Agent
BINDING				
5.	Maize Starch	BP	2.80	Binder
6.	Purified Water	BP	Q.S.	Vehicle
LUBRICATION				
6.	Magnesium Stearate	BP	1.20	Lubricant
7.	Purified Talc	BP	1.20	Lubricant
8.	Sodium starch Glycolate	BP	2.40	Lubricant
9.	Microcrystalline Cellulose Powder	BP	12.50	Lubricant
10.	Croscarmellose Sodium	BP	2.40	Disintegrant
11.	Aspartame	BP	1.20	Sweetening agent
Theoretical Avg. Weight (Core)			**130.00**	

- (A) = Quantity to be calculated on the basis of its potency

3. PHARMACEUTICAL FORM

Dosage Form: **Oral Tablet**
Visual & Physical characteristics of the product: **Yellow coloured, Round shaped, Biconvex, Un-coated Tablet.**

4. Clinical particulars

4.1 Therapeutic indications

Aripiprazole is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.

4.2 Posology and method of administration

Adults

Schizophrenia: the recommended starting dose for Aripiprazole is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals.

Aripiprazole is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Special populations

Paediatric population

Schizophrenia in adolescents aged 15 years and older: the recommended dose for Aripiprazole is 10 mg/day administered on a once-a-day schedule 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. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg.

Aripiprazole is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg 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

Irritability associated with autistic disorder: the safety and efficacy of Aripiprazole in children and adolescents aged below 18 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Tics associated with Tourette's disorder: the safety and efficacy of Aripiprazole in children and adolescents 6 to 18 years of age have not yet been established.

Hepatic impairment

No dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment.

Renal impairment

No dosage adjustment is required in patients with renal impairment.

Elderly

The effectiveness of Aripiprazole in the treatment of schizophrenia and other psychiatric disorder in patients aged 65 years and older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant

Smoking status

According to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers.

Dose adjustments due to interactions

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose.

Method of administration

Aripiprazole tablet is for oral use.

4.3 Contraindications:

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

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 behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with aripiprazole. Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among adult patients with schizophrenia or other psychiatric disorder.

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.

QT prolongation

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

Other extrapyramidal symptoms

In paediatric clinical trials of aripiprazole akathisia and parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

Seizure

In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole.

Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

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.

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, 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 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, or feeding disorder. Consequently, newborn infants should be monitored carefully.

Breast-feeding

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:

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 other psychiatric disorder have an increased incidence of somnolence and fatigue

4.8 Undesirable effects:

Description of selected adverse reactions

Extrapyramidal symptoms (EPS)

Schizophrenia: in a long term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8%) of EPS including parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3%).

Other indication - in a 12-week controlled trial, the incidence of EPS was 23.5% for aripiprazole-treated patients and 53.3% for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6% for patients treated with aripiprazole and 17.6% for those treated with lithium.
Akathisia

In placebo-controlled trials, the incidence of akathisia in other psychiatric patients was 12.1% with aripiprazole and 3.2% with placebo. In schizophrenia patients the incidence of akathisia was 6.2% with aripiprazole and 3.0% with placebo.

Paediatric population

Schizophrenia in adolescents aged 15 years and older

In a short-term placebo-controlled clinical trial involving 302 adolescents (13-17 years) with schizophrenia, the frequency and type of undesirable effects were similar to those in adults except for the following reactions that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo):

somnolence/sedation and extrapyramidal disorder were reported very commonly (≥ 1/10), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly (≥ 1/100, < 1/10).

The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

4.9 Overdose:
Signs and symptoms

In clinical trials and post-marketing experience, accidental or intentional acute overdose of aripiprazole alone 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

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:

It has been proposed that aripiprazole's efficacy in schizophrenia 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.

Aripiprazole doses ranging from 0.5 to 30 mg administered once a day 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.

Schizophrenia

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

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.

Distribution

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 l/kg, indicating extensive extravascular distribution.

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, Easy coat SR Powder, Maize Starch, , Microcrystalline Cellulose, Povidone, Purified Water, Magnesium Stearate, Purified Talc, Filmcoated Titanium dioxide, Colour Lake Tartrazine yellow, Iso Propyl Alcohol, Methylene Di Chloride, Diethylphalate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C, Protect from light.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Alu-alu Blister Pack

6.6 Special precautions for disposal and other handling

No special instructions needed

7 APPLICANT/MANUFACTURER

Name of the manufacturer	:	**Zenith HealthCare Ltd.**
Production site address	:	388/34, Changodar Industrial Estate, Sarkhej-Bawla Highway, Changodar-382213 **Email id:** info@zenithhealthcare.com mahendrazenith@hotmail.com **Phone No.**: +91-99-79-503977 + 91-92-28-020010

8. Manufacturer:

Name of the manufacturer	:	**Zenith HealthCare Ltd.**
Production site address	:	388/34, Changodar Industrial Estate, Sarkhej-Bawla Highway, Changodar-382213 **Email id:** info@zenithhealthcare.com mahendrazenith@hotmail.com **Phone No.**: +91-99-79-503977 + 91-92-28-020010

9. Date of revision of the text

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10. Dosimetry (If Applicable):

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11. Instructions for Preparation Of Radiopharmaceuticals (If Applicable):

Not Applicable