Dr. Reddy's Laboratories (Pty) Ltd.
APPROVED PROFESSIONAL INFORMATION
XOPHANU ODT (orodispersible tablets 10, 15 mg)

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

XOPHANU ODT 10 mg orodispersible tablets

XOPHANU ODT 15 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

XOPHANU ODT 10 mg:

Each orodispersible tablet contains aripiprazole 10 mg. Contains sugar: lactose monohydrate. Contains sweetener: aspartame.

Excipients with known effect

1,00 mg Aspartame (E 951) and 95,05 mg lactose (as monohydrate) per tablet.

XOPHANU ODT 15 mg:

Each orodispersible tablet contains aripiprazole 15 mg. Contains sugar: lactose monohydrate. Contains sweetener: aspartame.

Excipients with known effect

1,50 mg Aspartame (E 951) and 142,58 mg lactose (as monohydrate) per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablets.

XOPHANU ODT 10 mg:

Round, flat, pink tablets, engraved with '10' on one side and plain on the other side.

XOPHANU ODT 15 mg:

Round, flat, yellow tablets, engraved with '15' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Schizophrenia:

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

Bipolar Mania:

XOPHANU ODT 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 XOPHANU ODT treatment.

4.2 Posology and method of administration

Posology

Schizophrenia:

The recommended starting dose for XOPHANU ODT 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.

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

Recurrence prevention of manic episodes in Bipolar I disorder:

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

Concomitant Medications:

Dosage adjustment for patients taking XOPHANU ODT concomitantly with potent CYP3A4 or CYP2D6

inhibitors:

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

Dosage adjustment for patients taking potent CYP3A4 inducers:

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

Method of administration:

XOPHANU ODT is for oral use.

The orodispersible tablet should be placed in the mouth on the tongue, where it will rapidly disperse in saliva. It can be taken with or without liquid. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, disperse the tablet in water and drink the resulting suspension.

4.3 Contraindications

XOPHANU ODT is contra-indicated in patients who are hypersensitive to aripiprazole or any of the excipients.

Paediatric use

The safety and efficacy of XOPHANU ODT 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 occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany

antipsychotic treatment.

Prescriptions for XOPHANU ODT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular disorders:

XOPHANU ODT should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicines) or hypertension, including accelerated or malignant. Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicines. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with aripiprazole and preventive measures undertaken.

Orthostatic hypotension:

Potentially due to its α1-adrenergic receptor antagonist activity, XOPHANU ODT may be associated with orthostatic hypotension.

QT prolongation:

In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. XOPHANU ODT should be used with caution in patients with a family history of QT prolongation (see section 4.8).

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 XOPHANU ODT, a dose reduction or medicine discontinuation should be considered.

These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Other extrapyramidal symptoms:

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

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. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported.

If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including XOPHANU ODT must be discontinued.

Seizure:

XOPHANU ODT 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:

Increased mortality

In clinical trials (mean age: 82.4 years; range: 56 to 99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were 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 deaths were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature (see section 4.8).

Cerebrovascular adverse reactions

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

Aripiprazole 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 aripiprazole, as contained in XOPHANU ODT. 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 XOPHANU ODT, 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 XOPHANU ODT should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when XOPHANU ODT was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Hypersensitivity:

Hypersensitivity reactions, characterised by allergic symptoms, may occur with XOPHANU ODT (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 and poorly managed life-style might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults. In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

Dysphagia:

Oesophageal dysmotility and aspiration have been associated with antipsychotic medicine use, including aripiprazole. XOPHANU ODT and other antipsychotic medicines 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 XOPHANU ODT. Other urges, reported include: increased sexual urges, compulsive spending, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for medical practitioners 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 XOPHANU ODT. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced or the medication was discontinued.

Impulse control disorders may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole (see section 4.8).

Patients with attention deficit hyperactivity (ADHD) comorbidity

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

Falls

XOPHANU ODT 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).

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 XOPHANU ODT 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.

Laboratory Findings:

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

Aspartame

XOPHANU ODT orodispersible tablets contain aspartame.

Aspartame is a source of phenylalanine. It may be harmful for people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Lactose:

XOPHANU ODT orodispersible tablets contain lactose. Patients with rare hereditary problems of galactose intolerance e.g., galactosaemia, total lactase deficiency, glucose-galactose malabsorption should not take XOPHANU ODT.

Sodium

XOPHANU ODT orodispersible tablets contain sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive medicines.

Given the primary CNS effects of aripiprazole, caution should be used when XOPHANU ODT is administered in combination with other CNS medicines with overlapping adverse reactions such as sedation (see section 4.8).

Combination use of XOPHANU ODT with alcohol should be avoided.

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

Potential for other medicines to affect XOPHANU ODT

A gastric acid blocker, the H_2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant. Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for

smokers.

Quinidine and other CYP2D6 inhibitors

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

Ketoconazole and other CYP3A4 inhibitors

In a clinical trial in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole and dehydro-aripiprazole AUC and C_{max} substantially. 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 metabolizers. When considering concomitant administration of ketoconazole or other strong CYP3A4 inhibitors with XOPHANU ODT, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with XOPHANU ODT occurs, XOPHANU ODT 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 dosage of XOPHANU ODT 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 XOPHANU ODT, modest increases in plasma aripiprazole concentrations may be expected.

Carbamazepine and other CYP3A4 inducers

Concomitant administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizoaffective disorder, resulted in decreased plasma exposure of aripiprazole and metabolite dehydro-aripiprazole compared to when aripiprazole (30 mg) was administered alone. XOPHANU ODT dose should be doubled when concomitant administration of XOPHANU ODT occurs with carbamazepine. Concomitant administration of XOPHANU ODT 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 dosage of XOPHANU ODT should be reduced to the recommended dose.

Valproate and lithium

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

Potential for XOPHANU ODT to affect other medicines

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

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

Serotonin syndrome

Cases of serotonin syndrome have been reported 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 selective serotonin reuptake inhibitor/selective serotonin noradrenaline reuptake inhibitor (SSRI/SNRI), or with medicines that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety of use of XOPHANU ODT during pregnancy and lactation has not been established.

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

Neonates exposed to antipsychotics (including XOPHANU ODT) 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:

Aripiprazole is excreted in human breast milk.

Fertility:

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

4.7 Effects on ability to drive and use machines

Patients should be cautioned about operating hazardous machinery, including motor vehicles until they are reasonably certain that XOPHANU ODT does not adversely affect them.

XOPHANU ODT 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, dizziness, syncope, vision blurred, diplopia (see section 4.8).

4.8 Undesirable effects

Tabulated list of adverse reactions

	Frequent	Less frequent	Frequency not known
Blood and lymphatic system disorders			Leukopenia, neutropenia, thrombocytopenia.
Immune system disorders			Allergic reaction (e.g., anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, or urticaria).
Endocrine disorders		Hyperprolactinaemia, Blood prolactin decreased.	Diabetic hyperosmolar coma, Diabetic ketoacidosis.

Metabolism and nutrition disorders			Hyponatremia, Anorexia, Hyperglycaemia, Diabetes mellitus.
Psychiatric disorders	Insomnia, Anxiety, Restlessness.	Depression.	Suicide attempt, suicidal ideation and completed suicide, Pathological gambling, Hypersexuality, Impulse-control disorders, Binge eating, Compulsive shopping Poriomania, Aggression, Agitation, Nervousness.
Nervous system disorders	Akathisia, Extrapyramidal disorder, Tremor, Headache, Sedation, Somnolence, Dizziness.	Dystonia.	Neuroleptic Malignant Syndrome (NMS), Seizures, Grand mal convulsion, Serotonin syndrome, Speech disorder, Tardive dyskinesia, Restless leg syndrome.
Eye disorders	Vision blurred.	Photophobia.	Diplopia, Oculogyric crisis.
Cardiac	Tachycardia	Tachycardia (Bipolar	Sudden unexplained

disorders	(Schizophrenia condition).	Mania condition).	death, Torsades de pointes, Ventricular-dysrhythmia, Cardiac arrest, Bradycardia.
Vascular disorders	Orthostatic hypotension (Schizophrenia condition).	Orthostatic hypotension (Bipolar Mania condition).	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis), Hypertension, Syncope.
Respiratory, thoracic and mediastinal disorders			Aspiration pneumonia, Laryngospasm, Oropharyngeal, spasm, Hiccups. .
Gastrointestinal disorders	Constipation, Dyspepsia, Nausea, Salivary hypersecretion, Vomiting, Abdominal discomfort.		Pancreatitis, Dysphagia, Diarrhoea, Stomach discomfort.
Hepatobiliary disorders			Hepatic failure, Hepatitis, Jaundice.

Skin and subcutaneous tissue disorders			Rash, Photosensitivity reaction, Alopecia, Hyperhidrosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
Musculoskeletal and connective tissue disorders	Musculoskeletal stiffness (Bipolar Mania condition).		Rhabdomyolysis, Myalgia, Stiffness, Prolonged abnormal contractions of muscle groups.
Renal and urinary disorders			Urinary incontinence, Urinary retention.
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal.
Reproductive system and breast disorders			Priapism.
General disorders and administration site conditions	Asthenia/ fatigue.	Peripheral oedema (Bipolar Mania condition).	Temperature regulation disorder (e.g., hypothermia, pyrexia), Chest pain,

			Peripheral oedema.
Investigations			Weight decreased, Weight gain, Alanine Aminotransferase increased, Aspartate Aminotransferase increased, Gamma-glutamyltransferase increased, Alkaline phosphatase increased, QT prolonged, Blood glucose increased, Glycosylated haemoglobin increased, Blood glucose fluctuation, Creatine phosphokinase increased.

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose

In clinical studies and post-marketing experience, accidental or intentional acute overdosage of aripiprazole alone was identified in patients with estimated doses up to 1260 mg with no fatalities. The potentially medically important signs and symptoms observed included lethargy, blood pressure increased, somnolence, tachycardia and vomiting. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities.

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

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple medicine involvement should be considered. Therefore, cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible dysrhythmias.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.6.5 Antipsychotic – miscellaneous structures.

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

Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of

partial agonist activity at dopamine D_2 and serotonin $5HT_{1a}$ receptors and antagonist activity at serotonin $5HT_2$ receptors.

Aripiprazole exhibited high binding affinity *in vitro* for dopamine D_2 and D_3, serotonin $5HT_{1a}$ and $5HT_{2a}$ receptors and moderate affinity for dopamine D_4, serotonin $5HT_{2c}$ and $5HT_7$, $alpha_1$-adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for serotonin reuptake site and no appreciable affinity for muscarinic receptors.

Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity.

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

5.2 Pharmacokinetic properties

Aripiprazole 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.

Absorption

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

Distribution

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4,9 L/kg. At therapeutic concentrations, aripiprazole is greater than 99 % bound to serum proteins, primarily albumin. Aripiprazole did not alter the pharmacokinetics and pharmacodynamics of highly protein-bound warfarin, suggesting that protein displacement of warfarin did not occur.

Biotransformation

Aripiprazole undergoes minimal pre-systemic metabolism. Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicine moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represented about 39 % of aripiprazole AUC in plasma.

Elimination

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).

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 section 4.4).

Gender:

C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40 % higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25 %) between men and women. No dosage adjustment is recommended based on gender.

Race:

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

Smoking:

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame (E951)

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose (E460)

Silica Colloidal Anhydrous

Iron oxide red (E172) – only for 10 mg

Iron oxide yellow (E172) – only for 15 mg

Vanilla flavour (containing maltodextrin, acacia gum, propylene glycol, benzyl alcohol and vanilla flavouring).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the original package in order to protect from moisture.

Store all medicines out of reach of children.

Keep blisters in the carton until required for use.

6.5 Nature and contents of container

XOPHANU ODT 10, 15 mg orodispersible tablets are packed in the Aluminium-Aluminium paper peel-off blisters, each blister contains 10 tablets, 3 X10's pack.

XOPHANU ODT 10, 15 mg blister foil consisting of aluminum layer coated with OPA (oriented polyamide) film on one side and polyvinyl chloride (PVC) film on the other side and sealed against a peel-off aluminium sealing foil consisting of aluminum layer, coated on one side with a print primer for better printing performance, a paper layer, an adhesive lacquer, a layer of PET (polyethylene terephthalate) and an adhesive lacquer on one side and with a heat seal lacquer on the other side.

6.6 Special precautions for disposal and other handling

Any unused medicines should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside, Sandton

2057

South Africa

8. REGISTRATION NUMBER(S)

XOPHANU ODT 10 mg: 57/1.2/0643

XOPHANU ODT 15 mg: 57/1.2/0644

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 January 2026

10. DATE OF REVISION OF TEXT

To be allocated