PROFESSIONAL INFORMATION

SCHEDULING STATUS S5

1. NAME OF THE MEDICINE

Arizofy® 5 mg (tablets)

Arizofy® 10 mg (tablets)

Arizofy® 15 mg (tablets)

Arizofy® 20 mg (tablets)

Arizofy® 30 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg, 10 mg, 15 mg, 20 mg or 30 mg aripiprazole respectively.

Each ARIZOFY 5 mg tablet contains sugar (lactose monohydrate 71,017 mg).

Each ARIZOFY 10 mg tablet contains sugar (lactose monohydrate 65,967 mg).

Each ARIZOFY 15 mg tablet contains sugar (lactose monohydrate 97,751 mg).

Each ARIZOFY 20 mg tablet contains sugar (lactose monohydrate 132,333 mg).

Each ARIZOFY 30 mg tablet contains sugar (lactose monohydrate 196,500 mg).

3. PHARMACEUTICAL FORM

ARIZOFY 5 mg: Blue coloured, mottled, round shaped tablets, debossed with ‘SZ’ on one side and ‘444’ on the other side.

ARIZOFY 10 mg: Pink coloured, mottled, round shaped tablets debossed with ‘SZ’ on one side and ‘446’ on the other side.

ARIZOFY 15 mg: Yellow coloured, mottled, round shaped tablets debossed with ‘SZ’ on one side and ‘447’ on the other side.

ARIZOFY 20 mg: White coloured round shaped tablets debossed with ‘SZ’ on one side and ‘448’ on the other side.

ARIZOFY 30 mg: Pink coloured, mottled, round shaped tablets debossed with ‘SZ’ on one side and ‘449’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARIZOFY is indicated for the treatment of schizophrenia as well as for the maintenance of clinical improvement in adults.

ARIZOFY is indicated for the treatment of acute manic episodes associated with Bipolar I Disorder and for the prevention of recurrence of new manic episodes in patients who experienced predominantly manic episodes and who responded to ARIZOFY treatment (see section 5.1).

4.2 Posology and method of administration

Posology

Schizophrenia:

The recommended starting dose for ARIZOFY 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.

ARIZOFY 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.

Manic episodes in Bipolar I Disorder:

The recommended starting dose for ARIZOFY is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). 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.

Special population

Hepatic impairment:

No dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Renal impairment:

No dosage adjustment is required in patients with renal impairment.

Elderly:

The safety and efficacy of ARIZOFY 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 (see section 4.4).

Gender:

No dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status:

According to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

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

When concomitant administration of strong CYP3A4 inducers with ARIZOFY occurs, the ARIZOFY dose should be doubled. Additional dose increases of ARIZOFY should be based on clinical evaluation.

When the CYP3A4 inducer is withdrawn from the combination therapy, the ARIZOFY dose should be reduced to the recommended dose (see section 4.5).

Method of administration

ARIZOFY is for oral use.

4.3 Contraindications

- Hypersensitivity to aripiprazole or to any of the excipients (see section 6.1).

Paediatric use:

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

4.4 Special warnings and precautions for use

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

Suicidality:

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 ARIZOFY (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic treatment. Prescriptions for ARIZOFY should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular disorders:

ARIZOFY should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolaemia and treatment with antihypertensive medicines) or hypertension, including accelerated or malignant.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicines such as ARIZOFY. 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 ARIZOFY and preventative measures undertaken.

QT-prolongation:

In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. ARIZOFY 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.

If signs and symptoms of tardive dyskinesia appear in a patient on ARIZOFY dose reduction or discontinuation of ARIZOFY should be considered (see section 4.8). These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Other extrapyramidal symptoms (EPS):

In paediatric clinical trials of aripiprazole akathisia and parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

Neuroleptic malignant syndrome (NMS):

NMS is a potentially fatal symptom complex associated with antipsychotics. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. 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 medication, including ARIZOFY must be discontinued.

Seizure:

In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, ARIZOFY should be used with caution in patients who have a history of seizures or have conditions associated with seizures (see section 4.8).

Elderly patients with dementia-related psychosis:

Increased mortality

In three placebo-controlled trials (n = 938; mean age: 82,4 years; range: 56 - 99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with at increased risk of death compared to placebo. The rate of death in aripiprazole-treated patients was 3,5 % compared to 1,7 % in the placebo group. 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 (see section 4.8).

Cerebrovascular adverse reactions

In the same trials, cerebrovascular adverse events (e.g. stroke, transient ischaemic attack) including fatalities, were reported in patients (mean age: 84 years; range: 78 - 88 years).

Overall, 1,3 % of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0,6 % of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole (see section 4.8).

ARIZOFY is not indicated 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 atypical antipsychotics, including ARIZOFY.

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

In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotics are not available to allow direct comparisons.

Patients treated with any antipsychotics, including ARIZOFY should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control (see section 4.8). Patients who develop symptoms of hyperglycaemia during treatment with ARIZOFY should undergo fasting blood

glucose testing. In some cases hyperglycaemia may resolve when ARIZOFY is discontinued; however, some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Hypersensitivity:

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

Weight gain:

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed ARIZOFY. 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 in adults (see section 5.1). If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

Dysphagia:

Oesophageal dysmotility and aspiration have been associated with the use of antipsychotics, including ARIZOFY. ARIZOFY should be used cautiously in patients at risk of 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 ARIZOFY. 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 ARIZOFY. 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 ARIZOFY (see section 4.8).

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 ARIZOFY and stimulants; therefore, extreme caution should be taken when these medicines are co-administered

Falls:

ARIZOFY 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 or patients with known hypotension; see section 4.2).

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

Lactose intolerance:

Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ARIZOFY.

ARIZOFY contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Due to its α1-adrenergic receptor antagonism, ARIZOFY has the potential to enhance the effect of certain antihypertensive medicines.

Given the primary CNS effects of ARIZOFY, caution should be used when ARIZOFY is taken in combination with alcohol or other CNS medicines with overlapping adverse reactions such as sedation (see section 4.8).

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

There is no effect of a high fat meal on the pharmacokinetics of ARIZOFY.

Potential for other medicines to affect ARIZOFY:

A gastric acid blocker, the H_2 antagonist famotidine, reduces aripiprazole rate of absorption, but this effect is deemed not clinically relevant.

ARIZOFY 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 potent inhibitor of CYP2D6 (quinidine) increased aripiprazole's AUC by 107 %, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32 – 47 %, respectively. ARIZOFY dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of ARIZOFY and 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's 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 compared to that in CYP2D6 extensive metabolisers. When considering concomitant administration of ketoconazole or other strong CYP3A4 inhibitors with ARIZOFY, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with ARIZOFY occurs, ARIZOFY dose should be reduced to approximately one-half of its prescribed dose. Other strong inhibitors of CYP3A4, such as itraconazole and 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 dose of ARIZOFY 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 ARIZOFY, modest increases in aripiprazole concentrations might be expected.

Carbamazepine and other CYP3A4 inducers

Following concomitant administration of carbamazepine , a strong inducer of CYP3A4, and aripiprazole to patients with schizophrenia or schizoaffective disorder, the geometric means of C_{max} and AUC for aripiprazole 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 AUC after carbamazepine co-administration were 69 % and 71 % lower respectively, than those following treatment with aripiprazole alone.

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

Concomitant administration of ARIZOFY and other inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John’s wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of strong CYP3A4 inducers, the dose of ARIZOFY should be reduced to the recommended dose.

Valproate and lithium:

The co-administration of valproate (500 – 1500 mg/day) and aripiprazole (30 mg/day) lead to a 25 % decrease of the C_{max} and AUC of aripiprazole.

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

Therefore, no dose adjustment is necessary when either valproate or lithium is administered with ARIZOFY.

Potential for ARIZOFY to affect other medicines:

In clinical studies, 10 – 30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole) and CYP3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, ARIZOFY is unlikely to cause clinically important interactions mediated by these enzymes.

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

ARIZOFY may enhance the effects of antihypertensive medicines.

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 medicinal products that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Safety and efficacy during pregnancy and lactation have not been established.

Pregnancy:

There are no adequate and well-controlled trials of ARIZOFY in pregnant women.

Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3).

Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with ARIZOFY.

Due to insufficient safety information in humans and concerns raised by animal reproductive studies, ARIZOFY should not be used in pregnancy.

New-born infants exposed to antipsychotics (including ARIZOFY) 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, new-born infants should be monitored carefully (see section 4.8).

Lactation

Aripiprazole is excreted in human milk.

A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from ARIZOFY therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility:

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

4.7 Effects on ability to drive and use machines

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

Patients should take special care when operating hazardous machinery or driving motor vehicles until they know how ARIZOFY will affect them.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported undesirable effects observed for aripiprazole in placebo-controlled trials are akathisia and nausea each occurring in more than 3 % of patients treated with oral aripiprazole.

Blood and the lymphatic system disorders:

***Frequency unknown*:** Leukopenia, neutropenia, thrombocytopenia

Immune system disorders:

***Frequency unknown*:** Allergic reaction (e.g., anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, urticaria)

Endocrine disorders:

Less frequent: Hyperprolactinaemia, blood prolactin decreased

Frequency unknown**:** Diabetic ketoacidosis (DKA), diabetic hyperosmolar coma

Metabolism and nutrition disorders:

Frequent: Diabetes mellitus

Less frequent: Hyperglycaemia

Frequency unknown**:** Hyponatraemia, weight gain, decreased weight, anorexia

Psychiatric disorders:

Frequent: Restlessness, anxiety, insomnia

Less frequent: Depression, hypersexuality

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

Nervous system disorders:

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

Less frequent: Tardive dyskinesia, seizures, dystonia, restless leg syndrome

Frequency unknown**:** Neuroleptic malignant syndrome (NMS), speech disorder, grand mal convulsion, serotonin syndrome

Eye disorders:

Frequent: Vision blurred

Less frequent: Diplopia

Frequency unknown: Oculogyric crisis

Cardiac disorders:

Less Frequent: Tachycardia

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

Vascular disorders:

Frequent: Orthostatic hypotension

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

Respiratory, thoracic and mediastinal disorders:

Less Frequent: Hiccups

Frequency unknown: Aspiration pneumonia, oropharyngeal spasm, laryngospasm

Gastrointestinal disorders:

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

Frequency unknown: Pancreatitis, dysphagia, abdominal discomfort, stomach discomfort, diarrhoea

Hepatobiliary disorders:

Frequency unknown: Hepatitis, jaundice, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased gamma-glutamyl transferase (GGT), increased alkaline phosphatase, hepatic failure

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, musculoskeletal stiffness

Renal and urinary disorders:

Frequency unknown: Urinary retention, urinary incontinence

Pregnancy, puerperium and perinatal conditions:

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

Reproductive system and breast disorders:

Frequency unknown: Priapism

General disorders and administration site conditions:

Frequent: Asthenia, fatigue

Frequency unknown: Temperature regulation disorder (e.g., hypothermia, pyrexia), chest pain, peripheral oedema

Investigations:

Frequency unknown: Increased creatinine phosphokinase, blood glucose, blood glucose fluctuation, glycosylated haemoglobin increased

Description of selected adverse reactions

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).

Reporting of suspected adverse reactions

Reporting suspecting 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

Suspected adverse reactions can also be reported directly to the Holder of the Certificate of Registration (HCR) via the link Sandoz (iqvia.com) or the e-mail address, adverse.event.sac@sandoz.com

4.9 Overdose

Signs and Symptoms:

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 in children include 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 medication involvement should be considered. Therefore, cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

Following any confirmed or suspected overdose of ARIZOFY, close medical supervision and monitoring should continue until patient recovers.

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

Haemodialysis

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 2.6.5 Tranquilisers – miscellaneous structures

5.1 Pharmacodynamic properties

Mechanism of action

Aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D_2 and serotonin $5HT_{1a}$ receptors and antagonism at serotonin $5HT_{2a}$ receptors.

Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibits a 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 exhibits moderate binding affinity for 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.

Aripiprazole doses ranging from 0,5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}C-raclopride, a D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical efficacy and safety

Adults

Schizophrenia

In three short-term (4 to 6 weeks) placebo-controlled trials involving 1228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

Aripiprazole is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77 % and haloperidol 73 %). The overall completion rate was significantly higher for patients on aripiprazole (43 %) than for haloperidol (30 %). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Asberg Depression Rating Scale showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in adult stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34 % in aripiprazole group and 57 % in placebo.

Weight gain

In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 adult patients and where the primary endpoint was weight gain, significantly less patients had at least 7 % weight gain over baseline (i.e. a gain of at least 5,6 kg for a

mean baseline weight of ~80,5 kg) on aripiprazole (n = 18, or 13 % of evaluable patients), compared to olanzapine (n = 45, or 33 % of evaluable patients).

Lipid parameters

In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, HDL and LDL.

Prolactin

Prolactin levels were evaluated in all trials of all doses of aripiprazole (n = 28242). The incidence of hyperprolactinaemia or increased serum prolactin in patients treated with aripiprazole (0,3 %) was similar to that of placebo (0,2 %). For patients receiving aripiprazole, the median time to onset was 42 days and median duration was 34 days.

The incidence of hypoprolactinaemia or decreased serum prolactin in patients treated with aripiprazole was 0,4 %, compared with 0,02 % for patients treated with placebo. For patients receiving aripiprazole, the median time to onset was 30 days and median duration was 194 days.

Manic episodes in Bipolar I Disorder

In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilisation phase prior to randomisation, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Y-MRS and MADRS total scores ≤ 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46 % decreased risk (hazard ratio of 0,54) in preventing bipolar recurrence and a 65 % decreased risk (hazard ratio of 0,35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into

depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure, CGI-BP Severity of Illness score (mania).

In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabiliser.

Stabilised patients were then randomised to continue the same mood stabiliser with double-blind aripiprazole or placebo. Four mood stabiliser subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate.

The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16 % in aripiprazole + lithium and 18 % in aripiprazole + valproate compared to 45 % in placebo + lithium and 19 % in placebo + valproate.

5.2 Pharmacokinetic properties

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

Absorption:

Aripiprazole is well absorbed after oral administration, with peak plasma concentrations occurring within 3 - 5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87 %. The

bioavailability of aripiprazole is not significantly affected by administration of food. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution:

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4,9 l/kg. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole is 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 moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represented about 40 % 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 % of the oral dose was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

Elderly:

Where aripiprazole was given as a single dose of 15 mg, clearance was 20 % lower in elderly (≥ 65 years) patients compared to younger adult patients (18 to 64 years).

There are no differences in the pharmacokinetics of aripiprazole after multiple doses in healthy elderly adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenia patients. No dosage adjustment is recommended for elderly patients (see section 4.2 and section 4.4 - 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. 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.

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 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 required based on smoking status.

Race:

Population pharmacokinetic evaluation showed no evidence of race-related differences on the pharmacokinetics of aripiprazole.

Renal impairment:

In patients with severe renal impairment (creatinine clearance < 30 ml/min), C_{max} of aripiprazole (given as 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 for both unchanged aripiprazole and dehydro-aripiprazole is less than 1 % of the dose. No dosage adjustment is required in patients with renal impairment.

Hepatic impairment:

After a single dose administration (15 mg of aripiprazole) in patients with varying degrees of liver cirrhosis (Child-Pugh Classes A, B and C), the AUC of aripiprazole, compared to healthy patients, 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats

after 104 weeks at 20 to 60 mg/kg/day (3 to 10 times the mean steady-state AUC at the maximum recommended human dose) and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 7 times the human exposure at the recommended dose.

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m^2). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6 % of the bile concentrations found in the monkeys in the 39 week study and are well below (6 %) their limits of *in vitro* solubility.

In repeat-dose studies in juvenile rats and dogs, the toxicity profile of aripiprazole was comparable to that observed in adult animals, and there was no evidence of neurotoxicity or adverse reactions on development.

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic.

Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in sub-therapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the

maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, maize starch, and microcrystalline cellulose.

ARIZOFY 5 mg: Aluminium lake (FD & C blue no. 2 aluminium lake) and indigo carmin (E132)

ARIZOFY 10 mg & 30 mg: Iron oxide red (E172)

ARIZOFY 15 mg: Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove from outer carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

ARIZOFY 5 mg: Aluminium/aluminium foil blister packs containing 10 tablets.

ARIZOFY 10 mg: Aluminium/aluminium foil blister packs containing 10 tablets.

ARIZOFY 15 mg: Aluminium/aluminium foil blister packs containing 10 tablets.

ARIZOFY 20 mg: Aluminium/aluminium foil blister packs containing 10 tablets.

ARIZOFY 30 mg: Aluminium/aluminium foil blister packs containing 10 tablets.

The blister packs are packed into an outer cardboard carton containing 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBER(S)

ARIZOFY 5 mg: 46/2.6.5/0874

ARIZOFY 10 mg: 46/2.6.5/0875

ARIZOFY 15 mg: 46/2.6.5/0876

ARIZOFY 20 mg: 46/2.6.5/0877

ARIZOFY 30 mg: 46/2.6.5/0878

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 September 2017

10. DATE OF REVISION OF THE TEXT

11 April 2023

[1]Company Reg. No.: 1990/001979/07