**PROPOSED PROFESSIONAL INFORMATION FOR**

**APRIZON TABLETS**

## SCHEDULING STATUS

S5

## 1. NAME OF THE MEDICINE

APRIZON 5 Tablets

APRIZON 10 Tablets

APRIZON 15 Tablets

APRIZON 30 Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

APRIZON 5 tablets contain 5 mg aripiprazole.

APRIZON 10 tablets contain 10 mg aripiprazole.

APRIZON 15 tablets contain 15 mg aripiprazole.

APRIZON 30 tablets contain 30 mg aripiprazole.

Contains sugar: maltose

For the full list of excipients, see **section 6.1**.

## 3. PHARMACEUTICAL FORM

APRIZON 5: Blue, round, biconvex tablets, marked with “5” on one side.

APRIZON 10: Pink, round, biconvex tablets, marked with “10” on one side.

APRIZON 15: Yellow, round, biconvex tablets, marked with “15” on one side.

APRIZON 30: Pink, oval, biconvex tablets, marked with “30” on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Schizophrenia:*

APRIZON is indicated for the treatment of schizophrenia and for the maintenance of clinical improvement in adults.

*Bipolar Mania:*

APRIZON is indicated for the treatment of acute manic episodes associated with Bipolar I Disorder and for the prevention of recurrence of new manic episodes in patients who experienced predominantly manic episodes and who responded to APRIZON treatment.

### 4.2 Posology and method of administration

*Schizophrenia:*

The recommended initial dose of APRIZON is 10 mg or 15 mg daily with a maintenance dose of 15 mg per day, administered once daily without regard to meals. APRIZON is effective in a dose range of 10 mg to 30 mg daily. Doses higher than the recommended daily dose of 15 mg have not demonstrated enhanced efficacy, although some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

*Bipolar Mania:*

The recommended initial dose of APRIZON is 15 mg administered once daily, without regard to meals, as monotherapy or combination therapy (see “INTERACTIONS”). 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:*

In order to prevent recurrence of manic episodes in patients who have been receiving aripiprazole, therapy should be continued with the same dose of APRIZON. Dose adjustments, including dose reduction, should be based on clinical status. The use of aripiprazole monotherapy in the prevention of depressive episodes has not been established. Clinically appropriate supplemental therapy should be considered for the prevention or treatment of depressive episodes

*Concomitant Medications:*

Dose adjustments for patients taking APRIZON concomitantly with potent CYP3A4 or CYP2D6 inhibitors:

When APRIZON is co-administered with a potent CYP3A4 or CYP2D6 inhibitor, the APRIZON dose should be reduced to half of the usual dose. When co-administration of the CYP3A4 or CYP2D6 inhibitor is ceased, the APRIZON dose should be increased.

Dose adjustments for patients taking APRIZON concomitantly with potent CYP3A4 inducers:

When APRIZON is co-administered with a potent CYP3A4 inducer, the APRIZON dose should be doubled. Additional increases in the dose of APRIZON should be based on clinical evaluation. When co-administration of the CYP3A4 inducer is ceased, the APRIZON dose should be reduced.

***Paediatric population***

The safety and efficacy of APRIZON in patients under 18 years of age have

not been established.

## 4.3 Contraindications

APRIZON is contraindicated in patients who are hypersensitive to aripiprazole or any of the excipients.

APRIZON is not indicated for the treatment of dementia – related psychosis in the elderly (see section 4.4)

### 4.4 Special warnings and precautions for use

Patients should be monitored closely during antipsychotic treatment, as an improvement in the patient's clinical condition may take several days to weeks

*Suicide:*

High-risk patients being treated with APRIZON should be closely supervised, as the possibility of a suicide attempt is inherent in psychotic illnesses. In order to reduce the risk of overdose, APRIZON prescriptions should be written for the smallest quantity of tablets consistent with good patient management.

*Tardive Dyskinesia:*

Since the risk of tardive dyskinesia increases with long-term exposure to antipsychotic treatment, a dose reduction or medicine discontinuation should be considered if a patient treated with APRIZON presents with signs and symptoms of tardive dyskinesia. After discontinuation of this treatment, these symptoms can temporally deteriorate or even arise.

*Neuroleptic Malignant Syndrome (NMS):*

NMS, a potentially fatal symptom complex, has been reported in patients

taking aripiprazole. The following clinical manifestations of NMS has been reported: 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. All antipsychotic medicines, including APRIZON must be discontinued if a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS.

*Body Temperature Regulation:*

Antipsychotic medicines may affect the body's ability to reduce core body temperature. Care should be taken when treating patients with APRIZON who will be exposed to conditions which may contribute to an elevation in core body temperature, e.g. strenuous exercise, extreme heat exposure, concomitant use of anticholinergic medicine or dehydration.

*Seizure:*

Patients who have a history of seizure disorder or have conditions associated with seizures, should use APRIZON with caution.

*Orthostatic hypotension:*

APRIZON may be associated with orthostatic hypotension, which may possibly be attributed to its $\alpha_1$-adrenergic receptor antagonism. During pre-marketing clinical trials with aripiprazole, symptomatic orthostatic hypotension occurred in 1,3 % of the aripiprazole-treated patients.

Patients with known cardiovascular disease (a history of myocardial infarction or ischaemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions predisposing patients to hypotension (dehydration, hypovolaemia) and treatment with antihypertensive medicines should use APRIZON with caution.

*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.

*Elderly patients with Dementia-related psychosis:*

*Increased mortality:*

There is an increased risk of death in elderly patients with dementia-related psychosis when treated with aripiprazole, compared to the placebo. Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g. heart failure, sudden death) or infection (e.g. pneumonia) related.

*Cerebrovascular adverse events:*

Cerebrovascular adverse events (e.g. stroke, transient ischaemic attack), including fatalities, were reported in three placebo-controlled trials of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease.

APRIZON is not approved for the treatment of patients with 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 APRIZON.

Patients with an established diagnosis of diabetes mellitus who are started on APRIZON 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 APRIZON should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with APRIZON should undergo fasting blood glucose testing.

In some cases, hyperglycaemia has resolved when APRIZON was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

*Dysphagia:*

Antipsychotic medicine use has been associated with aspiration and oesophageal dysmotility. Patients at risk of aspiration pneumonia should use APRIZON and other antipsychotic medicines with caution.

*Laboratory Findings:*

Routine laboratory parameters did not present with medically important differences

in patients treated with aripiprazole or placebo.

*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 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. Aripiprazole has not been shown to induce clinically relevant weight gain in adults. In adolescent with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered.

*Mental function:*

Cases of the following impulse-control problems associated with aripiprazole have been reported:

- Pathological gambling
- Compulsive sexual behaviour
- Compulsive buying
- Compulsive eating

- Multiple impulse-control problems

Symptoms were resolved on withdrawal or dose reduction of aripiprazole.

*Other extrapyramidal symptoms:*

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

APRIZON contains the sugar maltose and may affect the glycaemic index. Caution is advised in diabetic patients and those with maltose intolerance or congenital sucrase-isomaltase deficiency.

**4.5 Interaction with other medicines and other forms of interaction**

*Medicine Interactions and other forms of Interactions:*

*General:*

Caution should be exercised when APRIZON is co-administered with other centrally acting medicines, owing to its primary CNS effects. Patients treated with APRIZON should not consumption any alcohol. APRIZON may potentiate the effects of certain antihypertensive medicines, due to its α1-adrenergic receptor antagonist activity.

The pharmacokinetics of aripiprazole are not affected by a high fat meal.

Caution should be exercised when APRIZON is co-administered with medicines which prolong the QT interval or medicines which cause electrolyte imbalance.

*Valproate:*

The Cmax and AUC of aripiprazole were decreased by 25 %, following co-administration of valproate (500 – 1500 mg/day) and aripiprazole (30 mg/day) at steady-state. Co-administration of APRIZON with valproate does not require a dosage adjustment.

*Lithium:*

A pharmacokinetic interaction of APRIZON with lithium is unlikely, owing to the fact that lithium does not bind to plasma proteins, is not metabolised and is almost entirely excreted unchanged in the urine.

The co-administration of therapeutic doses of lithium (1200 – 1800 mg/day) and aripiprazole (30 mg/day) over a period of 21 days did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (Cmax and AUC increased by less than 20 %). Co-administration of APRIZON with lithium does not require a dosage adjustment.

*Effect of other medicines on APRIZON:*

The H2 antagonist, famotidine, does not have a clinically significant effect on the pharmacokinetics of aripiprazole

Since APRIZON is metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A4, but not CYP1A, no dosage adjustment is required for smoking.

During a clinical study with healthy subjects, a potent inhibitor of CYP2D6 (quinidine) resulted in a 107 % increase in aripiprazole AUC, whilst the Cmax remained unchanged. Decreases of 32 % and 47 % were observed for AUC and Cmax respectively for dehydro-aripiprazole, the active metabolite of aripiprazole. Similar effects may be expected when APRIZON is co-administered with other potent inhibitors of CYP2D6 (e.g. fluoxetine, paroxetine).
When concomitant administration of APRIZON with quinidine or other potent inhibitors of CYP2D6 is required, the APRIZON dose should be reduced to half the prescribed dose.

During a clinical study involving healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and Cmax by 63 % and 37 % respectively. There were 77 % and 43 % increases in the AUC and Cmax respectively of dehydro-aripiprazole.

The concomitant use of potent inhibitors of CYP3A4 in CYP2D6 poor metabolisers may result in higher plasma concentrations of aripiprazole compared to CYP2D6 extensive metabolisers. Similar effects may be expected when APRIZON is co-administered with other potent inhibitors of CYP3A4 (e.g. itraconazole, HIV protease inhibitors).

The dose of APRIZON should be reduced to half its prescribed dose when co-administered with ketoconazole or other potent inhibitors of CYP3A4. The APRIZON dose should be increased to that used prior to the initiation of concomitant therapy when the use of ketoconazole, the CYP2D6 inhibitor or the 3A4 inhibitor are discontinued.

After the concomitant administration of carbamazepine, a potent inducer of CYP3A4, geometric means of Cmax and steady-state AUC were reduced by 68 % and 73 % respectively, compared to aripiprazole (30 mg) alone. A similar observation was made for the active metabolite of aripiprazole, dehydro-aripiprazole, whereby the geometric means of Cmax and steady-state AUC were reduced by 69 % and 71 % respectively, following co-administration with carbamazepine, as compared to aripiprazole alone. Similar effects may be expected when APRIZON is co-administered with other potent inducers of CYP3A4 (e.g. rifampicin, rifabutin, phenytoin, phenobarbitone, primidone, efavirenz, nevirapine, St.John's Wort).

The dose of APRIZON should be doubled when it is co-administered with carbamazepine or potent inducers of CYP3A4. The APRIZON dose should be increased to that used prior to the initiation of concomitant therapy when the use of carbamazepine or the potent inducers of CYP3A4 are discontinued. When APRIZON is co-administered with a combination of potent, moderate or weak inhibitors of inhibitors of CYP2D6 and CYP3A4, the APRIZON dose should be reduced to a quarter of the usual dose.

*Medicine Interactions:*

It was established in clinical studies that aripiprazole doses of 10 - 30 mg/day had no significant effects on the metabolism of substrates of CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole) and CYP3A4 (dextromethorphan). Additionally, in vitro studies demonstrated that aripiprazole and its active metabolite, dehydro-aripiprazole, presented with no potential to alter CYP1A2-mediated metabolism. APRIZON is therefore unlikely to cause clinically important medicine interactions mediated by these enzymes.

**4.6 Fertility, pregnancy and lactation**

The safety APRIZON of during pregnancy and lactation has not been established.

Newborn infants exposed to antipsychotics (including APRIZON) 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:*

Patients should be advised not to breast-feed if they are taking APRIZON as APRIZON is excreted in human milk.

**4.7 Effects on the ability to drive and use machines**

Caution should be taken when patients are operating hazardous machinery, including motor vehicles, making reasonably certain that APRIZON does not

adversely affect their ability operate these machines or vehicles.

**4.8 Undesirable effects**

**Psychiatric disorders:**

*Frequent:* Insomnia, restlessness.

**Nervous system disorders:**

*Frequent:* Akathisia, dizziness, extrapyramidal disorder, headache, somnolence / sedation, tremor.

*Less frequent:* Neuroleptic malignant syndrome, tardive dyskinesia, seizures.

**Eye disorders:**

*Frequent:* Blurred vision.

**Cardiac disorders:**

*Frequent:* Tachycardia.

**Vascular disorders:**

*Frequent:* Orthostatic hypotension.

**Gastrointestinal disorders:**

*Frequent:* Constipation, dyspepsia, nausea, vomiting, salivary hypersecretion, stomach discomfort

**Musculoskeletal, connective tissue and bone disorders:**

*Frequent:* Musculoskeletal stiffness

**General disorders and administration site conditions:**

*Frequent:* Asthenia/fatigue

*Less frequent:* Peripheral oedema

***The following post-marketing adverse events have been reported for aripiprazole:***

**Blood and the lymphatic system disorders:**

Agranulocytosis, leukopaenia, neutropaenia, thrombocytopaenia.

**Immune system disorders:**

Allergic reaction (e.g. anaphylactic reaction, angioedema, pruritus or urticaria, rash, laryngospasm).

**Endocrine disorders:**

Diabetic hyperosmolar coma, diabetic ketoacidosis (DKA), diabetes mellitus, hyperglycaemia.

**Metabolism and nutrition disorders:**

Anorexia, hyponatraemia.

**Psychiatric disorders:**

Anxiety.

Agitation, pathological gambling.

Completed suicide, suicide attempt, suicidal ideation.

**Nervous system disorders:**

Dizziness, drowsiness, headache, insomnia.

Akathisia, extrapyramidal disorder, grand mal convulsion, neuroleptic malignant syndrome, speech disorder, seizures, tardive dyskinesia.

**Cardiac disorders:**

Bradycardia, cardiac arrest, QT prolongation, sudden unexplained death, , torsade de pointes, ventricular arrhythmias.

**Vascular disorders:**

Hypertension, orthostatic hypertension, syncope.

**Respiratory, thoracic and mediastinal disorders:**

Aspiration pneumonia.

**Gastrointestinal disorders:**

Constipation, dyspepsia, nausea, vomiting.

Diarrhoea, dysphagia, pancreatitis.

**Hepatobiliary disorders:**

Hepatitis, jaundice.

**Skin and subcutaneous tissue disorders:**

Hyperhidrosis.

**Musculoskeletal, connective tissue and bone disorders:**

Musculoskeletal stiffness, myalgia, rhabdomyolysis.

**Renal and urinary disorders:**

Urinary incontinence, urinary retention.

**Reproductive system and breast disorders:**

Priapism.

**General disorders and administrative site conditions:**

Chest pain, temperature regulation disorder (e.g. hypothermia, pyrexia).

**Investigations:**

Blood glucose fluctuation, blood glucose increased, glycosylated haemoglobin increased, increased alanine aminotransferase [or increased ALT or increased SGPT], increased aspartate aminotransferase [or increased AST or increased SGOT], increased creatine phosphokinase, increased GGT, weight decreased, weight increased.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of APRIZON is important. It allows continued monitoring of the benefit/risk balance of APRIZON. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Report all side effects to Unicorn Pharmaceuticals (Pty) Ltd to enquiries@unicornpharma.co.za

By reporting side effects, you can help provide more information on the safety of APRIZON.

**4.9 Overdose**

**Symptoms**

The potentially medically important signs and symptoms observed following overdosage included lethargy, increased blood pressure, somnolence, tachycardia and vomiting.

Overdose treatment should be focused on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility that multiple medicines could be involved with the overdose should be considered and as such, cardiovascular monitoring should be initiated immediately, together with continuous electrocardiographic monitoring for the detection of possible dysrhythmias. If an overdose is confirmed or suspected with APRIZON, the patient should be placed under close medical supervision and should be monitored continuously until recovery.
When activated charcoal (50 g) was administered one hour after aripiprazole, aripiprazole AUC and Cmax decreased by 51 % and 41 % respectively, thus suggesting that charcoal may be used effectively during overdose management.

Whilst no information is available in respect of the use of haemodialysis to treat an overdose with aripiprazole, it is unlikely that haemodialysis will be useful in overdose management with APRIZON, as aripiprazole is highly protein bound and is not eliminated unchanged by the kidneys.

## 5. PHARMACOLOGICAL PROPERTIES

**Pharmacological Class**: A 2.6.5 Tranquillisers – Miscellaneous structures.

### 5.1 Pharmacodynamic properties

The efficacy of aripiprazole in schizophrenia is deemed to be mediated through a combination of partial agonist activity at serotonin $5HT_{1a}$ and dopamine $D_2$ receptors together with antagonist activity at serotonin $5HT_2$ receptors.

*In vitro* studies have shown that aripiprazole exhibits high binding affinity for dopamine $D_2$ and $D_3$, serotonin $5HT_{1a}$ and $5HT_{2a}$ receptors, and moderate affinity for dopamine $D_4$, serotonin $5HT_{2c}$ and $5HT_7$, $alpha_1$-adrenergic and histamine $H_1$ receptors. Aripiprazole also presented with moderate binding affinity for serotonin reuptake site, with no appreciable affinity for muscarinic receptors.

In animal models of dopaminergic hyperactivity, aripiprazole exhibited antagonist properties, while agonist properties were exhibited in animal models of dopaminergic hypoactivity. Some of the other clinical effects attributable to aripiprazole may be as a result of its interaction with receptors other than dopamine and serotonin subtypes.

**5.2 Pharmacokinetic properties:**

The activity of APRIZON is primarily attributed to the parent medicine, aripiprazole. Multiple dosing may result in an aripiprazole accumulation by a factor of 5. The pharmacokinetics of aripiprazole are dose-proportional at steady state. There is minimal diurnal variation in the disposition of aripiprazole and its active metabolite, dehydro-aripiprazole. Dehydro-aripiprazole is the predominant metabolite in human plasma and has been shown to present with similar affinities for $D_2$ receptors as aripiprazole.

*Absorption:*

Aripiprazole is well absorbed, following administration by the oral route, with peak plasma concentrations being achieved within 3 - 5 hours post-dose. The aripiprazole tablet formulation has an absolute oral bioavailability of approximately 87 %. Food administration does not have a significant effect on the bioavailability of aripiprazole. Within 14 days of dosing, steady-state concentrations are attained.

*Distribution:*

Aripiprazole is widely distributed throughout the body and presents with an apparent volume of distribution of 4,9 l/kg. Aripiprazole is highly bound (>99 %) to serum proteins (primarily albumin) at therapeutic concentrations. The pharmacokinetics and pharmacodynamics of warfarin, which is highly protein-bound, was not altered during concomitant administration with aripiprazole, thus suggesting that protein displacement of warfarin by aripiprazole did not occur.

*Metabolism:*

The pre-systemic metabolism of aripiprazole is minimal. Aripiprazole undergoes extensive hepatic metabolism via three primary biotransformation pathways: dehydrogenation, hydroxylation and N-dealkylation.

*In vitro* studies indicated that CYP3A4 and CYP2D6 enzymes are responsible for the dehydrogenation and hydroxylation of aripiprazole, whilst N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicine moiety in systemic circulation. At steady state, the active metabolite, dehydro-aripiprazole, represents approximately 39 % of the aripiprazole plasma AUC.

*Elimination:*

Aripiprazole has a mean elimination half-life of about 75 hours. After the administration of a single oral dose of [$^{14}$C]-labelled aripiprazole, approximately 27 % and 60 % of the administered radioactivity was recovered in the urine and faeces, respectively. Approximately 18 % of the oral dose was recovered unchanged in the faeces and less than 1 % of the unchanged aripiprazole was recovered in the urine. Aripiprazole has a total body clearance of is 0,7 ml/min/kg, primarily via the hepatic route.

**Special Populations:**

*Hepatic impairment*:

During a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B and C), aripiprazole AUC increases of 31 % (mild hepatic impairment) and 8 % (moderate hepatic

impairment) were observed, compared to healthy subjects. An aripiprazole AUC decrease of 20 % was observed in patients with severe hepatic impairment, compared to healthy subjects. Dose adjustments are not required as a result of these differences.

*Renal impairment*:
Where patients had severe renal impairment (creatinine clearance < 30 ml/min), the $C_{max}$ of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36 % and 53 % respectively, whilst the AUC values were 15 % lower for aripiprazole and 7 % higher for dehydro-aripiprazole. Less than 1 % of the administered dose is renally excreted (unchanged aripiprazole and dehydro-aripiprazole). Dosage adjustments are not required in subjects with renal impairment.

*Elderly*:
Aripiprazole clearance was found to be 20 % lower in elderly (≥ 65 years) subjects compared to younger adult subjects (18 to 64 years), following the administration of single doses of 15 mg aripiprazole in formal single-dose pharmacokinetic studies.

A population pharmacokinetic analysis in schizophrenia patients did not reveal any detectable age effect.

The pharmacokinetics of aripiprazole appeared to be similar in elderly and younger, healthy subjects, following multiple dosing. Based on the foregoing, a dosage adjustment is not recommended for elderly patients (see

"WARNINGS and SPECIAL PRECAUTIONS, Elderly patients with Dementia-related psychosis").

*Gender*:

30 to 40 % higher aripiprazole and dehydro-aripiprazole (the active metabolite of aripiprazole) $C_{max}$ and AUC values of have been observed in women than in men and correspondingly, the apparent oral clearance of aripiprazole is also lower in women. Differences in body weight (25 %) between men and women are primarily responsible for these differences. Dosage adjustment based on gender is not recommended.

*Smoking*:

*In vitro* studies utilising human liver enzymes have shown that aripiprazole does not undergo direct glucuronidation and is not a substrate for CYP1A2. As such, the pharmacokinetics of aripiprazole should not be affected by smoking.

A population pharmacokinetic evaluation supports the *in vitro* study results, whereby no significant aripiprazole pharmacokinetic differences were observed between smokers and non-smokers.

Dosage adjustment based on smoking status is not recommended.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Inactive ingredients:*

APRIZON tablets contain the following inactive ingredients: Croscarmellose sodium, crystalline maltose, magnesium stearate, microcrystalline cellulose and pregelatinised starch.

APRIZON 5 tablets additionally contain: Indigo carmine (E132).

APRIZON 10 tablets additionally contain: Iron oxide red (E172).

APRIZON 15 tablets additionally contain: Iron oxide yellow (E172).

APRIZON 30 tablets additionally contain: Iron oxide red (E172).

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Store at or below 25 °C in the original container.

Keep well closed – HDPE bottles

Keep blister in carton until required for use

**6.5 Nature and contents of container**

APRIZON tablets are available in PA/ALL/PVC – Aluminium foil blister (alu-alu blister) packs of 14, 28, 30 or 98 tablets. Blisters are packed into cardboard cartons.

Additional pack size: 30 included.

APRIZON tablets are available in white opaque High-Density Polyethylene (HDPE) bottles with child resistant white polypropylene (PP) screw caps with mounted white low density polyethylene desiccant containing 14, 28 or 98 tablets. HDPE bottles are packed into cardboard cartons.

**6.6 Special precautions for disposal and other handling**

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Corner of Searle & Pontac Streets

Cape Town

South Africa 8001

## 8. REGISTRATION NUMBER

APRIZON 5: 51/2.6.5/0654

APRIZON 10: 51/2.6.5/0655

APRIZON 15: 51/2.6.5/0656

APRIZON 30: 51/2.6.5/0657

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

**Date of registration:** 26 June 2019

**Professional Information approval date:** 10 September 2020

## 10. DATE OF REVISION OF THE TEXT

10 September 2020