PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ABILIFY 5 mg, 10 mg and 15 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ABILIFY 5 mg tablets

Each tablet contains 5 mg of aripiprazole.

contains sugar: 67 mg lactose (as monohydrate) per tablet

ABILIFY 10 mg tablets

Each tablet contains 10 mg of aripiprazole.

Contains sugar: 62,18 mg lactose (as monohydrate) per tablet

ABILIFY 15 mg tablets

Each tablet contains 15 mg of aripiprazole.

Contains sugar: 57 mg lactose (as monohydrate) per tablet

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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ABILIFY 5 mg: Blue, modified, rectangular tablets, debossed on one side with “A-007” and “5”.

ABILIFY 10 mg: Pink, modified, rectangular tablets, debossed on one side with “A-008” and “10”.

ABILIFY 15 mg: Yellow, round tablets, debossed on one side with “A-009” and “15”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Schizophrenia:

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

Bipolar Mania:

ABILIFY 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 ABILIFY treatment.

4.2 Posology and method of administration

Posology

Schizophrenia:

The recommended starting dose for ABILIFY 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.

ABILIFY 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 ABILIFY is 15 mg administered on a once-a-day

schedule without regard to meals as monotherapy or combination therapy (see *Medicine Interactions and other forms of Interactions*). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I disorder: 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 ABILIFY concomitantly with potent CYP3A4 or CYP2D6 inhibitors: When concomitant administration of a potent CYP3A4 or CYP2D6 inhibitor with ABILIFY occurs, the ABILIFY dose should be reduced to one-half of the usual dose. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, the ABILIFY dose should then be increased.

Dosage adjustment for patients taking potent CYP3A4 inducers: When a potent CYP3A4 inducer is added to ABILIFY therapy, the ABILIFY dose should be doubled.

Additional dose increases of ABILIFY should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from the combination therapy, the ABILIFY dose should be reduced.

Method of administration

ABILIFY is for oral use

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4.3 Contraindications

ABILIFY is contra-indicated in patients who are hypersensitive to aripiprazole or any of the excipients listed in section 6.1.

Paediatric use

The safety and efficacy of ABILIFY 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.

Suicide: The possibility of a suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany medicine therapy. Prescriptions for ABILIFY 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 ABILIFY, 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 ABILIFY must be discontinued.

Cardiovascular disorders: ABILIFY 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 medicinal products) or hypertension, including accelerated or malignant. Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. 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.

Seizure: ABILIFY 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 ABILIFY, 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 three placebo-controlled trials of ABILIFY 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.

ABILIFY 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 ABILIFY.

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

Weight Gain: Antipsychotic drugs have been associated with metabolic changes, including weight gain. Weight gain has been reported post-marketing experience among patients prescribed oral ABILIFY. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials ABILIFY 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 ABILIFY. 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 ABILIFY. 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 ABILIFY.

Orthostatic Hypotension: Potentially due to its α_1-adrenergic receptor antagonist activity, ABILIFY may be associated with orthostatic hypotension. Symptomatic orthostatic hypotension occurred in 1,3 % of ABILIFY-treated patients during pre-marketing clinical trials.
ABILIFY 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 agents. Appropriate care is advised when prescribing ABILIFY 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. ABILIFY and other antipsychotic medicines should be used cautiously in patients at risk of aspiration pneumonia.

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Laboratory Findings: Comparisons between ABILIFY 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 medicinal products are co- administered.

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

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

4.5 Interaction with other medicines and other forms of interactions

General:

Given the primary CNS effects of ABILIFY, caution should be used when ABILIFY is taken in combination with other centrally acting medicines. Combination use of ABILIFY with alcohol should be avoided. Due to its α1-adrenergic receptor antagonist activity, ABILIFY has the potential to enhance the effect of certain antihypertensive agents.

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

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 ABILIFY is required when administered concomitantly with valproate.

Lithium: A pharmacokinetic interaction of ABILIFY 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 ABILIFY 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 less than 20 %). No dosage adjustment of ABILIFY is required when administered concomitantly with lithium.

Effect of other medicines on ABILIFY:

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

ABILIFY is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Accordingly, no dosage adjustment is required for smoking.

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 %. ABILIFY dose should be reduced to one-half of its prescribed dose when concomitant administration of ABILIFY 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.

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 ABILIFY, potential benefits should overweigh the potential risks to the patient.

When concomitant administration of ketoconazole with ABILIFY occurs, ABILIFY 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 ABILIFY should be increased to the level prior to the initiation of the concomitant therapy.

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 ABILIFY (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 ABILIFY alone treatment.

ABILIFY dose should be doubled when concomitant administration of ABILIFY 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 ABILIFY should be reduced to the recommended dose.

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Medicine Interactions:

In clinical studies, 10 - 30 mg/day doses of oral ABILIFY 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, ABILIFY 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 medicinal products, 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 of use of ABILIFY during pregnancy and lactation has not been established.

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

Neonates exposed to antipsychotics (including ABILIFY) 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.

Aripiprazole is excreted in human breast milk.

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4.7 Effects on ability to drive and use machines

ABILIFY 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 ABILIFY does not adversely affect them.

4.8 Undesirable effects

Frequency is defined as very common (≥ 1/10 or ≥ 10 %); common (≥ 1/100, < 1/10 or ≥ 1 % and < 10 %); uncommon (≥ 1/1,000, < 1/100 or ≥ 0,1 % and < 1 %), rare (≥ 1/10 000, < 1/1 000 or ≥ 0,01 % and < 0,1 %) or very rare (< 1/10 000 or < 0,01 %).

Adverse events that occurred during placebo-controlled trials with ABILIFY tablets and were considered treatment–related:

Schizophrenia:

Endocrine disorders:

Uncommon: Hyperprolactinaemia, blood prolactin decreased

Psychiatric disorders

Very Common: Insomnia

Common: Restlessness

Nervous System disorders

Very Common: Headache

Common: Dizziness, akathisia, somnolence/sedation, tremor, extrapyramidal disorder

Eye disorders

Common: Blurred vision

Cardiac disorders

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Common: Tachycardia

Vascular disorders

Common: Orthostatic hypotension

Gastrointestinal disorders

Common: Nausea, vomiting, constipation, dyspepsia

General disorders and administration site conditions

Common: Asthenia/fatigue

Bipolar Mania:

Endocrine disorders

Uncommon: Hyperprolactinaemia, blood prolactin decreased

Psychiatric disorders

Common: Restlessness, anxiety

Nervous System disorders

Very Common: Headache, akathisia

Common: Sedation, tremor, extrapyramidal disorder, somnolence

Eye disorders

Common: Blurred vision

Cardiac disorders

Uncommon: Tachycardia

Vascular disorders

Uncommon: Orthostatic hypotension

Gastrointestinal disorders

Very common: Nausea

Common: Constipation, vomiting, salivary hypersecretion, dyspepsia, stomach discomfort

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General disorders and administration site conditions

Common: Fatigue

Uncommon: Peripheral oedema

Musculoskeletal and Connective Tissue disorders

Common: Musculoskeletal stiffness

Other Findings:

There have been rare reports of neuroleptic malignant syndrome and uncommon occurrences of tardive dyskinesia or seizures.

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment.

Post-Introduction Treatment Emergent Adverse Medicine Reactions:

Blood and Lymphatic System Disorders

Leukopenia, neutropenia, thrombocytopenia

Endocrine Disorders

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

Psychiatric Disorders

Agitation, Pathological gambling, Hypersexuality, Impulse control Disorders, suicide attempt, suicidal ideation and completed suicide, binge eating, poriomania, compulsive shopping, aggression, nervousness

Nervous System Disorders

Speech disorder, grand mal convulsion, serotonin syndrome, restless legs syndrome

Eye disorders

Diplopia, Oculogyric crisis

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Cardiac disorders

Sudden unexplained death, Torsades de pointes, QT prolongation, ventricular dysrhythmias, cardiac arrest, bradycardia

Vascular Disorders

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

Gastrointestinal Disorders

Pancreatitis, dysphagia, diarrhoea

General Disorders and Administration Site Conditions

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

Skin and Subcutaneous Tissue Disorders

Allergic reaction (e.g. anaphylactic reaction, angioedema, pruritus or urticaria, rash, laryngospasm), hyperhidrosis, alopecia, photosensitivity, drug reaction with eosinophilia and systemic symptoms (DRESS)

Investigations

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

Musculoskeletal and Connective Tissue Disorders:

Rhabdomyolysis, myalgia, musculoskeletal stiffness

Reproductive System and Breast Disorders:

Priapism

Renal and Urinary Disorders:

Urinary retention, urinary incontinence

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Respiratory, Thoracic and Mediastinal Disorders:

Aspiration pneumonia, hiccups, oropharyngeal spasm

Hepatobiliary Disorders:

Hepatic failure, hepatitis, jaundice

Metabolism and Nutrition disorders:

Hyponatraemia, anorexia, weight increased, weight decreased

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

In clinical studies and post-marketing experience, accidental or intentional acute overdosage of ABILIFY 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 ABILIFY 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 ABILIFY, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after ABILIFY, 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 ABILIFY, haemodialysis is unlikely to be useful in overdose management since ABILIFY is not eliminated unchanged by the kidneys and is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6.5 Antipsychotic – miscellaneous structures.

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.

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5.2 Pharmacokinetic properties

ABILIFY activity is primarily due to the parent medicine, aripiprazole. The mean elimination half- life of aripiprazole is about 75 hours. 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.

Aripiprazole is well absorbed after oral administration of ABILIFY, 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.

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.

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.

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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

The pharmacokinetics of aripiprazole in special populations are described below.

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).

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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.

PROFESSIONAL INFORMATION

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Maize starch

Microcrystalline cellulose

Hydroxypropyl cellulose

Magnesium stearate

Tablet coat

ABILIFY 5 mg tablets

Indigo carmine aluminium lake (E 132)

ABILIFY 10 mg tablets

Red iron oxide (E 172)

ABILIFY 15 mg tablets

Yellow iron oxide (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 Years

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6.4 Special precautions for storage

Store below 30 ºC in the original container.

Store all medicines out of reach of children.

6.5 Nature and contents of container

ABILIFY tablets are available in aluminium/aluminium blister packs of 30 or 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

H. LUNDBECK (Pty) Ltd.

Unit 9 Blueberry Office Park,

Apple Street,

Randpark Ridge Ext 114, 2156

South Africa

8. REGISTRATION NUMBERS

ABILIFY 5 mg: 41/2.6.5/0493

ABILIFY 10 mg: A38/2.6.5/0595

ABILIFY 15 mg: A38/2.6.5/0596

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

30 September 2011

PROFESSIONAL INFORMATION

10. DATE OF REVISION OF THE TEXT

08 September 2022

Under license from Otsuka Pharmaceutical Co. Ltd., Tokyo 101-8535 Japan