Professional Information for

ABIPIP 5 / 10 / 15 / 30

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ABIPIP 5, 5 mg tablets

ABIPIP 10, 10 mg tablets

ABIPIP 15, 15 mg tablets

ABIPIP 30, 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ABIPIP 5: each tablet contains 5 mg of aripiprazole.

ABIPIP 10: each tablet contains 10 mg of aripiprazole.

ABIPIP 15: each tablet contains 15 mg of aripiprazole.

ABIPIP 30: each tablets contains 30 mg of aripiprazole.

Contains sugar: crystalline maltose.

ABIPIP 5: each tablet contains 28 mg of crystalline maltose.

ABIPIP 10: each tablet contains 56 mg of crystalline maltose.

ABIPIP 15: each tablet contains 84 mg of crystalline maltose.

ABIPIP 30: each tablet contains168 mg of crystalline maltose.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Tablet

ABIPIP 5: Light blue to blue, mottled, round, biconvex tablets, engraved with “5” on one side.

ABIPIP 10: Pink, round, biconvex tablets, engraved with “10” on one side.

ABIPIP 15: Yellow, round, biconvex tablets, engraved with “15” on one side.

ABIPIP 30: Pink, oval, biconvex tablets, engraved with “30” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABIPIP is indicated for:

- the treatment of schizophrenia and for the maintenance of clinical improvement in adults,
- the treatment of acute manic episodes in bipolar I disorder and
- for the prevention of recurrence of new manic episodes in patients who experienced predominantly manic episodes and who responded to ABIPIP treatment.

4.2 Posology and method of administration

Posology

Schizophrenia

The recommended starting dose for ABIPIP 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. ABIPIP 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 ABIPIP 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.

Prevention of recurrence of manic episodes in bipolar I disorder

For preventing recurrence of manic episodes in patients who have been receiving ABIPIP, 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 ABIPIP monotherapy has not been established. Supplementary therapy should be considered for the prevention or treatment of depressive episodes, as clinically appropriate.

Concomitant medicines

Dosage adjustment for patients taking ABIPIP concomitantly with potent CYP3A4 or CYP2D6 inhibitors

- When a potent CYP3A4 or CYP2D6 inhibitor is given concomitantly with ABIPIP, the ABIPIP dose should be reduced to one-half of the usual dose.
- When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, the ABIPIP dose should be increased.

Dosage adjustment for patients taking potent CYP3A4 inducers

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

Paediatric population

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

Method of administration

ABIPIP is for oral use.

4.3 Contraindications

ABIPIP is contraindicated in:

- Patients who are hypersensitive to aripiprazole or any of the excipients of ABIPIP (see **section 6.1**).
- ABIPIP is not indicated for use in elderly patients with dementia-related psychosis (see **section 4.4**).

Paediatric use: The safety and efficacy of ABIPIP in children and adolescents under 18 years of age have not been established. The use of ABIPIP is therefore not indicated for this population.

4.4 Special warnings and precautions for use

Increased mortality in elderly patients with dementia-related psychosis

ABIPIP is not approved for the treatment of patients with dementia-related psychosis (see **section 4.3**). Elderly patients with dementia-related psychosis treated with ABIPIP, are at increased risk of death compared to placebo.

Most of the deaths reported in elderly patients with dementia-related psychosis appeared to be either due to cardiovascular causes (e.g. heart failure, sudden death) or infections like pneumonia (see **Cerebrovascular adverse events (CVAE), including stroke**).

Suicide

There is an increased risk of suicide attempts in patients with psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with ABIPIP (see **section 4.8**). High-risk patients (clinical worsening of depression, suicidal ideation and unusual changes in behaviour) should be closely observed when ABIPIP is prescribed. The risk of suicide persists beyond the first four weeks of treatment for atypical antipsychotics including ABIPIP.

To reduce the risk of overdose, prescriptions for ABIPIP should be written for the smallest quantity of tablets consistent with good patient management.

Extrapyramidal symptoms

Extrapyramidal dysfunction and resultant disorders may occur. These disorders include acute dystonia, a parkinsonism-like syndrome and akathisia; late effects include tardive dyskinesia and perioral tremor (see **section 4.8**).

Tardive dyskinesia

The risk of tardive dyskinesia increases with long-term exposure to antipsychotic treatment, such as ABIPIP (see **section 4.8**). If signs and symptoms of tardive dyskinesia appear in a patient, it should be considered to reduce the dose of, or to discontinue, ABIPIP. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Elderly patients with dementia, especially Lewy-body dementia, are reported to be highly susceptible to the extrapyramidal side effects of antipsychotic medicines (such as ABIPIP), and the reaction can be extremely serious, even fatal. ABIPIP is, however, contraindicated in this population (see **section 4.3**).

Pathological Gambling and Other Impulse-Control Disorders

Pathological gambling has been reported. Patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully. Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking ABIPIP. Other urges reported include increased sexual urges, compulsive spending, 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 spending, binge or compulsive eating, or other urges while being treated with ABIPIP. 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 medicine if a patient develops such urges while taking ABIPIP (see **section 4.8**).

Neuroleptic malignant syndrome

A potentially fatal symptom complex, neuroleptic malignant syndrome (NMS), has been reported. NMS may manifest as hyperpyrexia, muscle rigidity, altered mental status and 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 ABIPIP, must be discontinued.

Seizures / convulsions

Seizures may occur with ABIPIP (the frequency is less frequent). It should therefore be used with care in those with a history of seizures or with conditions that lower the seizure threshold (see **section 4.8**).

Cerebrovascular adverse events (CVAE), including stroke

Cerebrovascular adverse events (e.g. stroke, transient ischaemic attack), including fatalities, have also been reported in elderly patients with psychosis associated with Alzheimer's disease. ABIPIP is contraindicated in patients with dementia-related behavioural disturbances (see **section 4.3** and **Increased mortality in elderly patients with dementia-related psychosis**). A significant dose response relationship for cerebrovascular adverse reactions in patients treated with

aripiprazole (such as ABIPIP) has been established.

- Before prescribing to elderly patients, medical practitioners should take into account risk predictions for stroke in the individual patient (e.g. hypertension, diabetes, current smoking, atrial fibrillation, and age > 80 years).
- Where the use of antipsychotics in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances (see **Falls and fractures**), over-sedation and complications associated with hyperglycaemia.

Cardiovascular disorders

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.

ABIPIP 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 that would predispose patients to hypotension (dehydration, hypovolaemia and treatment with antihypertensive medicines) or hypertension, including accelerated or malignant (see **section 4.8**).

Conduction abnormalities

Tachycardia and orthostatic hypotension may occur frequently with ABIPIP treatment; bradycardia, ventricular dysrhythmias, cardiac arrest, and sudden

unexplained death have been reported at unknown frequency, as have QT prolongation and *torsade de pointes* (see **section 4.8**).

QT prolongation

Aripiprazole as in ABIPIP should be used with caution in patients with a family history of QT prolongation (see **section 4.8**).

Orthostatic hypotension

ABIPIP may cause orthostatic hypotension, which may be attributed to its α_1-adrenergic receptor antagonism (see **section 4.8**). ABIPIP must be used with caution in patients with hypotension predisposition.

Falls and fractures

ABIPIP 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).

The risk of falls and hip fracture has been reported to be increased in elderly patients given antipsychotics. Where the use of antipsychotics such as ABIPIP in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances and over-sedation.

Metabolic changes

ABIPIP alters endocrine and metabolic functions. Patients have developed

amenorrhoea, galactorrhoea, hyperprolactinaemia and gynaecomastia, weight gain, hyperglycaemia and altered glucose tolerance. Body temperature regulation may be impaired and may result in hypo- or hyperthermia depending on environment. There have also been reports of hypercholesterolaemia.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported (see **section 4.8**).

Patients treated with ABIPIP 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 (with a family history of diabetes or who are obese), should be monitored regularly for worsening of glucose control.

Patients who develop symptoms of hyperglycaemia during treatment with ABIPIP should undergo fasting blood glucose testing. Hyperglycaemia may be resolved when ABIPIP is discontinued, however, some patients may still need continuation of anti-diabetic treatment, despite discontinuation of the suspect medicine.

Dyslipidaemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, such as ABIPIP.

Weight gain

Weight gain has been reported. When seen, it is usually in those with significant risk factors such as a history of diabetes, thyroid disorder or pituitary adenoma.

Aripiprazole as in ABIPIP has not been shown to induce clinically relevant weight gain. If weight gain is clinically significant, dose reduction should be considered.

Hypersensitivity

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

Blood dyscrasias

Blood dyscrasias, including agranulocytosis, leucopenia, neutropenia, and thrombocytopenia may occur (see **section 4.8**).

Patients with a history of clinically significant low white blood cell count (WBC) or medicine-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy. Discontinuation of ABIPIP should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Potential for cognitive and motor impairment

Antipsychotics, including ABIPIP, may have the potential to impair judgment, thinking, or motor skills (see **section 4.8** and **section 4.7**).

Body temperature Regulation

Antipsychotic medicines, such as ABIPIP, may disrupt the body's ability to reduce the core body temperature. Appropriate care is advised when prescribing ABIPIP 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 a concomitant medicine with anticholinergic activity, or being subject to dehydration.

Dysphagia

Oesophageal dysmotility and aspiration have been associated with the use of antipsychotic medicines, including ABIPIP. ABIPIP and other antipsychotic medicines should be used with caution in patients at risk of aspiration pneumonia.

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

Maintenance therapy

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

Patients should be periodically re-assessed to determine the usefulness of continuation of maintenance treatment; the effectiveness of long-term use (more than 6 months) has not been documented.

Other medicines

Simultaneous administration of ABIPIP and parenteral benzodiazepine may be associated with excessive sedation and cardiorespiratory depression (see **section 4.5**). If supplementation with parenteral benzodiazepine therapy is deemed

necessary, patients should be monitored for excessive sedation and for orthostatic hypotension.

Crystalline Maltose

ABIPIP contains maltose, which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase / isomaltase insufficiency should not take ABIPIP.

4.5 Interaction with other medicines and other forms of interaction

General

There was no effect of a high fat meal on pharmacokinetic of aripiprazole as in ABIPIP**.**

Valproate and lithium

When either valproate or lithium was administered concomitantly with aripiprazole as in ABIPIP, there was no clinically significant change in aripiprazole as in ABIPIP concentrations and therefore no dose adjustment is necessary when either valproate or lithium is administered with ABIPIP.

Potential effect of other medicines on ABIPIP

Aripiprazole as in ABIPIP is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

CYP2D6 inhibitors (quinidine, fluoxetine, paroxetine etc.)

The AUC of aripiprazole is significantly increased by CYP2D6 inhibitors, but the C_{max} is not affected. ABIPIP dose should be reduced to about one-half of its prescribed dose when concomitant administration with these medicines occurs.

CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, HIV protease inhibitors)

Concomitant use of CYP3A4 inhibitors causes significant increases in aripiprazole and dehydro-aripiprazole's AUC and C_{max}.

In CYP2D6 poor metabolisers, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole (contained in ABIPIP) compared to that in CYP2D6 extensive metabolisers.

When concomitant administration of strong CYP3A4 inhibitors with ABIPIP occurs, ABIPIP dose should be reduced to approximately one-half of its prescribed dose.

If the CYP2D6 or the CYP3A4 inhibitor is discontinued, the dosage of ABIPIP 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 as in ABIPIP, modest increases in plasma aripiprazole concentrations may be expected.

CYP3A4 inducers (e.g. carbamazepine, rifampicin, rifabutin, phenytoin, phenobarbital (phenobarbitone), primidone, efavirenz, nevirapine and St. John's Wort)

Concomitant use of CYP3A4 inducers causes significant decreases in aripiprazole

and dehydro-aripiprazole's AUC and C_{max}.

ABIPIP dose should be doubled when prescribed concomitantly with potent CYP3A4 inducers.

The use of CYP3A4 inducers for longer than 14 days should be avoided.

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

Other serotonergic medicines

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

Famotidine, a gastric acid blocker and an H_2-antagonist, reduces the rate of absorption of aripiprazole as in ABIPIP, but has no clinically significant effect on its pharmacokinetics.

Potential effect of ABIPIP on other medicines

Due to its α_1-adrenergic receptor antagonist activity, ABIPIP may enhance the effect of certain antihypertensive medicines (see **section 4.4**).

Caution should be used if ABIPIP is prescribed concomitantly with medicines that prolong the QT interval or cause electrolyte imbalance (see **section 4.4** and **section 4.8**).

Given the primary central nervous system (CNS) effects of aripiprazole as in ABIPIP, ABIPIP should be used with caution in combination with alcohol or other CNS medicines, such as benzodiazepines, with overlapping adverse reactions such as sedation (see **section 4.8**).

It is not expected that aripiprazole as in ABIPIP would cause clinically important effects on medicines metabolised by substrates of CYP2D6 (dextromethorphan/ 3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole) and CYP3A4 (dextromethorphan). Additionally, aripiprazole as in ABIPIP and its predominant human metabolite dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism in vitro. Thus, ABIPIP is unlikely to cause clinically important medicine interactions mediated by these enzymes.
When aripiprazole as in ABIPIP was administered concomitantly with lamotrigine, there was no clinically important change in lamotrigine concentrations.

Effect of food and drink

Use of alcohol with ABIPIP should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of use of ABIPIP during pregnancy has not been established.
Congenital anomalies have been reported. Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during treatment with ABIPIP.
Neonates exposed to antipsychotics (including ABIPIP) during the third trimester of

pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breastfeeding

Safety of use of aripiprazole as in ABIPIP during lactation has not been established. Aripiprazole as in ABIPIP is excreted in human breast milk. ABIPIP should not be prescribed during pregnancy and lactation.

4.7 Effects on ability to drive and use of machines

ABIPIP 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, fatigue, dizziness and light-headedness and may potentially impair judgment, thinking or motor skills (see **section 4.8**).

Patients should therefore not operate hazardous machinery, including motor vehicles before they are reasonably certain that ABIPIP does not adversely affect them.

4.8 Undesirable effects

a. Summary of the safety profile

The frequent adverse reactions are akathisia and nausea each occurring in more than 3 % of patients treated with oral aripiprazole as in ABIPIP.

b. Tabulated list of adverse reactions

Adverse reactions reported are shown below. Frequencies were defined using the following convention: *frequent, less frequent, frequency unknown*.

MedDRA system organ class	Frequency	Side effects
Blood and the lymphatic system disorders	*Frequency unknown*	Agranulocytosis, leukopenia, 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, blood prolactin decreased
	Frequency unknown	Diabetic ketoacidosis (DKA), diabetic hyperosmolar coma
Metabolism and nutrition disorders	*Frequent*	Weight gain, diabetes mellitus
	Less frequent	Hyperglycaemia
	Frequency unknown	Weight decreased, anorexia, hyponatraemia
Psychiatric disorders	*Frequent*	Insomnia, somnolence, sedation, restlessness, anxiety, agitation
	Less frequent	Depression*, hypersexuality

	Frequency unknown	Nervousness, pathological gambling, suicide attempt, suicidal ideation, suicide completed, impulse control disorders, binge eating, poriomania, compulsive shopping, aggression (see **section 4.4**)
Nervous system disorders	*Frequent*	Headache, dizziness, light-headedness, akathisia, tremor, extrapyramidal disorder
	Less frequent	Tardive dyskinesia, dystonia [1], seizures, restless legs syndrome
	Frequency unknown	Speech disorder, Neuroleptic Malignant Syndrome (NMS), grand mal convulsion, serotonin syndrome
Eye disorders	*Frequent*	Blurred vision
	Less frequent	Diplopia, photophobia
	Frequency unknown	Oculogyric crisis
Cardiac disorders	*Frequent*	Tachycardia*

	Frequency unknown	QT prolongation, ventricular dysrhythmias, sudden unexplained death, cardiac arrest, *torsade de pointes,* bradycardia
Vascular disorders	*Frequent*	Orthostatic hypotension*
	Frequency unknown	Syncope, hypertension, venous thromboembolism (including pulmonary embolism and deep vein thrombosis), cerebrovascular accident (fatal)[2]
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Hiccups
	Frequency unknown	Oropharyngeal spasm, laryngospasm, aspiration pneumonia, cough
Gastrointestinal disorders	*Frequent*	Vomiting, nausea, dyspepsia, constipation, salivary hypersecretion, stomach discomfort
	Less frequent	Pancreatitis, dysphagia, diarrhoea
	Frequency unknown	Dry mouth, abdominal discomfort

Hepatobiliary disorders	*Frequency unknown*	Jaundice, hepatitis, hepatic failure, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased gamma glutamyl transferase (GGT), increased alkaline phosphatase
Skin and subcutaneous tissue disorders	*Frequency unknown*	Rash, photosensitivity reaction, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), alopecia, hyperhidrosis
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Musculoskeletal stiffness
	Frequency unknown	Rhabdomyolysis, myalgia
Renal and urinary disorders	*Frequency unknown*	Urinary incontinence, urinary retention
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
	Less frequent	Peripheral oedema
	Frequency unknown	Temperature regulation disorder (e.g. hypothermia, pyrexia), chest pain,
Investigations	*Frequency unknown*	Increased creatine phosphokinase, increased blood glucose[3], blood glucose fluctuation, glycosylated haemoglobin increased

Notes

***** Possibly medically relevant side effects

[1]. 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 has been observed in males and younger age groups.

[2]. Cerebrovascular adverse reactions and increased mortality have been reported in elderly patients with dementia-related psychosis (see **section 4.3**).

[3]. Hyperglycaemia and diabetes mellitus have been reported (see **Metabolism and nutrition disorders** and **section 4.3**).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Symptoms of overdosage

Accidental or intentional acute overdose of aripiprazole as in ABIPIP alone was identified in adult patients after ingestion of doses up to 1260 mg with no fatalities. Symptoms of overdosage may include lethargy, increased blood pressure, somnolence, tachycardia and vomiting. The potentially medically serious signs and symptoms include somnolence, extrapyramidal symptoms and transient loss of consciousness.

Treatment of overdosage

Management of overdosage should include supportive therapy, maintenance of an adequate airway, oxygenation and ventilation and management of symptoms.

The possibility of multiple medicine involvement should be considered; cardiovascular monitoring should therefore commence immediately and should

include continuous electrocardiographic monitoring to detect possible dysrhythmias. Following any confirmed or suspected overdose of ABIPIP, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after ABIPIP, may be effective for overdose management.

There is no information on the effect of haemodialysis in treating an overdose with ABIPIP, but haemodialysis is unlikely to be useful in overdose management as ABIPIP 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 Tranquillisers — miscellaneous structures

Pharmacotherapeutic group: Psycholeptics, other antipsychotics

ATC code: N05AX12

Mechanism of action

Aripiprazole is a quinolinone derivative and is an atypical antipsychotic.

It is thought that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D_2 and serotonin $5HT_{1a}$ receptors and antagonism of serotonin $5HT_{2a}$ receptors.

Aripiprazole has 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 has

moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors.

Aripiprazole exhibited antagonist properties of dopaminergic hyperactivity and agonist properties of dopaminergic hypoactivity.

Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole as in ABIPIP.

5.2 Pharmacokinetic properties

ABIPIP activity is primarily due to the parent compound, aripiprazole.

Absorption

Aripiprazole is well absorbed after oral administration of ABIPIP, with peak plasma concentrations occurring within 3 to 5 hours after dosing.

The absolute oral bioavailability of aripiprazole as in ABIPIP is 87 %.

The bioavailability of aripiprazole as in ABIPIP is not significantly affected by administration with food. There is no effect of a high fat meal on pharmacokinetics.

Steady-state concentrations are reached within 14 days of dosing. At steady-state, the pharmacokinetics of aripiprazole is dose-proportional.

Distribution

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4,9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole as in ABIPIP is more than 99 % bound to serum proteins, primarily albumin.

With multiple dosing, aripiprazole accumulates by a factor of 5.

Biotransformation

Aripiprazole undergoes minimal pre-systemic metabolism; it is extensively metabolised by the liver, primarily via 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, with N-dealkylation being catalysed by CYP3A4.

Aripiprazole is the predominant active moiety in the systemic circulation.

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

At steady-state dehydro-aripiprazole, the active metabolite, represents about 40 % of aripiprazole AUC in plasma.

Elimination

The total body clearance of aripiprazole is 0,7 mL/ min per kg, which is primarily mediated by the hepatic system.

Following a single oral dose of [^{14}C]-labelled aripiprazole, approximately 27 % of the administered radioactivity is recovered in the urine and approximately 60 % in the faeces. Less than 1 % unchanged aripiprazole is excreted in the urine and approximately 18 % of the oral dose is recovered unchanged in the faeces.

The mean elimination half-life of aripiprazole is about 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

Special populations

Hepatic impairment

In patients with liver cirrhosis (Child-Pugh Classes A, B and C), the AUC of aripiprazole as in ABIPIP increases about 31 % with mild hepatic impairment and 8 % with moderate hepatic impairment; it decreases about 20 % with severe hepatic impairment. This does not reveal significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole. These differences do not require dose adjustment.

Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 mL/min), the C_{max} of aripiprazole and dehydro-aripiprazole increases, but the AUC is about 15 % lower for aripiprazole and 7 % higher for dehydro-aripiprazole.

No dosage adjustment is required in subjects with renal impairment.

The pharmacokinetics of aripiprazole and dehydro-aripiprazole are found to be similar in patients with severe renal disease compared to young healthy subjects.

Elderly

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

No dosage adjustments are recommended for elderly patients (see **section 4.4**).

Gender

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

No dosage adjustment is recommended based on gender.

Smoking

Population pharmacokinetic evaluation showed no evidence of clinically significant effect from smoking on the pharmacokinetic of aripiprazole.

Race

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

croscarmellose sodium

crystalline maltose

magnesium stearate

microcrystalline cellulose

pregelatinised starch

The colourants are:

indigo carmine (E132) (5 mg tablet)

iron oxide red (E172) (10 mg and 30 mg tablets)

iron oxide yellow (E172) (15 mg tablet)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Keep the blisters in the carton until required for use and keep the HDPE bottle well-closed. Protect from moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

ABIPIP 5, 10, 15 and 30 are packed in either of the following:

- A cardboard box containing 28, 30, 96 or 100 tablets, packed in silver PA/ALL/PVC-aluminium foil blisters (alu-alu blister).
- A white opaque high density polyethylene (HDPE) bottle with a child resistant polypropylene (PP) screw cap with a mounted desiccant, containing 28, 30, 96 or 100 tablets.

Not all packing systems or sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBERS

ABIPIP 5: 51/2.6.5/0667

Namibia: NS3 20/2.6/0035

ABIPIP 10: 51/2.6.5/0668

Namibia: NS3 20/2.6/0036

ABIPIP 15: 51/2.6.5/0669

Namibia: NS3 20/2.6/0037

ABIPIP 30: 51/2.6.5/0670

Namibia: NS3 20/2.6/0038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 15 May 2019

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

22 May 2025