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SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ARIPIPRAZOLE 5 mg ACCORD (Tablets)

ARIPIPRAZOLE 10 mg ACCORD (Tablets)

ARIPIPRAZOLE 15 mg ACCORD (Tablets)

ARIPIPRAZOLE 30 mg ACCORD (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARIPIPRAZOLE 5 mg ACCORD: Each tablet contains 5 mg aripiprazole.

Contains sugar: 66,43 mg lactose monohydrate per tablet.

ARIPIPRAZOLE 10 mg ACCORD: Each tablet contains 10 mg aripiprazole.

Contains sugar: 62,00 mg lactose monohydrate per tablet.

ARIPIPRAZOLE 15 mg ACCORD: Each tablet contains 15 mg aripiprazole.

Contains sugar: 93,00 mg lactose monohydrate per tablet.

ARIPIPRAZOLE 30 mg ACCORD: Each tablet contains 30 mg aripiprazole.

Contains sugar: 186,00 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

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ARIPIPRAZOLE 5 mg ACCORD: Blue coloured, modified rectangle shaped, biconvex, uncoated tablets, debossed with "A5" on one side and another side is plain.

ARIPIPRAZOLE 10 mg ACCORD: Pink coloured, modified rectangle shaped, biconvex, uncoated tablets, debossed with "A10" on one side and another side is plain.

ARIPIPRAZOLE 15 mg ACCORD: Yellow coloured, round shaped, bevelled edge, biconvex, uncoated tablets, debossed with "A15" on one side and another side is plain.

ARIPIPRAZOLE 30 mg ACCORD: Pink coloured, round shaped, bevelled edge, biconvex, uncoated tablets, debossed with "A30" on one side and another side is plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Schizophrenia

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

Bipolar Mania:

ARIPIPRAZOLE ACCORD 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 ACCORD treatment.

4.2 Posology and method of administration

Posology

Schizophrenia:

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

higher than the recommended daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Bipolar Mania

The recommended starting dose for ARIPIPRAZOLE ACCORD is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see Section 4.5). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I disorder:

For preventing recurrence of manic episodes in patients who have been receiving aripiprazole, continue therapy at the same dose. Adjustments of daily dose, including dose reduction should be considered on the basis of clinical status. Prevention of depressive episodes using aripiprazole monotherapy has not been established. Supplementary therapy should be considered for the prevention or treatment of depressive episodes, as clinically appropriate.

Concomitant Medications:

Dosage adjustment for patients taking ARIPIPRAZOLE ACCORD concomitantly with potent CYP3A4 or CYP2D6 inhibitors:

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

Dosage adjustment for patients taking potent CYP3A4 inducers:

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

Paediatric population

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

Method of administration

ARIPIPRAZOLE ACCORD is for oral use.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.

Suicide:

The possibility of a suicide attempt is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic treatment, including aripiprazole. Close supervision of high-risk patients should accompany medicine therapy. Prescriptions for ARIPIPRAZOLE ACCORD should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Tardive Dyskinesia:

As the risk of tardive dyskinesia increases with long-term exposure to antipsychotic treatment, if signs and symptoms of tardive dyskinesia appear in a patient on ARIPIPRAZOLE ACCORD, a dose reduction or medicine discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Neuroleptic Malignant Syndrome:

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia).
Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including ARIPIPRAZOLE ACCORD must be discontinued.

Cardiovascular disorders:

ARIPIPRAZOLE ACCORD 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 and preventive measures undertaken.

QT prolongation

Aripiprazole should be used with caution in patients with a family history of QT prolongation (see Section 4.8).

Seizure:

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

Elderly patients with Dementia-related psychosis:

Elderly patients with dementia-related psychosis treated with aripiprazole, as in ARIPIPRAZOLE ACCORD, are at increased risk of death compared to placebo. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g. heart

failure, sudden death) or infectious (e.g. pneumonia) in nature.

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

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

Hyperglycaemia and Diabetes Mellitus:

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with aripiprazole.

Patients treated with ARIPIPRAZOLE ACCORD should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Patients who develop symptoms of hyperglycaemia during treatment with ARIPIPRAZOLE ACCORD should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when aripiprazole was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Hypersensitivity

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

Weight Gain:

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotic medicines known to cause weight gain, or poorly managed lifestyle, and might lead to severe complications. Weight gain has been reported in post-marketing experience among patients prescribed oral aripiprazole. 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 has not been shown to induce clinically relevant weight gain.

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. Other urges reported include: increased sexual urges, compulsive spending, binge or compulsive eating, and other impulsive and compulsive behaviors. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive spending, binge or compulsive eating, or other urges while being treated with ARIPIPRAZOLE ACCORD. 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 ACCORD.

Orthostatic Hypotension:

Potentially due to its α_1-adrenergic receptor antagonist activity, aripiprazole may be associated with orthostatic hypotension. Symptomatic orthostatic hypotension occurred in 1,3 % of aripiprazole-treated patients during pre-marketing clinical trials.

ARIPIPRAZOLE ACCORD 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 or conditions which would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medications).

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 ACCORD 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.

Dysphagia:

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

Laboratory Findings:

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

Patients with ADHD comorbidity:

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

Falls:

ARIPIPRAZOLE ACCORD 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).

ARIPIPRAZOLE ACCORD contains lactose:

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

4.5 Interaction with other medicines and other forms of interaction

General:

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

There was no effect of a high fat meal on the pharmacokinetics of aripiprazole.

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

Valproate:

When valproate (500 – 1500 mg/day) and aripiprazole (30 mg/day) were co-administered at steady-state, the C_{max} and AUC of aripiprazole were decreased by 25 %. No dosage adjustment of ARIPIPRAZOLE ACCORD is required when administered concomitantly with valproate.

Lithium:

A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolised, and is almost entirely excreted unchanged in the urine.

Co-administration of therapeutic doses of lithium (1200 – 1800 mg/day) for 21 days with

aripiprazole 30 mg/day did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite dehydro-aripiprazole (C_{max} and AUC increased by less than 20 %). No dosage adjustment of ARIPIPRAZOLE ACCORD is required when administered concomitantly with lithium.

Effect of other medicines on ARIPIPRAZOLE ACCORD:

There was no clinically significant effect of the H_2 antagonist, famotidine, on the pharmacokinetics of aripiprazole. Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Accordingly, no dosage adjustment is required for
smoking.

Quinidine and other CYP2D6 inhibitors

In a clinical study with healthy subjects, a potent inhibitor of CYP2D6 (quinidine) increased 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 %. ARIPIPRAZOLE ACCORD dose should be reduced to one-half of its prescribed dose when concomitant administration of ARIPIPRAZOLE ACCORD with quinidine occurs. Other potent inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and therefore, should be accompanied by similar dose reductions.

Ketoconazole and other CYP3A4 inhibitors

In a clinical study with healthy subjects, a potent inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63 % and 37 %. The AUC and C_{max} of dehydro-
aripiprazole increased by 77 % and 43 %.

In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolisers. When considering

concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with ARIPIPRAZOLE ACCORD, potential benefits should overweigh the potential risks to the patient.

When concomitant administration of ketoconazole with ARIPIPRAZOLE ACCORD occurs, the ARIPIPRAZOLE ACCORD dose should be reduced to one-half of its prescribed dose. Other potent inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors, may be expected to have similar effects and therefore, should be accompanied by similar dose reductions.

Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of ARIPIPRAZOLE ACCORD 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, modest increases in plasma aripiprazole concentrations may be expected.

Carbamazepine and other CYP3A4 inducers

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

ARIPIPRAZOLE ACCORD dose should be doubled when concomitant administration of aripiprazole occurs 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.

Upon discontinuation of potent CYP3A4 inducers, the dosage of ARIPIPRAZOLE ACCORD should be reduced to the recommended dose.

Medicine Interactions:

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

Serotonin syndrome:

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy

Patients should be advised to notify their medical practitioner if they become pregnant or intend to become pregnant during treatment with ARIPIPRAZOLE ACCORD.

Neonates exposed to antipsychotics (including ARIPIPRAZOLE ACCORD) 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.

Lactation

Aripiprazole is excreted in human breast milk.

Fertility

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

4.7 Effects on ability to drive and use machines

ARIPIPRAZOLE ACCORD 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 operating hazardous machinery, including motor vehicles until they are reasonably certain that ARIPIPRAZOLE ACCORD does not adversely affect them.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions were akathisia and nausea.

Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Blood and lymphatic system disorders	Frequency unknown	Leucopenia, neutropenia, thrombocytopenia
Immune system disorders	Frequency unknown	Allergic reaction (e.g., anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, or urticaria)
Endocrine disorders	Less frequent	Hyperprolactinaemia
	Frequency unknown	Diabetic hyperosmolar coma, diabetic ketoacidosis

Metabolism and nutrition disorders	Frequent	Diabetes mellitus
	Less frequent	Hyperglycaemia
	Frequency unknown	Hyponatraemia, anorexia, weight increased, weight decreased
Psychiatric disorders	Frequent	Insomnia, anxiety, restlessness
	Less frequent	Depression
	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	Frequent	Akathisia, extrapyramidal disorder, tremor, headache, sedation, somnolence, dizziness
	Less frequent	Tardive dyskinesia, dystonia, restless legs syndrome
	Frequency unknown	Neuroleptic malignant syndrome, grand mal convulsion, serotonin syndrome, speech disorder
Eye disorders	Frequent	Vision blurred
	Less frequent	Diplopia, photophobia
	Frequency unknown	Oculogyric crisis
Cardiac disorders	Frequent	**Schizophrenia:** tachycardia
	Less frequent	**Bipolar mania:** tachycardia
	Frequency unknown	Sudden death unexplained, Torsades de pointes, QT prolongation, ventricular dysrhythmia, cardiac arrest, bradycardia
Vascular disorders	Frequent	**Schizophrenia:**

		Orthostatic hypotension
	Less frequent	**Bipolar mania:** Orthostatic hypotension
	Frequency unknown	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis), hypertension, syncope
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Aspiration pneumonia, hiccups, laryngospasm, oropharyngeal spasm
Gastrointestinal disorders	Frequent	Constipation, dyspepsia, nausea, salivary hypersecretion, vomiting, stomach discomfort
	Frequency unknown	Pancreatitis, dysphagia, diarrhoea, abdominal discomfort
Hepato-biliary disorders	Frequency unknown	Hepatic failure, hepatitis, jaundice
Skin and subcutaneous tissue disorders	Frequency unknown	Rash, photosensitivity reaction, alopecia, hyperhidrosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Rhabdomyolysis, myalgia, stiffness
Renal and urinary disorders	Frequency unknown	Urinary incontinence, 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	Frequent	**Schizophrenia:** Fatigue, asthenia
	Less frequent	**Bipolar mania:** Peripheral oedema
	Frequency unknown	Temperature regulation disorder (e.g., hypothermia, pyrexia), chest pain, peripheral oedema
Investigations	Frequency unknown	Weight decreased, weight gain, increased ALT, increased AST, increased GGT, increased alkaline phosphatase, QT prolonged, increased blood glucose, increased glycosylated haemoglobin, blood glucose fluctuation, increased creatine phosphokinase

Description of selected adverse events

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.

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. Healthcare professionals 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

In clinical studies and post-marketing experience, accidental or intentional acute overdosage of aripiprazole alone was identified in patients with estimated doses up to 1260 mg with no fatalities.

The potentially medically important signs and symptoms observed included lethargy, blood pressure increased, somnolence, tachycardia and vomiting. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities.

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

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 ARIPIPRAZOLE ACCORD, close medical supervision and monitoring should continue until the patient recovers.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.6.5 Antipsychotic – miscellaneous structures

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX12

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.

Aripiprazole exhibited high binding affinity *in vitro* for dopamine D_2 and D_3, serotonin $5HT_{1a}$ and $5HT_{2a}$ receptors and moderate affinity for dopamine D_4, serotonin $5HT_{2c}$ and $5HT_7$, alpha$_1$-adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for serotonin reuptake site and no appreciable affinity for muscarinic receptors.

Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4,9 l/kg. At therapeutic concentrations, aripiprazole is greater than 99 %

bound to serum proteins, primarily albumin. Aripiprazole did not alter the pharmacokinetics and pharmacodynamics of highly protein-bound warfarin, suggesting that protein displacement of warfarin did not occur.

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.

Biotransformation

There is minimal diurnal variation in the disposition of aripiprazole and its active metabolite, dehydro-aripiprazole. This predominant metabolite in human plasma, dehydro-aripiprazole, has been shown to have similar affinities for D_2 receptors as the parent compound.

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

hydroxylation, and N-dealkylation.

Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicine moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represented about 39 % of aripiprazole AUC in plasma.

Elimination

The mean elimination half-life of aripiprazole is about 75 hours.

Following 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. The total body clearance of aripiprazole is 0,7 mℓ/min/kg, which is primarily hepatic.

Special populations

Hepatic impairment

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B and C), the AUC of aripiprazole, compared to healthy subjects, increased 31 % in mild hepatic impairment, increased 8 % in moderate hepatic impairment and decreased 20 % in severe hepatic impairment. None of these differences would require dose adjustment.

Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min, C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased 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.

Elderly

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20 % lower in elderly (≥ 65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients (see Warnings on increased mortality in elderly patients with dementia-related psychosis).

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.

Smoking

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Microcrystalline cellulose

Maize starch

Hydroxypropylcellulose

Magnesium stearate

Colorants

ARIPIPRAZOLE 5 mg ACCORD: Indigo carmine aluminium lake (E132)

ARIPIPRAZOLE 10 mg ACCORD & 30 mg: Ferric oxide red (E172)

ARIPIPRAZOLE 15 mg ACCORD: Ferric oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

ARIPIPRAZOLE ACCORD tablets are packed in :

- Alu-Alu blisters comprising lidding foil made of hard tempered aluminium foil, with HSL coating on bright side; and forming foil made of aluminium strip, soft temper, plain, one side bright, dull side lacquer laminated to OPA, bright side lacquer laminated to PVC. Pack sizes: 14, 28, 49, 56 or 98 tablets
- HDPE containers comprising wide mouth white opaque HDPE container fitted with white opaque polypropylene closure (with wad having induction sealing liner), desiccant canister and cotton coil. Pack sizes: 30 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

Accord Healthcare (Pty) Ltd

Building 2, Tuscany Office Park,

6 Coombe Place

Rivonia

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

ARIPIPRAZOLE 5 mg ACCORD (Tablets): 56/2.6.5/1169

ARIPIPRAZOLE 10 mg ACCORD (Tablets): 56/2.6.5/1169

ARIPIPRAZOLE 15 mg ACCORD (Tablets): 56/2.6.5/1169

ARIPIPRAZOLE 30 mg ACCORD (Tablets): 56/2.6.5/1169

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be confirmed.

10. DATE OF REVISION OF THE TEXT