Approved package insert

PRIZAL 5/10/15/30 mg tablets

SCHEDULING STATUS:

S5

PROPRIETARY NAME AND DOSAGE FORM:

PRIZAL 5 mg, 10 mg, 15 mg and 30 mg tablets

COMPOSITION:

Each **PRIZAL** 5 mg tablet contains 5 mg aripiprazole.

Each **PRIZAL** 10 mg tablet contains 10 mg aripiprazole.

Each **PRIZAL** 15 mg tablet contains 15 mg aripiprazole.

Each **PRIZAL** 30 mg tablet contains 30 mg aripiprazole.

Excipients:

Lactose monohydrate, microcrystalline cellulose, anhydrous colloidal silica, croscarmellose sodium, aspartame, magnesium

Colourants

PRIZAL 5 mg tablets contain indigo carmine aluminum lake, **PRIZAL** 10 and 30 mg tablets contain iron oxide red and **PRIZAL** 15 mg tablets contain iron oxide yellow as colourants.

Sugars and sweeteners

PRIZAL 5 mg: Each tablet contains sugar (47.53 mg lactose monohydrate) and sweetener (0.50 mg aspartame).

PRIZAL 10 mg: Each tablet contains sugar (95.05 mg lactose monohydrate) and sweetener (1.00 mg aspartame).

PRIZAL 15 mg: Each tablet contains sugar (142.58 mg lactose monohydrate) and sweetener (1.50 mg aspartame).

PRIZAL 30 mg: Each tablet contains sugar (285.15 mg lactose monohydrate) and sweetener (3.00 mg aspartame).

PHARMACOLOGICAL CLASSIFICATION:

A 2.6.5 Tranquilizers – miscellaneous structures

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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 $5HT_2$ receptors.

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

In animal models of dopaminergic hyperactivity aripiprazole has been shown to have antagonist properties and in animal models of dopaminergic hypoactivity aripiprazole has shown agonist properties. Other clinical effects of aripiprazole may be explained by interaction of aripiprazole with receptors other than dopamine and serotonin subtypes.

Pharmacokinetic properties:

Absorption:

Following oral administration, aripiprazole is well absorbed with peak plasma concentrations occurring within 3- 5 hours after dosing. Absolute oral bioavailability of aripiprazole is 87 % and 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 litres/kg. Protein binding of aripiprazole at therapeutic concentrations is greater than 99 %, primarily to albumin. The pharmacokinetics and pharmacodynamics of highly protein-bound warfarin were not altered by aripiprazole suggesting that protein displacement of warfarin did not occur.

Metabolism:

Aripiprazole undergoes minimal pre-systemic metabolism and is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation.

Based on *in vitro* studies, cytochrome P450 enzymes, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole and CYP3A4 catalyses N-dealkylation.

Aripiprazole is the predominant medicine moiety in systemic circulation and **PRIZAL** activity is primarily due to the parent medicine. At steady-state, dehydro-aripiprazole, the active metabolite, represented about 39 % of aripiprazole AUC in plasma. Minimal diurnal variation in the disposition of aripiprazole and its predominant metabolite, dehydro-aripiprazole occurs. Dehydro-aripiprazole has been shown to have similar affinities for D_2 receptors as the parent compound.

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 are dose proportional.

Excretion:

The mean elimination half-life of aripiprazole is about 75 hours. The total body clearance of aripiprazole is 0,7 mℓ/min/kg, primarily hepatic. Following administration of a single oral dose of [^{14}C]-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.

Special populations:

Hepatic impairment:

In subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), administered aripiprazole as a single-dose of 15 mg, the AUC of aripiprazole increased by 31 % in mild hepatic impairment, increased by 8 % in moderate hepatic impairment and decreased by 20 % in severe hepatic impairment, when compared to healthy subjects. No dose adjustment is considered necessary in hepatic impairment.

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 by 36 % and 53 % respectively, but AUC was 15 % lower for aripiprazole and 7 % higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1 % of the dose. No dosage adjustment is considered necessary in patients with renal impairment.

Elderly:

No significant differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects were noted, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients. No dosage adjustment is recommended in elderly patients (see WARNINGS AND SPECIAL PRECAUTIONS).

Smoking:

Population pharmacokinetic evaluation has revealed no evidence of clinically significant effects from smoking on the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on smoking status.

INDICATIONS:

Schizophrenia:

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

Bipolar Mania:

PRIZAL 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 **PRIZAL** treatment.

CONTRAINDICATIONS:

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

Paediatrics

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

WARNINGS AND SPECIAL PRECAUTIONS:

Improvement of the patient's clinical condition during antipsychotic treatment, may take several days to some weeks. Close monitoring of patients should occur during this period.

Suicide:

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

Tardive Dyskinesia:

The risk of tardive dyskinesia increases with long-term exposure to antipsychotic treatment. Should signs and symptoms of tardive dyskinesia appear in a patient on **PRIZAL**, a dose reduction or medicine discontinuation should be considered. These symptoms can temporally deteriorate or even arise following discontinuation of treatment.

Extrapyramidal Symptoms (EPS):

Extrapyramidal symptoms such as akathisia and parkinsonism have been reported. If signs and symptoms of EPS appear in a patient taking **PRIZAL**, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome:

Neuroleptic Malignant Syndrome (NMS) may occur.

This is a potentially fatal symptom complex with the following clinical manifestations: 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 creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. Should a patient develop signs and symptoms indicative of NMS, or present with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including **PRIZAL** must be discontinued.

Seizures:

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

Elderly patients with dementia-related psychosis:

In elderly patients with dementia-related psychosis treated with **PRIZAL**, there is an increased risk of death. Although causes of death are varied, most of the deaths appears to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature.

PRIZAL is not approved for the treatment of patients with dementia-related psychosis.

In elderly patients with psychosis associated with Alzheimer's disease, cerebrovascular adverse events (e.g. stroke, transient ischaemic attack), including fatalities, were reported.

Hyperglycaemia and diabetes mellitus:

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, may occur in patients treated with **PRIZAL**.

Patients with an established diagnosis of diabetes mellitus who are started on **PRIZAL** should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with **PRIZAL** should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness.

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

Orthostatic Hypotension:

PRIZAL may be associated with orthostatic hypotension, possibly due to its α_1-adrenergic receptor antagonistic activity.

Cardiovascular disorders:

In patients with known cardiovascular disease such as a history of myocardial infarction or ischaemic heart disease, heart failure or conduction abnormalities; cerebrovascular disease; or conditions which would predispose patients to hypotension such as dehydration, hypovolaemia and treatment with antihypertensive medicines, or hypertension, including malignant or accelerated, **PRIZAL** should be used with caution. As cases of venous thromboembolism (VTE) have been reported with antipsychotics such as **PRIZAL** and considering that patients receiving antipsychotics such as **PRIZAL** often present with acquired risk factors for VTE, all possible risks for VTE should be identified before and during treatment with **PRIZAL** and preventative measures taken.

QT prolongation:

PRIZAL should be used with caution in patients with a family history of QT prolongation.

Body Temperature Regulation:

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicine. Appropriate care is advised when prescribing **PRIZAL** 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 medication with anticholinergic activity, or being subject to dehydration.

Weight gain:

Weight gain has been reported post-marketing among patients receiving aripiprazole, such as contained in **PRIZAL**. It has usually presented in patients with significant risk factors for weight gain, such as those with a history of diabetes, thyroid disorder or pituitary adenoma.

Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered.

Pathological gambling:

Post-marketing reports of pathological gambling have been reported, regardless of whether these patients had a previous history of gambling. Patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully when receiving **PRIZAL**.

Dysphagia:

Oesphageal dysmotility and aspiration have been associated with **PRIZAL** use. **PRIZAL** and other antipsychotic medicines should be used cautiously in patients at risk of aspiration pneumonia.

Effects on ability to drive and use of machines:

Patients should be cautioned about driving and operating hazardous machinery until they are reasonably certain that **PRIZAL** does not adversely affect their abilities.

General:

PRIZAL tablets contain lactose and therefore should not be administered to patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption.

PRIZAL tablets also contain aspartame, which is a source of phenylalanine and should be used with caution in patients with phenylketonuria.

INTERACTIONS:

General:

As **PRIZAL** is primarily effective in the CNS, caution should be used when **PRIZAL** is administered in combination with other centrally acting medicines. The concomitant use of **PRIZAL** with alcohol should be avoided.

PRIZAL has the potential to enhance the effect of certain antihypertensive medicines due to its α_1-adrenergic receptor antagonist activity.

A high fat meal has no effect on the pharmacokinetics of **PRIZAL**.

Caution is advised if **PRIZAL** is administered concomitantly with medicines known to cause QT prolongation.

Valproate:

Co-administration of valproate (500 – 1500 mg/day) and aripiprazole (30 mg/day), the C_{max} and AUC at steady-state of aripiprazole were decreased by 25 %. Dosage adjustment of **PRIZAL** is not required when administered concomitantly with valproate.

Lithium:

Lithium is not bound plasma proteins, is not metabolised, and is almost entirely excreted unchanged in the urine and hence is not likely to interact with **PRIZAL**.

Dosage adjustment of **PRIZAL** is not required when administered concomitantly with lithium.

Effect of other medicines on PRIZAL:

Famotidine:

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

Inducers of CYP1A enzymes:

As **PRIZAL** is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes, no dosage adjustment is required for patients who are smokers.

Inhibitors of CYP2D6 and CYP3A4 enzymes:

A potent inhibitor of CY2D6 (quinidine) has been shown to increase aripiprazole AUC by 107 %, while C_{max} was not changed. The AUC and C_{max} of dehydro-aripiprazole, its active metabolite, decreased by 32 % and 47 %. When **PRIZAL** is concomitantly administered with quinidine, the **PRIZAL** dose should be reduced to one-half of its prescribed dose. 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.

A potent inhibitor of CYP3A4 (ketoconazole) has been shown to increase aripiprazole AUC and C_{max} by 63 % and 37 %. The AUC and C_{max} of dehydro-aripiprazole increased by 77 % and 43 %.

In patients who are poor CYP2D6 metabolisers, concurrent 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 **PRIZAL**, the following is recommended.

During concomitant administration of ketoconazole with **PRIZAL**, the dose of **PRIZAL** 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 therefore be accompanied by a similar reduction in dose.

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

Inducers of CYP3A4:

During concomitant administration of carbamazepine, a potent inducer of CYP3A4 with aripiprazole, the geometric means of C_{max} and steady-state AUC were 69 % and 71 % lower respectively than those following **PRIZAL** treatment alone. The dose of **PRIZAL** should be doubled during concomitant administration of **PRIZAL** with carbamazepine. Other potent inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbitone, primidone, efavirenz, nevirapine and St.John's Wort) may be expected to have similar effects and therefore, should be accompanied by similar dose increases.

Once discontinuation of potent CYP3A4 inducers occurs, the dosage of **PRIZAL** should be reduced to the recommended dose.

Other Medicine Interactions:

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

Cases of serotonin syndrome have been reported in patients taking aripiprazole, such as in **PRIZAL**. In cases of concomitant use of **PRIZAL** with other serotonergic medicines, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine (noradrenalin) reuptake inhibitors (SNRIs) or other serotonergic medicines, or with medicines which are known to increase

aripiprazole concentrations; possible signs and symptoms of serotonin syndrome can occur (see SIDE EFFECTS).

PREGNANCY AND LACTATION:

The safety of **PRIZAL** use during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Schizophrenia:

- Recommended starting dose for **PRIZAL**: 10 or 15 mg day
- Maintenance dose: 15 mg/day

PRIZAL should be administered on a once-a-day schedule without regard to meals.

PRIZAL is effective in a dose range 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:

- Recommended starting dose for **PRIZAL**: 15 mg/day

PRIZAL should be administered on a once-a-day schedule without regard to meals either as monotherapy or as combination therapy (see INTERACTIONS).

Some patients may benefit from a higher dose.

The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I disorder:

In order to prevent recurrence of manic episodes in patients who have been receiving **PRIZAL**, therapy should be continued at the same dose. Adjustments of daily dose, including dose reduction should be considered on the basis of

clinical status. Supplementary therapy should be considered for the prevention or treatment of depressive episodes, as clinically appropriate as prevention of depressive episodes using **PRIZAL** monotherapy has not been established.

Concomitant medicines:

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

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

- Dosage adjustment for patients taking potent CYP3A4 inducers:

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

SIDE EFFECTS

Endocrine disorders

Less frequent: Hyperprolactinaemia

Psychiatric disorders

Frequent: Insomnia, restlessness, anxiety

Less frequent: Depression

Nervous system disorders

Frequent: Headache, dizziness, akathisia, somnolence/sedation, tremor, extrapyramidal disorder

Less frequent: Tardive dyskinesia, dystonia

Eye disorders

Frequent: Blurred vision

Less frequent: Diplopia

Cardiac disorders

Frequent: Tachycardia

Vascular disorders

Frequent: Orthostatic hypotension

Frequency not known: Hypertension

Gastrointestinal disorders

Frequent: Nausea, vomiting, constipation, dyspepsia, salivary hypersecretion, stomach discomfort

Musculoskeletal, connective tissue and bone disorders

Frequent: Musculoskeletal stiffness

General disorders and administrative site conditions

Frequent: Asthenia, fatigue

Less frequent: Peripheral oedema

Post marketing data

Blood and lymphatic system disorders

Leucopenia, neutropenia, thrombocytopenia

Immune system disorders

Anaphylactic reaction, angioedema

Endocrine disorders

Hyperglycaemia, diabetes mellitus, diabetic ketoacidosis (DKA), diabetic hyperosmolar coma

Metabolism and nutrition disorders

Hyponatraemia, anorexia

Psychiatric disorders

Agitation

Nervous system disorders

Speech disorder, grand mal convulsion

Vascular disorders

Syncope

Respiratory, thoracic and mediastinal disorders

Aspiration pneumonia

Gastrointestinal disorders

Pancreatitis, dysphagia, diarrhoea

Hepato-biliary disorders

Hepatitis, jaundice

Skin and subcutaneous tissue disorders

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

Musculoskeletal, connective tissue and bone disorders

Rhabdomyolysis, myalgia, musculoskeletal stiffness

Renal and urinary disorders

Urinary retention, urinary incontinence

Reproductive system and breast disorders

Priapism

General disorders and administrative site conditions

Temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain

Investigations

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

Other findings:

Suicide attempt, suicidal ideation and completed suicide have been reported post-marketing.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms:

The potentially medically important signs and symptoms observed include: lethargy, blood pressure increased, somnolence, tachycardia and vomiting.

The potentially medically serious signs and symptoms in children include somnolence and transient loss of consciousness.

Management:

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 dysrhythmias. Following any confirmed or suspected overdose of **PRIZAL**, close medical supervision and monitoring of the patient should continue until recovery.

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

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

IDENTIFICATION:

PRIZAL 5 mg: Rectangular, biconvex, blue tablets, engraved with “5” on one side and plain on the other.

PRIZAL 10 mg: Rectangular, biconvex pink tablets, engraved with “10” on one side and plain on the other.

PRIZAL 15 mg: Round, flat, yellow tablets, engraved with “15” on one side and plain on the other.

PRIZAL 30 mg: Round, flat, pink tablets, engraved with “30” on one side and plain.

PRESENTATION:

PRIZAL tablets are packed in aluminium-aluminium blisters of 7 or 10 tablets, which are further packed in printed cartons, in pack sizes of 10, 14, 28, 30, 35, 49, 56, 70, 98 or 112 tablets. Not all pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS:

Store in the original packaging until required for use.

Store at or below 25 °C. Protect from light.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER

PRIZAL 5 mg: 49/2.6.5/0984

PRIZAL 10 mg: 49/2.6.5/0985

PRIZAL 15 mg: 49/2.6.5/0986

PRIZAL 30 mg: 49/2.6.5/0987

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

Johannesburg, 2193

South Africa

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