Professional Information for ARIPIPRAZOLE KIARA

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ARIPIPRAZOLE KIARA 5 mg, 10 mg, 15 mg and 30 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARIPIPRAZOLE 5 KIARA: Each tablet contains 5 mg aripiprazole.

ARIPIPRAZOLE 10 KIARA: Each tablet contains 10 mg aripiprazole.

ARIPIPRAZOLE 15 KIARA: Each tablet contains 15 mg aripiprazole.

ARIPIPRAZOLE 30 KIARA: Each tablet contains 30 mg aripiprazole.

Excipients with known effect:

Contains sugar.

ARIPIPRAZOLE 5 KIARA: Each tablet contains 68,2 mg lactose monohydrate.

ARIPIPRAZOLE 10 KIARA: Each tablet contains 63,2 mg lactose monohydrate.

ARIPIPRAZOLE 15 KIARA: Each tablet contains 94,8 mg lactose monohydrate.

ARIPIPRAZOLE 30 KIARA: Each tablet contains 189,6 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

ARIPIPRAZOLE 5 KIARA: White to off-white, rounded off rectangular shaped, biconvex tablets debossed with “A5” on one side and plain on the other side.

ARIPIPRAZOLE 10 KIARA: Pink coloured, oval shaped, biconvex tablets debossed with “A10” on one side and plain on the other side.

ARIPIPRAZOLE 15 KIARA: Pink coloured, round, biconvex tablets debossed with "A15" on one side and plain on the other side.

ARIPIPRAZOLE 30 KIARA: Pink coloured, oval shaped, biconvex tablets debossed with "A30" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Schizophrenia

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

Bipolar Mania

ARIPIPRAZOLE KIARA 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 ARIPIPRAZOLE KIARA treatment.

4.2 Posology and method of administration

Schizophrenia

The recommended starting dose for ARIPIPRAZOLE KIARA is 10 mg/day or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals. ARIPIPRAZOLE KIARA is effective in a dose range of 10 mg/day to 30 mg/day. Enhanced efficacy at doses higher than a 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 ARIPIPRAZOLE KIARA 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 dosage, 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

Dose adjustments for patients taking ARIPIPRAZOLE KIARA concomitantly with potent CYP3A4 or CYP26 inhibitors

When concomitant administration of a potent CYP3A4 or CYP2D6 inhibitor with ARIPIPRAZOLE KIARA occurs, the ARIPIPRAZOLE KIARA dose should be reduced to one-half of the usual dose. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, ARIPIPRAZOLE KIARA dose should then be increased (see section 4.5).

Dose adjustments for patients taking potent CYP3A4 inducers

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

Smoking

No dosage adjustment is recommended based on smoking status.

Method of administration

ARIPIPRAZOLE KIARA tablets are for oral use.

4.3 Contraindications

ARIPIPRAZOLE KIARA is contraindicated in patients who are hypersensitive to aripiprazole or to any of the excipients listed in section 6.1.

The safety and efficacy of ARIPIPRAZOLE KIARA 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 throughout this period.

Suicide

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with ARIPIPRAZOLE KIARA (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic treatment. Prescriptions for ARIPIPRAZOLE KIARA should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular disorders

ARIPIPRAZOLE KIARA should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicines) or

hypertension, including accelerated or malignant. Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicines. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ARIPIPRAZOLE KIARA and preventive measures undertaken.

QT prolongation

ARIPIPRAZOLE KIARA should be used with caution in patients with a family history of QT prolongation (see section 4.8).

Tardive dyskinesia

In clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with ARIPIPRAZOLE KIARA. As the risk of tardive dyskinesia increases with long-term exposure, if signs and symptoms of tardive dyskinesia appear in a patient on ARIPIPRAZOLE KIARA, dose reduction or discontinuation should be considered (see section 4.8). These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Other extrapyramidal symptoms

If signs and symptoms of other extrapyramidal symptoms (EPS) appear in a patient taking ARIPIPRAZOLE KIARA, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially fatal symptom complex associated with antipsychotic medicines and cases of NMS have 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. However,

elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. 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 ARIPIPRAZOLE KIARA, must be discontinued.

Seizure

ARIPIPRAZOLE KIARA should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures (see section 4.8).

Elderly patients with dementia-related psychosis

Increased mortality

Elderly patients with dementia-related psychosis treated with ARIPIPRAZOLE KIARA were at increased risk of death compared to placebo. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8).

Cerebrovascular adverse reactions

In three placebo-controlled trials of aripiprazole, as contained in ARIPIPRAZOLE KIARA, in elderly patients with psychosis associated with Alzheimer's disease, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in elderly patients (see section 4.8).

ARIPIPRAZOLE KIARA is not indicated for the treatment of patients with dementia-related psychosis.

Elderly

The safety and efficacy of ARIPIPRAZOLE KIARA in the treatment of schizophrenia or manic episodes in Bipolar I Disorder in patients aged 65 years and older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered

when clinical factors warrant.

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 ARIPIPRAZOLE KIARA. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes.

Patients with risk factors for diabetes mellitus treated with ARIPIPRAZOLE KIARA should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with an established diagnosis of diabetes mellitus who are started on ARIPIPRAZOLE KIARA should be monitored regularly for worsening of glucose control (see section 4.8). Patients who develop hyperglycaemia during treatment with ARIPIPRAZOLE KIARA should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when ARIPIPRAZOLE KIARA was discontinued, however, some patients may require continuation of anti-diabetic treatment despite discontinuation of ARIPIPRAZOLE KIARA.

Hypersensitivity

Hypersensitivity reactions, characterised by allergic symptoms, may occur with ARIPIPRAZOLE KIARA (see section 4.8).

Weight gain

Weight gain has been reported post-marketing among patients prescribed ARIPIPRAZOLE KIARA. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials ARIPIPRAZOLE KIARA has not been shown to induce clinically relevant weight gain.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with the use of antipsychotic medicines. ARIPIPRAZOLE KIARA should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling and other impulse control disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking ARIPIPRAZOLE KIARA. 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 KIARA. 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 recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking ARIPIPRAZOLE KIARA (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 KIARA and stimulant medicines; therefore, extreme caution should be taken when these medicines are co-administered with ARIPIPRAZOLE KIARA.

Falls

ARIPIPRAZOLE KIARA 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 (such as elderly or debilitated patients).

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 ARIPIPRAZOLE KIARA for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, such as exercising strenuously, exposure to extreme heat, receiving concomitant medicines with anticholinergic activity, or being subject to dehydration.

ARIPIPRAZOLE KIARA contains lactose

ARIPIPRAZOLE KIARA contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ARIPIPRAZOLE KIARA.

4.5 Interaction with other medicines and other forms of interaction

General

Due to its α_1-adrenergic receptor antagonism, ARIPIPRAZOLE KIARA has the potential to enhance the effect of certain antihypertensive medicines (see section 4.4).

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

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

Potential for other medicines to affect ARIPIPRAZOLE KIARA

Smoking

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

Quinidine and other CYP2D6 inhibitors

In a clinical trial in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole area under the curve (AUC), while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased. ARIPIPRAZOLE KIARA dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ARIPIPRAZOLE KIARA with quinidine occurs. Other strong inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

Ketoconazole and other CYP3A4 inhibitors

In a clinical trial in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole and dehydro-aripiprazole AUC and C_{max} by 63 % and 37 %, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77 % and 43 %, respectively.
In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of ARIPIPRAZOLE KIARA compared to that in CYP2D6 extensive metabolizers.

When concomitant administration of ketoconazole with ARIPIPRAZOLE KIARA occurs, ARIPIPRAZOLE KIARA dose should be reduced to approximately one-half of its prescribed dose. Other strong inhibitors of CYP3A4, such as itraconazole and Human Immunodeficiency Virus (HIV) protease inhibitors may be expected to have similar effects and similar dose reductions should therefore be applied (see section 4.2). Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of ARIPIPRAZOLE KIARA should be increased to the level prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g. diltiazem) or CYP2D6 (e.g. escitalopram) are used concomitantly with ARIPIPRAZOLE KIARA, modest

increases in plasma ARIPIPRAZOLE KIARA concentrations may be expected.

Carbamazepine and other CYP3A4 inducers

Following concomitant administration of carbamazepine, a strong inducer of CYP3A4, to patients with schizophrenia or schizoaffective disorder, the geometric means of C_{max} and AUC were 68 % and 73 % lower, respectively, compared to when ARIPIPRAZOLE KIARA (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of C_{max} and AUC after carbamazepine co-administration were 69 % and 71 % lower, respectively, than those following treatment with ARIPIPRAZOLE KIARA alone.

ARIPIPRAZOLE KIARA dose should be doubled when concomitant administration of ARIPIPRAZOLE KIARA occurs with carbamazepine.

Concomitant administration of ARIPIPRAZOLE KIARA and other 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 similar dose increases should therefore be applied. Upon discontinuation of strong CYP3A4 inducers, the dosage of ARIPIPRAZOLE KIARA should be reduced to the recommended dose.

Valproate and lithium

When either valproate or lithium was administered concomitantly with ARIPIPRAZOLE KIARA, there was no clinically significant change in ARIPIPRAZOLE KIARA concentrations. Therefore, no dose adjustment is necessary when either valproate or lithium is administered with ARIPIPRAZOLE KIARA.

Potential for ARIPIPRAZOLE KIARA to affect other medicines

In clinical studies, 10 mg/day to 30 mg/day doses of ARIPIPRAZOLE KIARA had no significant effect on the 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, ARIPIPRAZOLE KIARA is unlikely to cause clinically important medicine interactions mediated by these enzymes.

When ARIPIPRAZOLE KIARA was administered concomitantly with either valproate, lithium or lamotrigine, there was no clinically important change in valproate, lithium or lamotrigine concentrations.

Serotonin syndrome

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of ARIPIPRAZOLE KIARA during pregnancy has not been established.
There are no adequate and well-controlled trials of ARIPIPRAZOLE KIARA in pregnant women. Congenital anomalies have been reported; however, causal relationship with ARIPIPRAZOLE KIARA could not be established. Animal studies could not exclude potential developmental toxicity.

Patients must be advised to notify their prescriber if they become pregnant or intend to become pregnant during treatment with ARIPIPRAZOLE KIARA. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, ARIPIPRAZOLE KIARA is not recommended for use during pregnancy.

Newborn/neonate

Newborn infants exposed to antipsychotic medicines (including ARIPIPRAZOLE KIARA) 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.

Breastfeeding

ARIPIPRAZOLE KIARA is excreted in human milk. Safety of the use of ARIPIPRAZOLE KIARA during breastfeeding has not been established.

Fertility

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

4.7 Effects on ability to drive and use machines

ARIPIPRAZOLE KIARA 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 advised not to drive or operate machinery until they are certain of how ARIPIPRAZOLE KIARA affects them.

4.8 Undesirable effects

List of adverse reactions

The following adverse reactions were reported during placebo-controlled clinical trials and were considered treatment-related:

Endocrine disorders

Less frequent: hyperprolactinaemia

Metabolism and nutrition disorders

Frequent: diabetes mellitus

Less frequent:	hyperglycaemia

Psychiatric disorders

Frequent:	insomnia[1], restlessness, anxiety[2]
Less frequent:	depression, hypersexuality

Nervous system disorders

Frequent:	headache, dizziness[1], akathisia, somnolence, sedation, tremor, extrapyramidal disorder
Less frequent:	neuroleptic malignant syndrome, tardive dyskinesia, seizures, dystonia[3]

Eye disorders

Frequent:	blurred vision
Less frequent:	diplopia

Cardiac disorders

Frequent:	tachycardia

Vascular disorders

Frequent:	orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Less frequent:	hiccups

Gastrointestinal disorders

Frequent:	nausea, vomiting, constipation, salivary hypersecretion[2],

	dyspepsia, stomach discomfort[2]

Musculoskeletal and connective tissue disorders

Frequent:	musculoskeletal stiffness[2]

General disorders and administration site conditions

Frequent:	asthenia/fatigue
Less frequent:	peripheral oedema[2]

[1] Reported only in patients treated for schizophrenia

[2] Reported only for patients treated for bipolar mania

[3] May occur in susceptible individuals during the first few days of treatment.

The following adverse reactions were reported during post-marketing use.

Blood and lymphatic system disorders

Frequency unknown:	leukopenia, neutropenia, thrombocytopenia

Immune system disorders

Frequency unknown:	allergic reaction (such as anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritis allergic or urticaria)

Metabolism and nutrition disorders

Frequency unknown:	diabetic hyperosmolar coma, diabetic ketoacidosis (DKA), hyponatraemia, anorexia, hyperglycaemia, diabetes mellitus, weight decreased, weight gain

Psychiatric disorders

Frequency unknown: suicide attempt, suicidal ideation and completed suicide (see section 4.4), pathological gambling, impulse-control disorder, binge eating, compulsive shopping, poriomania, aggression, agitation, nervousness, hypersexuality

Nervous system disorders

Frequency unknown: neuroleptic malignant syndrome, grand mal convulsion, serotonin syndrome, speech disorder

Eye disorders

Frequency unknown: diplopia, oculogyric crisis

Cardiac disorders

Frequency unknown: sudden death unexplained, torsades de pointes, QT prolongation, ventricular dysrhythmia, cardiac arrest, bradycardia

Vascular disorders

Frequency unknown: venous thromboembolism (including pulmonary embolism and deep vein thrombosis), hypertension, syncope

Respiratory, thoracic and mediastinal disorders

Frequency unknown: aspiration pneumonia, laryngospasm, oropharyngeal spasm, hiccups

Gastrointestinal disorders

Frequency unknown: pancreatitis, dysphagia, diarrhoea, abdominal discomfort, stomach 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 incontenence, urinary retention

Pregnancy, puerperium and perinatal conditions

Frequency unknown: drug withdrawal syndrome neonatal (see section 4.6)

Reproductive system and breast disorders

Frequency unknown: priapism

General disorders and administration site conditions

Frequency unknown: temperature regulation disorder (such as hypothermia, pyrexia), chest pain, peripheral oedema

Investigations

Frequency unknown:	alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, alkaline phosphatase increased, blood glucose increased, glycosylated haemoglobin increased, blood glucose fluctuation, creatine phosphokinase increased

Description of selected adverse reactions

Extrapyramidal symptoms (EPS)

Schizophrenia: a long-term 52-week controlled trial revealed that aripiprazole-treated patients had an overall-lower incidence of EPS including Parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol.

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 medicines. 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**.**

Laboratory parameters

Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters revealed no

medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed.

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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms of overdosage

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

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 be started immediately and should include continuous electrocardiographic monitoring to detect possible dysrhythmias. Following any confirmed or suspected overdose with ARIPIPRAZOLE KIARA, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal administered one hour after ARIPIPRAZOLE KIARA, decreased aripiprazole C_{max} by about 41 % and AUC by about 51 %, suggesting that charcoal may be effective in the treatment of overdose.

Although there is no information on the effect of haemodialysis in treating an overdose with ARIPIPRAZOLE KIARA, haemodialysis is unlikely to be useful in overdose management since ARIPIPRAZOLE KIARA is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6.5 Tranquillisers – miscellaneous structures

Pharmacotherapeutic group: Psycholeptics, other antipsychotics

ATC code: N05AX12

Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism of serotonin 5-HT_{2A} receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7 , alpha-1 adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole. The predominant metabolite in human plasma, dehydro-aripiprazole, has been shown to have similar affinities for D_2 receptors as the parent compound.

5.2 Pharmacokinetic properties

Absorption

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 to 5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation of aripiprazole is 87 %. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole. Steady-state concentrations are attained within 14 days of dosing. Aripiprazole accumulation by a factor of 5 is predictable with multiple dosing. At steady state, the pharmacokinetics of aripiprazole is dose proportional.

Distribution

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4,9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99 % bound to serum proteins, binding primarily to 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 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, represents about 40 % of aripiprazole AUC in plasma.

Elimination

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0,7 mL/min/kg, which is primarily hepatic.
Following a single oral dose of [^{14}C]-labelled aripiprazole, approximately 27 % of the administered radioactivity was recovered in the urine and approximately 60 % in the faeces. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

Elderly

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a 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.

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.
There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients. No dosage adjustment is recommended based on gender.

Smoking

Population pharmacokinetic evaluation has revealed no evidence of clinically significant effects from smoking on the pharmacokinetics of aripiprazole.

Race

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

Renal impairment

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects. 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 required in subjects with renal impairment.

Hepatic impairment

During a single-dose study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31 % in mild hepatic impairment, increased 8 % and in moderate hepatic impairment and decreased 20 % in severe hepatic impairment. None of these differences would require dose adjustment.

Paediatric population

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ARIPIPRAZOLE 5 KIARA:

Hydroxypropyl cellulose (E463)

Lactose monohydrate

Magnesium stearate (E572)

Maize starch

Microcrystalline cellulose (E460)

ARIPIPRAZOLE 10, 15 and 30 KIARA:

Hydroxypropyl cellulose (E463)

Iron oxide red (E172)

Lactose monohydrate

Magnesium stearate (E572)

Maize starch

Microcrystalline cellulose (E460).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture.

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

6.5 Nature and contents of container

OPA/Aluminium/PVC and aluminium blister strips packed in an cardboard carton.

Pack size: 10, 30, 60 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unichem SA (Pty) Ltd

San Domenico

Ground Floor, Unit G4

10 Church Street

Durbanville

Cape Town

7551

8. REGISTRATION NUMBERS

ARIPIPRAZOLE 5 KIARA: 48/2.6.5/0510.506

ARIPIPRAZOLE 10 KIARA: 48/2.6.5/0511.507

ARIPIPRAZOLE 15 KIARA: 48/2.6.5/0512.508

ARIPIPRAZOLE 30 KIARA: 48/2.6.5/0513.509

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 March 2021.

10. DATE OF REVISION OF THE TEXT

16 March 2021.