Front Side

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 (80,94 mg lactose monohydrate).

RADZIL 10 mg
Each tablet contains 10 mg aripiprazole.
Contains sugar (53,94 mg lactose monohydrate).

RADZIL 15 mg
Each tablet contains 15 mg aripiprazole.
Contains sugar (80,94 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 'CL73' on one side and plain on the other side.

RADZIL 10 mg
Pink, modified rectangle shaped, uncoated tablets debossed with 'CL74' on one side and plain on the other side.

RADZIL 15 mg
Yellow, round shaped, uncoated tablets debossed with 'CL75' 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 previous 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 temporarily 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.

Seizures:
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 recorded in 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, recorded 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_1 antagonist, famotidine, on the pharmacokinetics of aripiprazole.
RADZIL is metabolized by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A antizymes. 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 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 syndromes:
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 (In 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
		Hyponatraemia, 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, paraphrenia, 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 "SAHPRA Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.hpra.org.za/wp-content/uploads/2020/01/ADR_Form_v6.1_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.

5. 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 $5HT_2$ 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 $5HT_2$ receptors and moderate affinity for dopamine D_1, 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 several 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 accumulates by a factor of 8 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 in 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 58 % 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 schizophrenic 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 4.4 on 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 (23 %) 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 tablet in the carton until required for use.
Keep the container 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 aluminium foil/60 µm PVC and plain 36 µm aluminium foil/84 µm HSL as the lidding material.
Pack sizes include 10, 28, 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 heat sealing 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, Bissonia Estate Office Park (East),
1 Curacao Drive, Bonnie Rock, Ext. 12,
Bivertion, South Africa.

8. REGISTRATION NUMBER(S)

RADZIL 5 mg: 47/2.5/0707
RADZIL 10 mg: 47/2.5/0708
RADZIL 15 mg: 47/2.5/0709

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 April 2021

10. DATE OF REVISION OF THE TEXT

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RADZIL 5/10/15
(Tablet)
PM03840501

400 mm

435 mm

Back Side

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS S5

RADZIL 5 mg, 10 mg and 15 mg Tablets
Aripiprazole
Contains sugar (60,94 mg/5,94 mg/83,94 mg lactose monohydrate)

Read all of this leaflet carefully before you start taking RADZIL
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- RADZIL has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet
1. What RADZIL is and what it is used for
2. What you need to know before you take RADZIL
3. How to take RADZIL
4. Possible side effects
5. How to store RADZIL
6. Contents of the pack and other information

1. What RADZIL is and what it is used for

Schizophrenia:
RADZIL contains the active substance aripiprazole and belongs to a group of medicines called antipsychotics.
RADZIL is used to treat adults and adolescents aged 15 years and older who suffer from a disease characterised by symptoms such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspicionsness, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.
RADZIL is used to treat adults who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. It also prevents this condition from returning in patients who have responded to the treatment with RADZIL.

2. What you need to know before you take RADZIL

Do not take RADZIL:
- If you are allergic to aripiprazole or any of the ingredients of RADZIL.
- RADZIL should not be given to children under 15 years of age.

Warnings and precautions
Take special care with RADZIL: Suicidal thoughts and behaviours have been reported during aripiprazole treatment. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself.
Before treatment with RADZIL, tell your doctor if you suffer from:
- Seizures (fits).
- High blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite, and feeling weak) or family history of diabetes.
- Cardiovascular disease (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure or very rapid or irregular heart beat.
- Dementia (loss of memory and other mental abilities) in the elderly.
- Past experience with excessive gambling or other impulsive behaviours.

While taking RADZIL:
Tell your doctor, pharmacist, nurse or other health care provider if the following occur:
- Medicines of this type may cause unusual movements mainly of the face or tongue. If you experience a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness.
- If you notice you are gaining weight. If you or your family/caregiver notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.
- If you experience increases in your core body temperature especially during strenuous exercise, exposure to extreme heat. This could happen when you take medicines known as anticholinergics or when you are dehydrated.
- If you experience difficulty in swallowing while taking RADZIL.
- If you are experiencing tiredness, sleepiness, getting dizzy when standing up, and experience changes in your ability to move and balance, which may lead to falls. Caution should be taken, particularly if you are an elderly patient or have some debility.

Other medicines and RADZIL
Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines).
Taking RADZIL with some medicines may mean the doctor will need to change your dose of RADZIL or the other medicines.
You might feel drowsy if RADZIL is taken in combination with alcohol, antidepressants or medicines taken for anxiety or to help you sleep (tranquillisers).
You should tell your doctor, pharmacist or other healthcare provider if you are taking the following medicines:
- Blood pressure-lowering medicines: RADZIL may increase the effect of medicines used to lower blood pressure.
- Quinidine (to correct heart rhythm)
- Fluoxetine and paroxetine (anti-depressants)
- Ketoconazole and itraconazole (antifungals)
- Efavirenz, nevirapine and HIV Protease Inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir and amprenavir (for HIV treatment)
- Carbamazepine, phenytoin, phenobarbital and primidone (for epilepsy)
- Rifampicin and rifabutin (for TB treatment)
St. John's Wort (herbal medicine for the treatment of depression)
These medicines may increase the risk of side effects or reduce the effect of RADZIL. If you get any unusual symptoms taking any of these medicines together with RADZIL, you should see your doctor, pharmacist or other healthcare provider.

RADZIL with food and drink and alcohol
RADZIL can be administered regardless of meals.
Alcohol should be avoided when taking RADZIL.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking RADZIL.
- You should not use RADZIL if you are pregnant or breastfeeding.
- The following symptoms may occur in newborn babies, of mothers that have used RADZIL in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Driving and using machines
RADZIL can cause dizziness and vision problem. If you feel dizzy while taking RADZIL do not drive and do not use any tools or machines.

RADZIL contains sugar
RADZIL contains lactose monohydrate.
Patients with rare hereditary conditions of lactose/fructose or galactose intolerance should not take RADZIL.

3. How to take RADZIL

- Do not share medicines prescribed for you with any other person.
- Always take RADZIL exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
- Your doctor will tell you how long your treatment with RADZIL will last. Do not stop treatment early.
- If you have the impression that the effect of RADZIL is too strong or too weak, tell your doctor or pharmacist.
- Stay under a healthcare provider's care when taking RADZIL. Do not change your treatment or stop treatment without first talking with your healthcare provider.
- The usual dose is:
  The recommended dose for adults is 15 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.
- Take RADZIL with or without food.
- Always take the tablet with water and swallow it whole. Try to take your tablets at the same time each day.

If you take more RADZIL than you should
If you realise you have taken more RADZIL than you should (or if someone else has taken your RADZIL), consult your doctor or pharmacist, other healthcare provider immediately.
In the event of overdosage consult your doctor or pharmacist. If neither is available contact the nearest hospital or casualty/central centre and take the pack of RADZIL with you.
Patients who have taken more RADZIL than they should may experience the following symptoms: drowsiness or sleepiness, increased blood pressure, rapid beating of the heart and reduced level of consciousness.

If you forget to take RADZIL
If you forget to take a dose, take it as soon as you remember and then continue as before. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take two doses in one day to make up for forgotten individual doses.

If you stop taking RADZIL
Do not stop taking your tablets just because you feel better. It is important that you carry on taking RADZIL for as long as your doctor tells you.

4. Possible side effects

RADZIL can have side effects.
Not all side effects reported for RADZIL are included in this leaflet. Should your personal health worsen or if you experience any untoward effects while taking RADZIL, please consult your doctor, pharmacist or other healthcare professional for advice.
If any of the following happens, stop taking RADZIL and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Allergic reaction. Symptoms of a severe allergic reaction such as:
  - Swelling of face, tongue or throat
  - Difficulties in swallowing
  - Hives and difficulties in breathing
  - Severe skin reactions that can include blistering of the skin.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to RADZIL. You may need urgent medical attention or hospitalization.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
- Thoughts of suicide, attempted suicide, completed suicide.
- Diabetic coma, diabetes ketoacidosis (symptoms include excessive thirst or urination, nausea and vomiting, abdominal pain, loss of appetite, shortness of breath, fruity-scented breath, confusion).
- A combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness.
- Severe convulsions (fits).
- Sudden unexplained death, life-threatening irregular heartbeat, heart attack, slower heartbeat.
- Blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing.
- Accidental inhalation of food with risk of pneumonia (lung infection).
- Inflammation of the pancreas (symptoms include severe stomach pain, nausea and vomiting).
- Liver failure, inflammation of the liver, yellowing of the skin and whites part of eyes.
- Withdrawal symptoms in newborn babies in case of exposure during pregnancy.
- Prolonged and/or painful erection.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:
Frequent side effects:
- Difficulty sleeping, feeling anxious, feeling restless and unable to keep still.
- Uncontrollable twitching, jerking or writhing movements, restless legs, trembling, headache, sleepiness, dizziness.
- Blurred vision.
- Constipation, indigestion, nausea, more saliva in mouth than normal, vomiting, stomach discomfort.
- Muscle stiffness.
- Feeling tired, weakness.

Less frequent side effects:
- Depression, altered or increased sexual interest.
- Uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia), muscle disorder causing twisting movements (dystonia).
- Double vision.
- A fall in blood pressure on standing up which causes dizziness, light-headedness or fainting.
- Hiccups.
- Swelling of the hands and feet.

Frequency unknown:
- Decreases in the amount of white blood cells (increased risk of infections) or cells in the blood known as platelets needed for clotting (increased risk of bleeding and bruising).
- Onset or worsening of diabetes.
- Loss of appetite (anorexia).
- Excessive gambling, impulsive behaviour, binge eating, compulsive shopping, aimless wandering, feeling aggressive, agitation, nervousness.
- Speech disorder.
- Flotation of the eyeballs in one position.
- High blood pressure, fainting.
- Spasm of the muscles around the voice box.
- Difficulty swallowing, diarrhoea, stomach discomfort.
- Skin rash, sensitivity to light, unusual hair loss or thinning, excessive sweating.
- Abnormal muscle breakdown which may lead to kidney problems, muscle pain and stiffness.
- Involuntary loss of urine (incontinence), difficulty in passing urine.
- Difficulty controlling core body temperature (e.g. low or high body temperature), chest pain.

Less frequent side effects that may show up in laboratory tests are:
- Increased blood levels of the hormone prolactin.
- Low blood sodium levels.
- Increased blood glucose levels, blood glucose fluctuations.
- Increased haemoglobin levels.
- Abnormal liver test values.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects
If you get side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via the "6.64 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://hpcaonline.za.pc-content/uploads/2020/01/6.64_ADR1_v3.1_27Jan2020.pdf. By reporting side effects, you can help provide more information on the safety of RADZIL.

5. How to store RADZIL

Store all medicines out of reach of children.
Store at or below 25 °C (room temperature).
Keep the blister in the carton until required for use.
Keep the container tightly closed.
Protect from light and moisture.
Do not store in a bathroom.
Do not use after the expiry date stated on the label / carton / bottle.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of pack and other information

What RADZIL contains
- The active substance is aripiprazole 5 mg or 10 mg or 15 mg.
- The other ingredients are: 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)

What RADZIL looks like and contents of the pack
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.
Blister pack:
Tablets are packed in cold form laminate, 25 µm OPA/45 µm aluminium foil/60 µm PVC and plain 30 µm aluminium foil/6-8 gsm HSL as the lidding material.
Pack size include 10, 28, 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 size include 30 or 100 tablets.
Not all packs and pack sizes are necessarily marketed.

Holder of Certificate of Registration and Manufacturer
MACLEODS PHARMACEUTICALS SA (PTY) LTD
Office Block 1, Bassons Estate Office Park (East),
1 Cassonia Drive, Bassonia Rock, Ext. 12,
Alberton, South Africa.

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Registration number
RADZIL 5 mg: 47/2.6.5/0707
RADZIL 10 mg: 47/2.6.5/0708
RADZIL 15 mg: 47/2.6.5/0709

Access to the corresponding Professional Information
The corresponding professional information can be accessed at https://www.macleodspharma.com/ or email macleodsrsa@macleodspharma.com or contact 011 682 1169.

PASIËNTINLIGTINGSTUK

SKEDULERINGSTATUS: S5

RADZIL 5 mg, 10 mg en 15 mg Tablette
Aripiprasol
Bevat suiker (60,94 mg/5,94 mg/83,94 mg laktosemonohidraat)

Lees die hele inligtingsblad voordat u begin om RADZIL te neem

- Hou hierdie bladsie. U mag dit moontlik weer wil lees.
- As u enige verdere vrae het, moet u asseblief u dokter of apteker raadpleeg.
- RADZIL is vir u persoonlik voorgeskryf en u behoort nie u medisyne met ander mense deel nie. Dit mag hulle skade aandoen, selfs al lyk hulle dieselfde simptome as u.

Wat bevat hierdie inligtingsblad
1. Wat RADZIL is en waarvoor dit gebruik word.
2. Wat behoort te weet voordat u RADZIL neem
3. Hoe om RADZIL te neem.
4. Moontlike newe-effekte.
5. Hoe om RADZIL op te berg.
6. Inhoud van die verpakking en ander inligting

1. Wat is RADZIL en waarvoor word dit gebruik

Skisofrenie

RADZIL bevat die aktiewe bestanddeel aripiprasol en behoort aan die groep medisyne wat antipsigotiese middels genoem word.

RADZIL word gebruik om volwassenes en adolessente ouer as 18 jaar oud is wat aan 'n siekte lyk waar gekenmerk word deur simptome soos die hoor, sien of dinge vermoed wat nie daar is nie, wanopinies, ongewone verdagtheid, onbevatlikheidspraak en gebrek en emosionasieele gedrag. Mense met hierdie toestand mag ook depressief, 'n skuldgevoel, bekommerd of gespanne voel.

RADZIL word gebruik om volwassenes wat aan 'n kondisie ly met simptome soos 'n gevoel van "hoog" met oormatige hoeveelhede energie, baie minder slaap as gewoonlik nodig het, vinnige spraak met fluidees en soms ege geïrriteerdheid. Dit voorkom ook die terugkeer van hierdie kondisie in pasiënte wat goed op RADZIL gereageer het.

2. Wat u behoort te weet voordat u RADZIL neem

Moenie RADZIL gebruik nie
- As u allergies kan aripiprasol of enige van die bestanddele van RADZIL is.
- RADZIL behoort nie aan kinders jonger as 18 jaar oud gegee word nie

Waarskuwings en voorsorgsmaatreëls
Neem spesiale sorg met RADZIL: Selfmoordideses en -gedrag is gerapporteer die behandeling met aripiprasol aangeneem. Skel onmiddellik u dokter daarvan in kennis as u daarvan dink of steeds lyk om u self te beseer. Voor u behandeling met RADZIL kry, moet u u dokter in kennis stel as u aan die volgende lyk:

- Stuipaanvalle.
- Hoë bloedsuiker (gekenmerk deur oormatige dors, baie urinering, 'n toename in eetlus en 'n gevoel van swakheid) of 'n familiële geskiedenis van diabetes mel.
- Kardiovaskulêre siekte (siektes van die hart en sirkulasie), familiële geskiedenis van kardiovaskulêre siekte, beroerte of mini-beroerte, abnormale bloeddruk of baie vinnige of ongereelde hartklop.
- Demensie (verlies aan geheue en ander geestesvaardighede) in bejaardes.
- Vorige ondervinding met oormatige dobbelary of ander impulsiewe gedrag.

Terwyl u RADZIL gebruik:
Stel u dokter of apteker of verpleegster of enige ander gesondheidsorgverskaffer in kennis as die volgende gebeur:

- Medisyne van hierdie soort mag ongewone bewegings, hoofsaaklik van die gesig of lang veroorsaak. As u 'n kombinasie van koors, vinniger asemhaling, sweet, spierstyfheid of toenemende of slaperigheid ondervind.
- As u waarneem dat u gewig optel. As u of u familielverteenwoordiger opmerk dat u aangee toon om anders as gewoonlik op te tree en u kan nie die impuls weerstaan nie, poging aanwend of die temptasie het om sekere aktiwiteite uit te voer wat u self of ander kan beseer. Dit word impulsbeheerafwykings genoem en kan gedrag soos gewoontedobbel, oormatige eet of spandabelgedrag en 'n abnormale hoë seksdrang met 'n toename in seksuele gedagtes of gevoel insluit. U dokter mag dit nodig vind om die dosis aan te pas of te staak.
- Indien u 'n toename in liggaamstemperatuur ondervind, veral tydens strawwe oefening, of bloedstelling aan buitengewone hoë temperatuur. Dit kan gebeur wanneer u medisyne wat as anticholinergiese middels bekend staan gebruik, of wanneer u gedehidreer is.
- As u sukkel om te sluk.
- As u moeghied, slaperigheid en duiselighied ondervind wanneer u opstaan ensae, en veranderinge in u bewegingsvermoë en probleme met u balans ondervind wat daartoe gelei kan dat u te val kry. Sorg behoort aan die dag gelê te word, veral as u 'n bejaarde persoon is of aan een of ander gestremdheid ly.

Ander middels en RADZIL

Stel altyd u professionele gesondheidswerker in kennis as u enige ander medisyne neem. (Dit sluit komplementêre en tradisionele medisyne in).

Dwar RADZIL saam met ander medisyne te neem mag u dokter moontlik die dosis van RADZIL of die ander medisyne verander.

U mag ligmoeg voel wanneer u RADZIL saam met alkohol, antidepressante of medisyne vir angs of om u te help slaap (kalmeermiddels) neem.

Stel u dokter, apteker of ander professionele gesondheidswerker in kennis as u enige van die volgende medisyne neem:
- Bloeddrukverlagende medisyne: RADZIL mag die effek van medisyne om bloeddruk te verlaag, laat toenem.
- Kinidien (om hartritme reg te stel)
- Fluoksetien en paroksetien (antidepressante)
- Ketokonasool en itrakonasool (swamweerdaers)
- Efavirenz, nevirapien en MIV proteaseinhibeerders soos sakunavir, ritonavir, indinavir, nelfinavir en amprenavir (vir behandeling van MIV)
- Karbamasepien, fenitoïen, fenobarbital en primidoon (vir epilepsie)
- Rifampisien en rifabutin (vir TB behandeling)

St. John se kruid (kruiemedisyne vir die behandeling van depressie)

Hierdie medisyne mag die risiko van newe-effekte laat toeneem of die effek van RADZIL laat afneem. Indien u enige ongewone simptome ontwikkel terwyl u enige van hierdie medisyne saam met RADZIL gebruik, behoort u dokter, apteker of ander professionele gesondheidswerker raadpleeg.

RADZIL saam met voedsel, vloeistof en alkohol
RADZIL kan met of sonder voedsel geneem word.
Alkohol behoort vermy te word terwyl u RADZIL neem.

Swangerskap, borsvoeding en vrugbaarheid
As u swanger is of u baba borsvoed, moet u asseblief u dokter, apteker of ander professionele gesondheidswerker raadpleeg voordat u RADZIL neem.

- U behoort nie RADZIL te neem terwyl u swanger is of u baba borsvoed nie.
- Die volgende simptome mag in pasgebore babas van moeders wat RADZIL in die laaste trimester van hul swangerskap gebruik het, voorkom: bewerasie, spierstyfheid en/of -swakheid, slaperigheid, agitasie, asemhalingsprobleme en moeite met voeding. As u baba enige van hierdie simptome ontwikkel, moet u asseblief u dokter raadpleeg.

Bestuur en die gebruik van masjinerie

RADZIL kan duiseligheid en gesigsprobleme veroorsaak, as u duiselig voel terwyl u RADZIL neem, moet u nie bestuur of met enige masjinerie of gereedskap werk nie.

RADZIL bevat suiker
RADZIL bevat laktosemonohidraat

Pasiënte met die seldsame voorkomende oorerflike kondisies van laktose/fruktose of galaktose-intoleransie behoort nie RADZIL te neem nie.

3. Hoe om RADZIL te neem

- Moenie medisyne wat aan u voorgeskryf is met ander mense deel nie.
- Neem RADZIL altyd presies soos deur u dokter of apteker voorgeskryf. Raadpleeg u dokter of apteker as u onseker is.
- U dokter sal vir hulle weet hoe lank u behandeling met RADZIL sal duur. Moenie te vroeg met die behandeling ophou nie.
- As u onder die indruk is dat die effek van RADZIL te sterk of te swak is, moet u asseblief u dokter of apteker in kennis stel.
- Bly onder u professionele gesondheidswerker se sorg terwyl u RADZIL neem. Moenie u behandeling verander of daarmee ophou voordat u nie met u professionele gesondheidswerker daaroor gepraat het nie.
- Die normale dosis is:
  Die aanbevole dosis vir volwassenes is 15 mg een keer per dag. U dokter mag egter 'n laer of hoër dosis tot 'n maksimum van 30 mg een keer per dag voorskryf.
- Vlug RADZIL met of sonder voedsel neem.
- Neem altyd die tablet met water en sluk dit heel in. Probeer om die tablette elke dag op dieselfde tyd te neem.

Indien u meer RADZIL geneem het as wat u moes
As u basel dit u te veel RADZIL geneem het (of as iemand anders u RADZIL geneem het), moet u onmiddellik u dokter of ander professionele gesondheidswerker raadpleeg.
In die geval van 'n oordosering moet u onmiddellik u dokter of professionele gesondheidswerker raadpleeg. As hulle nie beskikbaar is nie, neder asseblief die naaste hospitaal of gebeurtenisentrum en neem die pakkie RADZIL saam met u.

Pasiënte wat te veel RADZIL geneem het, mag die volgende simptome ondervind: lomerigheid of slaperigheid, toename in bloeddruk, vinnige hartklop en inkrimpe in bewussyn.

As u vergeet het om RADZIL te neem
As u vergeet het om 'n dosis RADZIL te neem, moet u dit neem sodra u daarvan ontbou en dan soos voorheen voortgaan. As dit egter byna tyd vir u volgende dosis is, slaan oor en neer dan nie normale dosisskedulering terug. Moenie twee dosisse op een dag neem nie om vir die oorgeslaande dosis op te maak.

As u ophou om RADZIL te neem
Moenie ophou om u tablette te neem net omdat u beter voel nie. Dit is belangrik om RADZIL te neem vir solank as wat u dokter dit vir u voorgeskryf het.

4. Moontlike newe-effekte

RADZIL kan newe-effekte teen.
Nie al die newe-effekte wat vir RADZIL aangeneem word, word in hierdie inligtingsblad genoem nie. Indien u algemeen gesondheid aanhoudend of indien u enige newe-effekte waarneem terwyl u RADZIL neem, moet u asseblief u dokter, apteker of ander professionele gesondheidswerker raadpleeg. Indien enige van die volgende gebeur, moet u onmiddellik u dokter raadpleeg of na die ongevalle afdeling van u naaste hospitaal gaan.
- Allergiese reaksie. Simptome van 'n ernstige allergiese reaksie soos:
  - Swelling van die mond, keel of kiewel.
  - Moeilie met sluk.
  - Urtikaria en moeite met asemhaling.
  - Erge velreaksies wat blaasvorming op die vel kan insluit.

Hierdie is almal baie ernstige newe-effekte. As u hulle ondervind mag u 'n ernstige allergiese reaksie teen RADZIL hê. U het dan ernstige mediese hulp of hospitalisering benodig.

Stel u dokter onmiddellik in kennis of gaan na die ongevalle afdeling van u naaste hospitaal as u enige van die volgende waarneem:
- Gedagtes aan selfmoord pleeg, poging tot selfmoord, voltooide selfmoord.
- Diabetiese koma, diabetiese keto-asidose (simptome sluit oormatige dors of urinering, naarheid en braking, buikpyn, vadlas aan eetlus, kortasemheid, vrugtegeurige asem, verwardheid in).
- 'n Kombinasie van koors, vinniger asemhaling, sweet, spierstyfheid en lomerigheid of slaperigheid.
- Stuiptrekkings.
- Skielike, onverklaarde dood, lewensbedreigende onreëlmatige hartklop, hartaanval, stadiger hartklop.
- Bloedstolsels in die are, veral in die bene (simptome sluit swelling (pyn en roodheid in) wat deur die bloedvate na die longe mag versprei en moeigheid en moeite met asemhaling mag veroorsaak.
- Toevallige inhalering van voedsel met die risiko van pneumonie (longontsteking).
- Inflammasie van die pankreas (simptome sluit erge maagpyn, naarheid en braking in).
- Lewensversaking, inflammasie van die lewer, geel verkleuring van die vel en die wit gedeelte van u oë.
- Onttrekkingsimptome in pasgebore babas in die geval blootstelling gedurende swangerskap
- Verlangde en pynlike ereksie

Hierdie is almal ernstige newe-effekte. U het ernstige mediese hulp nodig.

Stel u dokter in kennis as u enige van die volgende waarneem:
Dikwels voorkomende newe-effekte
- Moeite met slaap, gevoel van angsigheid, rusteloosheid en onvermoë om stil te sit.
- Onbeheerde bewerasie, ruksbewegings, of sitrytbewegings, rustelose bene, bewerasie, hoofpyn, slaperigheid, duiseligheid.
- Onduidelike gesig.
- Hardlywigheid, indigestie, naarheid, meer speeksel in die mond as normaal, braking, buikongemak.
- Spierstyfheid.
- Gevoel van moegheid, swakheid.

Minder dikwels voorkomende newe-effekte:
- Depressie, verandering of toename in seksdrang.
- Onwillekeurige bewegings van die gesig, lang en ledemate (tardiewe diskinesie), spierafwyking wat draaibewegings van die ledemate (distonie) veroorsaak.
- Dubbel visie.
- 'n Afname in bloeddruk wanneer u opstaan wat duiselighied, ligh oofdigheid of floute veroorsaak.
- Hik.
- Swelling van die hande en voete.

Frekwensie onbekend:
- Afname in die aantal witbloedselle (toename in die risiko van infeksies) of selle in die bloed wat as plaatjies bekend staan, wat nodig is vir die bloed om te stol (toename in die risiko van bloeding en kneusing).
- Aanvang of verergering van diabetes.
- Vorties aan eetlus (anoreksie).
- Oormatige dobbelary, impulsiewe gedrag, oormatige eet, kompulsiewe spandabelgedrag, doelbaie rondloper, ingewikkel van agressie, agitasie, senuweeagtigheid.
- Spraakafwyking.
- Flitsering van die oë in een posisie.
- Hoë bloeddruk, floute.
- Spasme van die spiere om die strembande.
- Moeite met sluk, diarree en buikongemak.
- Velsiekte, seldelvalkoon lei, abnormale haarverlies of verdunning, oormatige sweet.
- Abnormale spierafbraak, wat tot nierprobleme, spierpyn en -styfheid kan lei.
- Onwillekeurige verlies aan urien (urinêre insiene), moeite met urinering.
- Moeite met die behoud van liggaamstemperatuur (bv. lae of hoë liggaamstemperatuur, borspyn.

Hierdie afdeling voorkomende newe-effekte wat moontlik in laboratoriumtoetse mag wys:
- Toename in die hormoonvlakke van prolaktien in die bloed.
- Lae vlakke van natriumchloried in die bloed.
- Toename in bloedglukosevlakke, wisseling in bloedglukosevlakke.
- Toename in hemoglobienvlakke.
- Abnormale lewetoetswaardes.

Indien u enige newe-effekte ondervind wat nie in hierdie inligtingsblad genoem word nie, moet u asseblief u dokter of apteker in kennis stel.

Aanmelding van newe-effekte.
Indien u enige newe-effekte ondervind, moet u u dokter, apteker of verpleegste raadpleeg. U kan ook op newe-effekte aanmeld by SAHPRA aanvaid die "6.64 Adverse Drug Reactions & Quality Problem Reporting Form " wat aanlyn onder SAHPRA se publikasie gevind kan word: https://sahpra.org.za/wp-content/uploads/2020/01/6.64_ADR1_v3.1_27Jan2020.pdf
Deur newe-effekte aan te meld, kan u help om meer inligting oor die veiligheid van RADZIL te verskaf.

5. Hoe om RADZIL te stoor

Stoor alle medisyne buite bereik van kinders.
Stoor by of benede 25 °C (kamertemperatuur).
Houdie blisterstroke in die karton tot voor gebruik.
Houdie houers dig toe.
Beskerm teen lig en vog.
Moenie in die badkamer stoor nie.
Moenie na die vervaldatum op die etiket/kartonfoteel gebruik nie.
Neem alle ongebruikte medisyne na u apteker terug.
Moenie van ongebruikte medisyne in die dreine of riolisringsleisel (bv. toilet) weggdoen.

6. Inhoud van die pak en ander inligting

Wat RADZIL bevat
- Die aktiewe bestanddeel is aripiprasol 5 mg of 10 mg of 15 mg.
- Die ander bestanddele is: Laktosemonohidraat, miellestysel, mikrokristalline sellulose, hidroksipropielsellulose, magnesiumstearaat, FD&C blou nr. 2 (indigokarmien), aluminiumlak (E132)(5 mg) ysteroksied rooi (E172)(10 mg), ysleroksied geel (E172) (15 mg).

Hoe RADZIL lyk en inhoud van die pak
RADZIL 5 mg
Blou, gemoduleerde, reghoekvormige, onbedekte tablette met "CL73" op die een kant gedruk en glad aan die ander kant.

RADZIL 10 mg
Pienk, gemoduleerde, reghoekvormdonbedekte tablette met "CL74" op die een kant gedruk en glad aan die ander kant.

RADZIL 15 mg
Geel, ronde, onbedekte tablette met "CL75" op die een kant gedruk en glad aan die ander kant.

Stofverpakking:
Tablette word in koueversteinsnaat 25 µm OPA/45 µm aluminiumfoelie/60 µm PVC en 30 µm aluminiumfoelie/6-8 gsm HSL as deklaagmateriaal verpak.
Pakgroottes sluit 10, 28, 30 of 100 tablette in.

HDPE houer verpakking.
Tablette word in 'n wit, ondeursigtige, ronde 60 ml HDPE houer met 'n 33 mm nek en met 'n 33 mg wit ondeursigtige polipropileen geslote deksel met induksie seël voering gesluit
Pakgroottes sluit 30 of 100 tablette in.
Nie alle pakkie en pakgroottes word noodwendig bemark nie.

Houer van die sertifikaat van registrasie en Vervaardiger

MACLEODS PHARMACEUTICALS SA (PTY) LTD
Kantoorblok 1 Bassonia Estate Office Park (Oos)
Cassoniarylaan 1 Bassonia Rock, Litbr. 12 Alberton Suid Afrika

Hierdie inligtingsblad is laas hersien

28 April 2021

Registrasienommer

RADZIL 5 mg: 47/2.6.5/0707
RADZIL 10 mg: 47/2.6.5/0708
RADZIL 15 mg: 47/2.6.5/0709

Toegang tot die ooreenstemmende Professioneleinligting

Die ooreenstemmende professionele inligting kan by: http://www.macleodspharma.com of e-pos macleodsrsa@macleodspharma verkry word of kontak 011 682 1169

MASTER COPY

MACLEODS

PACKAGING RESEARCH & DEVELOPMENT

Restricted Circulation

(Front Page)

ARTWORK / PRINTPROOF APPROVAL FORM

1. Product: RADZIL 5/10/15 (Aripiprazole Tablets)	
2. Country: South Africa	3. Packaging component: Patient Information
4. No. of Colours: 1 Colour	5. Pantone Shade No.: Black
6. Specification: 40 gsm bible paper	
7. Machine Layout No.: NA	8. Dimensions: 435 (L) x 400 (W) mm
9. Design / Style: NA	10. Item code No.: PM03840501
11. Artwork has been made: Actual Size	12. Pharma code No.: 31468 mini
13. Barcode/NDC no: NA	14. Supersedes Item code No: NA
15. Revision no: 00	16. A/W File name: E:\ANDA Regulatory\South Africa\RADZIL PI&PIL-PM03840501.cdr
Approved By:	17. Location: Baddi

PRD	M.A. HOLDER	RAD	QC	PRODN	QA
12/08/22	Vanita Rajool	12/08/22	18/08/22	20/08/22	22/08/22

Note: 1. To follow overleaf checklist for approval of Artwork / Print proof.

QA 22/08/22

Instructions to Vendor :

1. Before processing, please ensure First pull out / Commercial supply should match with approved Artwork with respect to Design, Size, Fonts & Text.
2. Print proof to represent full printing area with Station Numbers.

FRM/CQA/021/04-01

Reason for revision :	Item code	Artwork Release Date	Artwork Implementation Date
1) New Artwork for South Africa	PM03840501		

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