

Approved Professional Information for Medicines for Human Use: PRIZAL

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

PRIZAL 5 mg tablets

PRIZAL 10 mg tablets

PRIZAL 15 mg tablets

PRIZAL 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRIZAL 5 mg tablet

Each tablet contains 5 mg aripiprazole.

Contains sugar: lactose monohydrate 47,53 mg.

Contains sweetener: aspartame 0,50 mg.

PRIZAL 10 mg tablet

Each tablet contains 10 mg aripiprazole.

Contains sugar: lactose monohydrate 95,05 mg.

Contains sweetener: aspartame 1,00 mg.

PRIZAL 15 mg tablet

Each tablet contains 15 mg aripiprazole.

Contains sugar: lactose monohydrate 142,58 mg.

Contains sweetener: aspartame 1,50 mg.

PRIZAL 30 mg tablet

Each tablet contains 30 mg aripiprazole.

Contains sugar: lactose monohydrate 285,15 mg.

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Contains sweetener: aspartame 3,00 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

PRIZAL 5 mg tablets:

Rectangular, biconvex, blue tablets, plain on both sides.

PRIZAL 10 mg tablets:

Rectangular, biconvex pink tablets, plain on both sides.

PRIZAL 15 mg tablets:

Round, flat, yellow tablets, plain on both sides.

PRIZAL 30 mg tablets:

Round, flat, pink tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Schizophrenia:

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

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 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:

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

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withdrawn from the combination therapy, the PRIZAL dose should be reduced.

Method of administration

PRIZAL is for oral use.

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

4.3 Contraindications

Hypersensitivity to aripiprazole or to any of the excipients listed in section 6.1.

Paediatrics

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

4.4 Special warnings and precautions for use

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):

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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:

Increased mortality:

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.

Cerebrovascular adverse reactions

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

PRIZAL 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, 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, hypovolemia 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 and other impulse control disorders:

Post-marketing reports of pathological gambling have been reported, regardless of whether these patients had a previous history of gambling. Other urges reported include increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Impulse control disorders may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole (see section 4.8).

Dysphagia:

Oesophageal 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.

Hypersensitivity

Hypersensitivity reactions, characterized by allergic symptoms, may occur with aripiprazole (see section 4.8).

Patients with attention deficit hyperactivity disorder (ADHD) comorbidity

Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these medicinal products are co-administered.

Falls

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

Excipient lactose

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.

Excipient aspartame

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

Excipient sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

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:

A potent inhibitor of CYP2D6 (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.

Inhibitors of CYP3A4 enzymes:

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

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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.

Potential for aripiprazole to affect other medicinal products

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.

Serotonin syndrome

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 section 4.8).

4.6 Fertility, pregnancy and lactation

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

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with PRIZAL. Neonates exposed to antipsychotics (including PRIZAL) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breastfeeding

Aripiprazole is excreted in human breast milk.

4.7 Effects on ability to drive and use machines

Aripiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia (see section 4.8).

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

4.8 Undesirable effects

a) 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.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with aripiprazole.

System Organ Class	Frequency		
	Frequent	Less Frequent	Not known
Blood and lymphatic system disorders			Leucopenia, neutropenia, thrombocytopenia
Immune system disorders			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, or urticaria)
Endocrine disorders		Hyperprolactinaemia, blood prolactin decreased	Diabetic ketoacidosis (DKA), diabetic hyperosmolar coma
Metabolism and nutrition disorders	Diabetes mellitus	Hyperglycaemia	Hyponatraemia, anorexia

Psychiatric disorders	Insomnia, restlessness, anxiety	Depression, hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4), pathological gambling, impulse-control disorder, binge eating, compulsive shopping, poriomania, aggression, agitation, nervousness
Nervous system disorders	Headache, dizziness, akathisia, somnolence/sedation, tremor, extrapyramidal disorder	Tardive dyskinesia, dystonia, restless legs syndrome	Neuroleptic Malignant Syndrome, serotonin syndrome, speech disorder, grand mal convulsion
Eye disorders	Blurred vision	Diplopia, photophobia	Oculogyric crisis
Cardiac disorders	Tachycardia		Sudden death unexplained, torsades de pointes, ventricular arrhythmia, cardiac arrest, bradycardia
Vascular disorders	Orthostatic hypotension		Hypertension, syncope, venous thromboembolism (including pulmonary embolism and deep vein thrombosis)
Respiratory, thoracic and mediastinal		Hiccups	Aspiration pneumonia, laryngospasm, oropharyngeal spasm

disorders			
Gastrointestinal disorders	Nausea, vomiting, constipation, dyspepsia, salivary hypersecretion, stomach discomfort		Pancreatitis, dysphagia, diarrhoea
Hepatobiliary disorders			Hepatic failure, hepatitis, jaundice
Skin and subcutaneous tissue disorders			Allergic reaction (e.g. pruritus or urticaria, rash, laryngospasm), photosensitivity reaction, alopecia, hyperhidrosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal-and connective tissue disorders	Musculoskeletal stiffness		Rhabdomyolysis, myalgia, musculoskeletal stiffness
Renal and urinary disorders			Urinary retention, urinary incontinence
Pregnancy,			Drug withdrawal syndrome neonatal (see section

puerperium and perinatal conditions			4.6)
Reproductive system and breast disorders			Priapism
General disorders and administration site conditions	Asthenia, fatigue	Peripheral oedema	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 gamma-glutamyltransferase (GGT), increased alkaline phosphatase increased, QT prolonged, weight decreased

c. Description of selected adverse reactions

Adults

Extrapyramidal symptoms (EPS)

Schizophrenia: in a long-term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25,8 %) of EPS including Parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57,3 %).

In a long-term 26-week placebo-controlled trial, the incidence of EPS was 19 % for aripiprazole-treated patients and 13,1 % for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14,8 % for aripiprazole-treated patients and 15,1 % for olanzapine-treated patients.

Manic episodes in Bipolar I Disorder: in a 12-week controlled trial, the incidence of EPS was 23,5 % for aripiprazole-treated patients and 53,3 % for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26,6 % for patients treated with aripiprazole and 17,6 % for those treated with lithium. In the long-term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18,2 % for aripiprazole-treated patients and 15,7 % for placebo-treated patients.

Akathisia

In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12,1 % with aripiprazole and 3,2 % with placebo. In schizophrenia patients the incidence of akathisia was 6,2 % with aripiprazole and 3,0 % with placebo.

Dystonia

Class effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing,

and/or protrusion of the tongue. While these symptoms can occur at low doses; they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

Prolactin

In clinical trials for the approved indications and post-marketing, both increase and decrease in serum prolactin as compared to baseline was observed with aripiprazole (section 5.1).

Laboratory parameters

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Elevations of CPK (creatine phosphokinase), generally transient and asymptomatic, were observed in 3,5 % of aripiprazole treated patients as compared to 2,0 % of patients who received placebo.

Pathological gambling and other impulse control disorders

Pathological gambling, hypersexuality, compulsive shopping and binge or compulsive eating can occur in patients treated with aripiprazole (see section 4.4).

d. Paediatric population

Schizophrenia in adolescents aged 15 years and older

In a short-term placebo-controlled clinical trial involving 302 adolescents (13 to 17 years) with schizophrenia, the frequency and type of adverse reactions

were similar to those in adults except for the following reactions that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo):

Somnolence/sedation and extrapyramidal disorder were reported very commonly, and dry mouth, increased appetite, and orthostatic hypotension were reported commonly. The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.

The safety profile of a long-term, double-blind, placebo-controlled trial was also similar except for the following reactions that were reported more frequently than paediatric patients taking placebo: weight decreased, blood insulin increased, arrhythmia, and leukopenia were reported commonly.

In the pooled adolescent schizophrenia population (13 to 17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) were 29,5 % and 48,3 %, respectively. In the adolescent (13 to 17 years) schizophrenia population with aripiprazole exposure of 5 mg to 30 mg up to 72 months, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) were 25,6 % and 45,0 %, respectively.

In two long-term trials with adolescent (13 to 17 years) schizophrenia and bipolar patients treated with aripiprazole, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 37,0 % and 59,4 %, respectively.

Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older

The frequency and type of adverse reactions in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly somnolence (23,0 %), extrapyramidal disorder (18,4 %), akathisia (16,0 %), and fatigue (11,8 %); and commonly abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.

The following adverse reactions had a possible dose response relationship; extrapyramidal disorder (incidences were 10 mg, 9,1 %; 30 mg, 28,8 %;

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placebo, 1,7 %); and akathisia (incidences were 10 mg, 12,1 %; 30 mg, 20,3 %; placebo, 1,7 %).

Mean changes in body weight in adolescents with Bipolar I Disorder at 12 and 30 weeks for aripiprazole were 2,4 kg and 5,8 kg, and for placebo 0,2 kg and 2,3 kg, respectively.

In the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.

In the paediatric bipolar population (10 to 17 years) with exposure up to 30 weeks, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) were 28,0 % and 53,3 %, respectively.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

Signs and symptoms:

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

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

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 2.6.5 Tranquilizers – miscellaneous structures

Pharmacotherapeutic group: Psycholeptics, other antipsychotics

ATC Code: N05AX12

Pharmacodynamic properties:

It has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonist activity at dopamine D₂ and serotonin 5HT_{1a} receptors and antagonist activity at serotonin 5HT₂ receptors.

In vitro, aripiprazole has shown high binding affinity for dopamine D₂ and D₃, serotonin 5HT_{1a} and 5HT_{2a} receptors and moderate affinity for dopamine D₄, serotonin 5HT_{2c}, and 5HT₇, alpha₁-adrenergic and histamine H₁ 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.

5.2 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 D₂ 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 [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.

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 section 4.4).

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.

Gender:

C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40 % 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Microcrystalline cellulose

Anhydrous colloidal silica

Croscarmellose sodium

Magnesium stearate

Aspartame

Vanilla flavour

Colourants

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original packaging until required for use.

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

Keep the blister packs in the outer carton until required for use.

6.5 Nature and contents of container

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 may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBERS

PRIZAL 5 mg tablets: 49/2.6.5/0984

PRIZAL 10 mg tablets: 49/2.6.5/0985

PRIZAL 15 mg tablets: 49/2.6.5/0986

PRIZAL 30 mg tablets: 49/2.6.5/0987

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 May 2019

10. DATE OF REVISION OF THE TEXT

10 February 2025