PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S5**

1. NAME OF THE MEDICINE

RADZIL 5 mg (tablets)

RADZIL 10 mg (tablets)

RADZIL 15 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RADZIL 5 mg

Each tablet contains 5 mg aripiprazole.

Contains sugar (60,94 mg lactose monohydrate).

RADZIL 10 mg

Each tablet contains 10 mg aripiprazole

Contains sugar (55,94 mg lactose monohydrate).

RADZIL 15 mg

Each tablet contains 15 mg aripiprazole

Contains sugar (83,94 mg lactose monohydrate).

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

RADZIL 5 mg

Blue, modified rectangle shaped, uncoated tablets debossed with 'CL 73' on one side and plain on the other side.

RADZIL 10 mg

Pink, modified rectangle shaped, uncoated tablets debossed with 'CL 74' on one side and plain on the other side.

RADZIL 15 mg

Yellow, round shaped, uncoated tablets debossed with 'CL 75' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Schizophrenia:

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

Bipolar Mania:

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

4.2 Posology and method of administration

Schizophrenia:

The recommended starting dose for **RADZIL** 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. **RADZIL** 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 **RADZIL** 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 aripiprazole, 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 aripiprazole 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 **RADZIL** concomitantly with potent CYP3A4 or CYP2D6 inhibitors:*

When concomitant administration of a potent CYP3A4 or CYP2D6 inhibitor with **RADZIL** occurs, the **RADZIL** dose should be reduced to one-half of the usual dose. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, the **RADZIL** dose should then be increased (see Section 5.2)

Dosage adjustment for patients taking potent CYP3A4 inducers:

When a potent CYP3A4 inducer is added to **RADZIL** therapy, the **RADZIL** dose should be doubled. Additional dose increases of **RADZIL** should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from the combination therapy, the **RADZIL** dose should be reduced. (see Section 5.2).

Special populations

Paediatric Population

The safety and efficacy of RADZIL in patients under 18 years of age have not been established.

Method of administration

RADZIL tablets are for oral use.

4.3 Contraindications

- **RADZIL** is contraindicated in patients who are hypersensitive to aripiprazole or any of the excipients listed in section 6.1.
- The safety and efficacy of **RADZIL** in patients under 18 years of age have 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 during this period.

Suicide:

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

Cardiovascular disorders

RADZIL 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, hypovolaemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. 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 RADZIL and preventive measures undertaken.

QT prolongation

RADZIL 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 **RADZIL**, a dose reduction or medicine discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Other extrapyramidal symptoms (EPS)

If signs and symptoms of other EPS appear in a patient taking RADZIL, dose reduction and close clinical monitoring should be considered (see Section 4.8).

Neuroleptic Malignant Syndrome:

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported. 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. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including **RADZIL** must be discontinued.

Seizure:

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

Elderly patients with dementia-related psychosis:

Elderly patients with dementia-related psychosis treated with **RADZIL**, are at increased risk of death compared to placebo. 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.

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

RADZIL 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 **RADZIL**. Patients treated with **RADZIL** 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 (see Section 4.8). Patients who develop symptoms of hyperglycaemia during treatment with **RADZIL** should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when **RADZIL** was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Hypersensitivity

Hypersensitivity reactions, characterised by allergic symptoms may occur with aripiprazole (see Section 4.8).

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 **RADZIL**. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma (see section 4.8).

Pathological gambling and other impulse-control disorders:

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking **RADZIL**. Other urges, reported include: increased sexual urges, compulsive spending, binge or compulsive eating, and other impulsive and compulsive behaviors. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive spending, binge or compulsive eating, or other urges while being treated with **RADZIL**. 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 **RADZIL** was discontinued (see section 4.8).

Impulse-control disorders may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medicine if a patient develops such urges while taking **RADZIL**.

Orthostatic hypotension:

Potentially due to its α_1-adrenergic receptor antagonist activity, **RADZIL** may be associated with orthostatic hypotension.

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 **RADZIL** 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 medicines with anticholinergic activity, or being subject to dehydration.

Dysphagia: Oesophageal dysmotility and aspiration have been associated with antipsychotic medicine use. **RADZIL** and other antipsychotic medicines should be used cautiously in patients at risk of aspiration pneumonia.

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

Falls:

RADZIL 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.

Lactose:

Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption should not take **RADZIL**.

4.5 Interaction with other medicines and other forms of interaction

General:

Given the primary CNS effects of **RADZIL**, caution should be used when **RADZIL** is taken in combination with other centrally acting medicines. Combination use of **RADZIL** with alcohol should be avoided. Due to its α_1-adrenergic receptor antagonist activity, **RADZIL** has the potential to enhance the effect of certain antihypertensive medicines.

There was no effect of a high fat meal on the pharmacokinetics of **RADZIL**. If RADZIL is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance, caution should be used.

Valproate and lithium

When valproate or lithium was administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations and therefore, no dosage adjustment of RADZIL is required when administered concomitantly with valproate or lithium.

Effect of other medicines on RADZIL:

There was no clinically significant effect of the H_2 antagonist, famotidine, on the pharmacokinetics of aripiprazole.

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

Quinidine and other CYP2D6 inhibitors

In a clinical study with healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased plasma exposure (AUC) of aripiprazole AUC. The AUC and C_{max} of dehydro-aripiprazole, its active metabolite, decreased. **RADZIL** dose should be reduced to one-half of its prescribed dose when concomitant administration of **RADZIL** with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and therefore, should be accompanied by similar dose reductions.

Ketoconazole and other CYP3A4 inhibitors

In a clinical study with healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased plasma exposure of aripiprazole and dehydro-aripiprazole In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolisers. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with **RADZIL**, potential benefits should overweigh the potential risks to the patient.

When concomitant administration of ketoconazole with **RADZIL** occurs, **RADZIL** dose should be reduced to 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 therefore, should be accompanied by similar dose reductions. Upon

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

Carbamazepine and other CYP3A4 inducers

RADZIL dose should be doubled when concomitant administration of **RADZIL** occurs with carbamazepine (a potent inducer of CYP3A4, due to decreased plasma exposure of aripiprazole). 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 therefore, should be accompanied by similar dose increases. Upon discontinuation of potent CYP3A4 inducers, the dosage of **RADZIL** should be reduced to the recommended dose.

Potential for RADZIL to affect other medicines:

In clinical studies, 10 - 30 mg/day doses of oral **RADZIL** had no significant effect on metabolism of substrates of CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (dextromethorphan). Additionally, aripiprazole and its predominant human metabolite dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, **RADZIL** is unlikely to cause clinically important medicine interactions mediated by these enzymes.

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 medicines, such as SSRI/SNRI, or with medicines that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Fertility

Aripiprazole did not impair fertility based on data from reproductive toxicity studies.

Pregnancy

Safety of use of RADZIL during pregnancy has not been established.

Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during treatment with **RADZIL**. Due to insufficient safety information in humans and the findings that animal studies could not exclude potential developmental toxicity, RADZIL should not be used in pregnancy.

Neonates exposed to antipsychotics (including **RADZIL**) 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.

Breastfeeding

Safety of use of RADZIL during lactation has not been established. Aripiprazole is excreted in human breast milk.

4.7 Effects on ability to drive and use machines

RADZIL has a 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, diplopia (see section 4.8). Patients should be cautioned about operating hazardous machinery, including motor vehicles until they are reasonably certain that **RADZIL** does not adversely affect them.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in placebo-controlled trials were akathisia and nausea each occurring in more than 3 % of patients treated with oral aripiprazole.

Tabulated summary of adverse reactions

The incidences of the Adverse Drug Reactions (ADRs) associated with aripiprazole therapy are tabulated below. The table is based on adverse events reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ class and frequency; within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "Frequency unknown"**.**

System Organ Class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Frequency unknown	Leukopenia, neutropenia, thrombocytopenia
Immune system disorders	Frequency unknown	Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus, or urticaria)
Endocrine disorders	Less frequent	Hyperprolactinaemia
	Frequency unknown	Diabetic ketoacidosis (DKA)
Metabolism and nutrition disorders	Frequent	Diabetes mellitus
	Less frequent	Hyperglycaemia
		Hyponatremia, anorexia, weight decreased, 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 disorders, 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
	Frequency unknown	Neuroleptic malignant syndrome (NMS), grand mal convulsion, serotonin syndrome, speech disorder
Eye disorders	Frequent	Blurred vision

	Less frequent	Diplopia
	Frequency unknown	Oculogyric crisis
Cardiac disorders	Less frequent	*Tachycardia*
	Frequency unknown	Sudden unexplained death, torsades de pointes, QT prolongation, ventricular arrhythmias, cardiac arrest, bradycardia
Vascular disorders	Less frequent	Orthostatic hypotension
	Frequency unknown	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis), hypertension, syncope
Respiratory, thoracic and mediastinal disorders	Less frequent	Hiccups
	Frequency unknown	Aspiration pneumonia, laryngospasm, oropharyngeal spasm
Gastrointestinal disorders	Frequent	Constipation, dyspepsia, nausea, salivary hypersecretion, vomiting, stomach discomfort

	Frequency unknown	Pancreatitis, dysphagia, diarrhoea, abdominal discomfort
Hepatobiliary disorders	Frequency unknown	Hepatic failure, hepatitis, jaundice
Skin and subcutaneous tissue disorders	Frequency unknown	Rash, photosensitivity reaction, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders	Frequency unknown	Rhabdomyolysis Myalgia, Musculoskeletal stiffness
Renal and urinary disorders	Frequency unknown	Urinary incontinence, urinary retention
Pregnancy, puerperium and perinatal conditions	Frequency unknown	Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	Frequency unknown	Priapism
General disorders and administration site conditions	Frequent	Asthenia, fatigue
	Frequency unknown	Peripheral oedema, temperature regulation disorder (e.g. hypothermia, pyrexia),

		chest pain
Investigations	Frequency unknown	Blood glucose increased, glycosylated haemoglobin increased, blood glucose fluctuation, Increased creatine phosphokinase, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased gamma glutamyl transferase (GGT), increased alkaline phosphatase.

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. Health care providers 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://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

Signs and symptoms

The potentially medically important signs and symptoms observed included lethargy, blood pressure increased, somnolence, tachycardia, nausea, vomiting and transient loss of consciousness.

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 medicine involvement should be considered. Therefore cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose of **RADZIL**, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after **RADZIL**, decreased aripiprazole plasma exposure, suggesting that charcoal may be effective for overdose management.

Haemodialysis

Although there is no information on the effect of haemodialysis in treating an overdose with **RADZIL**, haemodialysis is unlikely to be useful in overdose management since **RADZIL** is not eliminated unchanged by the kidneys and is highly bound to plasma proteins.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N05AX12

Psycholeptics, other antipsychotics

Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonist activity at dopamine D_2 and serotonin $5HT_{1a}$ receptors and antagonist activity at 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 $5HT_7$, $alpha_1$-adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for serotonin reuptake site and no appreciable affinity for muscarinic receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of 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

RADZIL activity is primarily due to the parent medicine, aripiprazole. The mean elimination half-life of aripiprazole is about 75 hours. Steady-state concentrations are attained within 14 days of dosing. Aripiprazole accumulation by a factor of 5 is predictable with multiple dosing. At steady state, the pharmacokinetics of aripiprazole is dose-proportional. There is minimal diurnal variation in the disposition of aripiprazole and its active metabolite, dehydro-aripiprazole. This predominant metabolite in human plasma, dehydro-aripiprazole, has been shown to have similar affinities for D_2 receptors as the parent compound.

Absorption:

Aripiprazole is well absorbed after oral administration of **RADZIL**, with peak plasma concentrations occurring within 3 - 5 hours after dosing. The absolute oral bioavailability of the tablet formulation of aripiprazole is 87 %. The bioavailability of aripiprazole is not significantly affected by administration with food.

Distribution:

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4,9 l/kg. At therapeutic concentrations, aripiprazole is greater than 99 % bound to serum proteins, primarily albumin. Aripiprazole did not alter the

pharmacokinetics and pharmacodynamics of highly protein-bound warfarin, suggesting that protein displacement of warfarin did not occur.

Biotransformation:

Aripiprazole undergoes minimal pre-systemic metabolism. 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 medicine moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represented about 39 % of aripiprazole AUC in plasma.

Elimination:

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 approximately 18 % of the oral dose was recovered unchanged in the faeces. The total body clearance of aripiprazole is 0,7 mℓ/min/kg, which is primarily hepatic.

Special populations:

Hepatic impairment:

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B and C), the AUC of aripiprazole, compared to healthy subjects, increased in mild hepatic impairment and in moderate hepatic impairment and decreased in severe hepatic impairment. None of these differences would require dose adjustment.

Renal impairment:

In patients with severe renal impairment (creatinine clearance < 30 ml/min, C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased, but AUC was lower for aripiprazole and higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1 % of the dose. No dosage adjustment is required in subjects with renal impairment.

Elderly:

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was lower in elderly (≥ 65 years) subjects compared to younger adult subjects (18 to 64 years).

There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients.

Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients (see section 4.4on increased mortality in elderly patients with dementia-related psychosis).

Gender:

C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25 %) between men and women. No dosage adjustment is recommended based on gender.

Race:

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

Smoking:

Based on studies utilising human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2, and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole.

Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and non-smokers. No dosage adjustment is recommended based on smoking status.

5.3 Preclinical safety data

Animal studies in rats and rabbits could not exclude potential foetal developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains: Lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, FD&C blue no. 2 (indigo carmine) aluminium lake (E132) (5 mg), Ferric oxide red (E172) (10 mg), Ferric oxide yellow (E172) (15 mg).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months for container and 36 months for blister packs from the date of manufacturing.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the blister in the carton until required for use.

Keep the containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister pack:

Tablets are packed in cold form laminate, 25 µm OPA/45 µm aluminum foil/60 µm PVC and plain 30 µm aluminum foil/6-8 gsm HSL as the lidding material.

Pack sizes include 10, 30 or 100 tablets.

HDPE container pack:

Tablets are packed in a white, opaque, round 60 ml HDPE container with 33 mm neck finish closed with a 33 mm white opaque polypropylene stock ribbed closure with wad having induction sealing liner.

Pack sizes include 30 or 100 tablets.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

RADZIL 5 mg: 47/2.6.5/0707

RADZIL 10 mg: 47/2.6.5/0708

RADZIL 15 mg: 47/2.6.5/0709

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10. DATE OF REVISION OF THE TEXT