1.3.1.1 PROFESSIONAL INFORMATION (FINAL)

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

Apize 5 mg Tablets

Apize 10 mg Tablets

Apize 15 mg Tablets

Apize 30 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Apize 5 mg: Each tablet contains 5 mg of aripiprazole

Apize 10 mg: Each tablet contains 10 mg of aripiprazole

Apize 15 mg: Each tablet contains 15 mg of aripiprazole

Apize 30 mg: Each tablet contains 30 mg of aripiprazole

Contains sugar.

Apize 5 mg: Each tablet contains 66,80 mg of lactose monohydrate

Apize 10 mg: Each tablet contains 62,49 mg of lactose monohydrate

Apize 15 mg: Each tablet contains 93,40 mg of lactose monohydrate

Apize 30 mg: Each tablet contains 187,47 mg of lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Apize 5 mg: Blue coloured, modified rectangular shaped uncoated tablets debossed with "ARI" on one side and "5" on other side.

Apize 10 mg: Pink coloured, modified rectangular shaped uncoated tablets debossed with "ARI" on one side and "10" on other side.

Apize 15 mg: Yellow coloured, round shaped uncoated tablets debossed with "ARI" on one side and "15" on other side.

Apize 30 mg: Pink coloured, round shaped uncoated tablets debossed with "ARI" on one side and "30" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Schizophrenia:

Apize is indicated for the treatment of schizophrenia and for the maintenance of clinical improvements in adults.

Bipolar Mania:

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

4.2 Posology and method of administration

Posology:

Schizophrenia:

The recommended starting dose for **Apize** 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. **Apize** is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than the recommended 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.

Bipolar Mania:

The recommended starting dose for **Apize** is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 4.5). 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:

For preventing recurrence of manic episodes in patients who have been receiving **Apize**, continue therapy at the same dose. Adjustments of daily dose, including dose reduction should be considered on the basis of clinical status. Prevention of depressive episodes using **Apize** monotherapy has not been established. Supplementary therapy should be considered for the prevention or treatment of depressive episodes, as clinically appropriate.

Concomitant Medicines:

*Dosage adjustment for patients taking **Apize** concomitantly with potent CYP3A4 or CYP2D6 inhibitors*:

When concomitant administration of a potent CYP3A4 or CYP2D6 inhibitor with **Apize** occurs, the **Apize** dose should be reduced to one-half of the usual dose. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, the **Apize** dose should then be increased.

Dosage adjustment for patients taking potent CYP3A4 inducers:

When a potent CYP3A4 inducer is added to **Apize** therapy, the **Apize** dose should be doubled. Additional dose increases of **Apize** should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from the combination therapy, the **Apize** dose should be reduced.

Method of administration:

Apize is for oral use.

4.3 Contraindications

Apize is contra-indicated in

- patients with hypersensitivity to aripiprazole or any other component of **Apize a**s listed in section 6.1.

The safety and efficacy of **Apize** in children under 18 years of age has not been established.

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.

Suicide:

The possibility of suicide attempt is inherent in psychotic illnesses and mood disorders and close supervision of high-risk patients should accompany medicine therapy. Prescriptions for **Apize** should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular disorders:

Aripiprazole as in **Apize** 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 medicines) or hypertension, including accelerated or malignant.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicines. 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 **Apize** and preventive measures undertaken.

QT prolongation:

Aripiprazole as in **Apize** should be used with caution in patients with a family history of QT prolongation (see section 4.8).

Tardive dyskinesia:

As the risk of tardive dyskinesia increases with long-term exposure to antipsychotic treatment, if signs and symptoms of tardive dyskinesia appear in a patient on **Apize**, dose reduction or discontinuation should be considered (see section 4.8). 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 antipsychotics. Clinical symptoms 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. Elevated creatine phosphokinase and rhabdomyolysis, not necessarily associated with NMS, were also reported. If a patient develops signs and symptoms indicative of NMS, or present with unexplained high fever without additional clinical manifestation of NMS, all antipsychotic medicine, including **Apize** must be discontinued.

Seizure:

Apize should be used cautiously in patients with a history of seizure disorder or have conditions or have associated with seizures.

Elderly Patients with Dementia-Related Psychosis:

Elderly patients with dementia-related psychosis treated with **Apize** are at an increased risk of death. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Cerebrovascular adverse events (e.g. stroke, transient ischaemic attack) including fatalities were reported in elderly patients with psychosis associated with Alzheimer's disease. **Apize** is not indicated for the treatment of patients with dementia-related psychosis.

Orthostatic hypotension:

Apize may be associated with orthostatic hypotension, perhaps due to its α_{-1} adrenergic receptor antagonism. **Apize** must be used with caution in patients with hypotension predisposition.

Hypersensitivity:

Hypersensitivity reactions, characterised by allergic symptoms, may occur with **Apize.**

Dysphagia:

Oesophageal dysmotility and aspiration have been associated with the use of antipsychotics, including **Apize. Apize** should be used cautiously in patients at risk for aspiration pneumonia.

Hyperglycaemia/ Diabetes Mellitus:

Hyperglycaemia, in some cases extreme and associated with diabetic ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with aripiprazole as in **Apize.** Risk factors that may predispose patients to severe complications include obesity and family history of diabetes.

Patients treated with any antipsychotics, including **Apize** should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control.

Patients who develop symptoms of hyperglycaemia during treatment with **Apize** should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when aripiprazole as in **Apize** was discontinued, however some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Weight Gain:

Antipsychotic medicines have been associated with metabolic changes, including weight gain. Weight gain has been reported post-marketing experience among patients prescribed oral aripiprazole as in **Apize**. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. Aripiprazole as in **Apize** has not been shown to induce clinically relevant weight gain.

Body temperature regulation:

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing **Apize** for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medicine with anticholinergic activity, or being subject to dehydration.

Pathological gambling and other impulse control disorders:

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking **Apize**. 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, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with **Apize**. 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 medicine was discontinued. Impulse control disorders may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medicine if a patient develops such urges while taking **Apize** (see section 4.8).

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 as in **Apize** and stimulants; therefore, extreme caution should be taken when these medicines are co-administered.

Falls:

Aripiprazole as in **Apize** may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls. Caution should be taken when treating patients at higher risk, and a lower starting dose should be considered (e.g. elderly or debilitated patients; see section 4.2).

Excipients:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **Apize**.

4.5 Interaction with other medicines and other forms of interaction

General:

Due to its α1-adrenergic receptor antagonism, **Apize** has the potential to enhance the effect of certain antihypertensive medicines.

There was no effect of a high fat meal on pharmacokinetic of **Apize.**

Given the primary central nervous system (CNS) effects of **Apize**, caution should be used when **Apize** is administered in combination with CNS medicines with overlapping adverse reactions such as sedation (see section 4.8). Combination use of **Apize** with alcohol should be avoided.

If **Apize** is administered concomitantly with medicines known to cause QT prolongation or electrolyte imbalance, caution should be used.

Valproate and Lithium:

When either valproate or lithium was administered concomitantly with aripiprazole as in **Apize**, there was was no clinically significant change in **Apize** concentrations and therefore no dose adjustment is necessary when either valproate or lithium is administered with **Apize.**

*Potential for other medicines to affect **Apize:***

A gastric acid blocker, the H_2 antagonist famotidine, reduces **Apize** rate of absorption but this effect is deemed not clinically relevant.

Apize is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

Ketoconazole and other CYP3A4 inhibitors:

A strong inhibitor of CYP3A4 (such as ketoconazole) increased **Apize** AUC and Cmax by 63 % and 37 %, respectively. The AUC and Cmax of dehydro-aripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of **Apize** compared to that in CYP_{2D6} extensive metabolisers.

When considering concomitant administration of ketoconazole or other strong CYP3A4 inhibitors with **Apize**, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with **Apize** occurs, **Apize** dose should be reduced to approximately one-half of its prescribed dose.

Other strong 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 (see SECTION 4.8).

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of **Apize** should be increased to the level prior to the initiation of the concomitant therapy.

When weak inhibitors of CYP3A4 (e.g. diltiazem) or CYP2D6 (e.g. escitalopram) are used concomitantly with **Apize**, modest increases in plasma **Apize** concentrations may be expected.

Quinidine and other CYP2D6 inhibitors:

A strong inhibitor of CYP2D6 (quinidine) increased aripiprazole as in **Apize** AUC by 107 %, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32 % and 47 %, respectively. **Apize** dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of **Apize** with quinidine occurs. Other strong inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

Carbamazepine and other CYP3A4 inducers:

After concomitant administration of carbamazepine, a potent inducer of CYP3A4, the geometric means of C_{max} and AUC for aripiprazole as in **Apize** were 68 % and 73 % lower, respectively, compared to when **Apize** (30 mg) was administered alone.

Similarly, for dehydro-aripiprazole the geometric means of C_{max} and AUC after carbamazepine co-administration were 69 % and 71 % lower, respectively, than those following treatment with aripiprazole as in **Apize** alone.

Apize dose should be doubled when concomitant administration of **Apize** 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 **Apize** should be reduced to the recommended dose.

Serotonin Syndrome:

Cases of serotonin syndrome have been reported in patients taking aripiprazole as in **Apize**, and possible signs and symptoms for this condition can occur especially in cases of concomitant use with other serotonergic medicines, such as SSRI/ SNRI, or with medicines that are known to increase **Apize** concentrations (see section 4.8).

Potential for **Apize** *to affect other medicines:*

10 – 30 mg/ day doses of **Apize** had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/ 3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (dextromethorphan).

Additionally, aripiprazole as in **Apize** and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro.* Thus, **Apize** is unlikely to cause clinically important medicine interactions mediated by these enzymes.

When **Apize** was administered concomitantly with lamotrigine, there was no clinically important change in lamotrigine concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety of use of **Apize** in pregnancy has not been established.

Patients should be advised to notify their medical practitioner if they become pregnant or intend to become pregnant during treatment with **Apize**.

Neonates exposed to antipsychotics (including **Apize**) 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, newborns should be monitored carefully.

Breastfeeding:

Safety of use of aripiprazole as in **Apize** during lactation has not been established.

Aripiprazole as in **Apize** is excreted in human breast milk.

4.7 Effects on ability to drive and use machines

Apize 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 (see section 4.8).

Patients should be cautioned about operating hazardous machinery, including motor vehicles until they are reasonably certain that **Apize** does not adversely affect them.

4.8 Undesirable effects

A. Summary of the safety profile

The frequent adverse reactions are akathisia and nausea each occurring in more than 3 % of patients treated with oral aripiprazole.

B. Tabulated list of the adverse reactions

Adverse reactions reported are shown below. Frequencies were defined using the following convention: *frequent, less frequent, frequency unknown*:

Class/ Frequency	***Adverse reactions***
Blood and the lymphatic system disorders	
Less frequent	Leukopenia, neutropenia, thrombocytopenia
Endocrine disorders	
Less Frequent	Hyperprolactinaemia, blood prolactin decreased
Metabolism and nutrition disorders	
Less frequent	Diabetes mellitus, hyperglycaemia, diabetic ketoacidosis, diabetic hyperosmolar coma, hyponatremia, anorexia

Frequency unknown	Weight decreased and weight gain
Psychiatric disorders	
Frequent	Insomnia, anxiety, restlessness
Less frequent	Depression, hypersexuality
Frequency unknown	Suicide attempt, suicidal ideation and completed suicide, pathological gambling, impulse-control disorder, binge eating, compulsive shopping, poriomania, aggression, agitation, nervousness
Nervous system disorders	
Frequent:	Akathisia, extrapyramidal disorder, tremor, headache, sedation, somnolence, dizziness
Less frequent	Tardive dyskinesia, dystonia, grand mal convulsion, speech disorder
Frequency unknown	Neuroleptic Malignant Syndrome, serotonin syndrome
Eye disorders	
Frequent	Vision blurred
Less frequent	Diplopia, photophobia
Frequency unknown	Oculogyric crisis
Cardiac disorders	
Less frequent	Tachycardia
Frequency unknown	Sudden death unexplained, Torsades de pointes, ventricular arrhythmia, cardiac arrest, bradycardia
Respiratory disorders	
Less frequent	Hiccups, aspiration pneumonia
Frequency unknown	Laryngospasm, oropharyngeal spasm
Hepatobiliary disorders	
Less frequent	Hepatic failure, hepatitis, jaundice
Gastrointestinal disorders	
Frequent	Constipation, dyspepsia, nausea, salivary hypersecretion, vomiting, stomach discomfort

Less frequent	Pancreatitis, dysphagia, diarrhoea
Frequency unknown	Abdominal discomfort
Skin and subcutaneous tissue disorders	
Frequency unknown	Rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal disorders	
Less frequent	Rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders	
Less frequent	Urinary incontinence, urinary retention
Pregnancy, puerperium and perinatal conditions	
Frequency unknown	Medicine withdrawal syndrome neonatal (see section 4.6)
Reproductive system disorders	
Less frequent	priapism
Immune system disorders	
Less frequent	Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, or urticaria).
General disorders	
Frequent	Fatigue, asthenia
Less frequent	Temperature regulation disorder e.g. (hypothermia, pyrexia), chest pain, peripheral oedema.
Investigations	
Less frequent	Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, alkaline phosphatase increased, QT prolonged, blood glucose increased, glycosylated haemoglobin increased, blood glucose fluctuation, creatine phosphokinase increased
Vascular disorders	
Less frequent	Orthostatic hypertension
Frequency unknown	Hypertension, syncope, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 Alternatively all adverse events can be reported to Ascend Laboratories vial the e-mail: pharmacist.rsa@alkem.com.

4.9 Overdose

Accidental or intentional acute overdose of **Apize** alone was identified in adult patients after ingestion of doses up to 1,260 mg with no fatalities. The signs and symptoms are lethargy, increased blood pressure, somnolence, tachycardia and vomiting. Accidental overdose with aripiprazole alone (up to 195 mg) in children had no fatalities. The serious signs and symptoms include somnolence and transient loss of consciousness.

Management of overdose:

Management of overdose concentrates on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple medicine involvement should be considered. Therefore, cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible dysrhythmias. Following any confirmed or suspected overdose with **Apize**, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after **Apize,** decreases aripiprazole C_{max} by about 41 % and AUC by about 51 %, suggesting that charcoal may be effective in the treatment of overdose management**.**

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

Category and Class: A 2.6.5 Antipsychotic – miscellaneous structures

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX12

Mechanism of action:

Mechanism of action is unknown. It has been proposed that the efficacy of aripiprazole in schizophrenia is mediated through a combination of partial agonism at dopamine D_2 and serotonin $5HT_{1a}$ receptors and antagonism of serotonin $5HT_{2a}$ receptors.

Aripiprazole exhibited high binding affinity *in vitro* 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 $5HT_7$, α_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.

Aripiprazole exhibited antagonist properties in dopaminergic hyperactivity and agonist properties in dopaminergic hypoactivity.

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 from the gastro-intestinal tract after oral administration of with peak plasma concentration reached in 3 – 5 hours. The absolute oral bioavailability is 87 %.

Aripiprazole can be administered with or without food. There is no effect of a high fat meal on pharmacokinetics.

Distribution:

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4, 9 L/Kg, indicating extravascular distribution.

The protein binding of aripiprazole and dehydro-aripiprazole (the active metabolite) is about than 99 %, primarily to albumin.

Metabolism:

Aripiprazole undergoes minimal pre-systemic metabolism. Aripiprazole is metabolized mainly in the liver by three biotransformation pathways: dehydrogenation and hydroxylation via cytochrome P_{450} isoenzymes, namely CYP3A4 and CYP2D6 enzymes are responsible for, and N-dealkylation via CYP3A4.

Aripiprazole is the predominant medicine moiety in the systemic circulation. The major metabolite, dehydro-aripiprazole, is also active and represents about 39 % of plasma levels of aripiprazole.

Elimination:

The mean elimination half-lives are approximately 75 hours for aripiprazole and 95 hours for dehydro-aripiprazole. The half-life is about 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 [14C]-labeled aripiprazole, approximately 27 % and 60 % of administered radioactivity was recovered in the urine and faeces, respectively. Less than 1 % of unchanged aripiprazole was excreted in the urine and about 18 % was found unchanged in the faeces.

Elderly: There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger 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.

Hepatic impairment: Subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), did not reveal significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole. None of these differences would require dose adjustment.

Renal impairment: The pharmacokinetics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Smoking: Population pharmacokinetic evaluation showed no evidence of clinically significant effect from smoking on the pharmacokinetic of aripiprazole.

Race: Population pharmacokinetic evaluation showed no evidence of race-related differences on the pharmacokinetic of aripiprazole.

6. Pharmaceutical particulars

6.1 List of excipients

Other ingredients are hydroxyl propyl cellulose, lactose monohydrate, magnesium stearate, maize starch and microcrystalline cellulose.

The tablets contain the following colourants:

Apize 5 mg: FD & Blue No.2/ Indigo carmine

Apize 10 mg: iron oxide red.

Apize 15 mg: iron oxide yellow

Apize 30 mg: iron oxide red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Apize tablets: 2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove strip from carton until required for use.

Protect from light and moisture.

Keep blister in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Apize are packed in aluminium/aluminium blister strip of 10 tablets and inserted in a printed cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Ascend Laboratories (Pty) Ltd.

R21 Corporate Park

121 Sovereign Drive

Block A, Irene Ext.30,

Centurion, 0157

8 MARKETING AUTHORISATION NUMBER(S)

To be allocated by authority.

9 DATE OF REVISION OF THE TEXT

To be allocated by authority