PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S5**

1. NAME OF THE MEDICINE

MAKTUDA 20 mg (film coated tablet)

MAKTUDA 40 mg (film coated tablet)

MAKTUDA 60 mg (film coated tablet)

MAKTUDA 80 mg (film coated tablet)

MAKTUDA 120 mg (film coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MAKTUDA 20 mg: Each film coated tablet contains 20 mg lurasidone hydrochloride.

MAKTUDA 40 mg: Each film coated tablet contains 40 mg lurasidone hydrochloride.

MAKTUDA 60 mg: Each film coated tablet contains 60 mg lurasidone hydrochloride.

MAKTUDA 80 mg: Each film coated tablet contains 80 mg lurasidone hydrochloride.

MAKTUDA 120 mg: Each film coated tablet contains 120 mg lurasidone hydrochloride.

Sugar free

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet

MAKTUDA 20 mg: White to off white, round biconvex, film coated tablets, debossed with “F3” on one side and plain on other side

MAKTUDA 40 mg: White to off white, round biconvex, film coated tablets, debossed with “F4” on one side and plain on other side

MAKTUDA 60 mg: White to off white, capsule biconvex, film coated tablets, debossed with “F5” on one side and plain on other side

MAKTUDA 80 mg: Pale green, oval, biconvex, film coated tablets, debossed with “F6” on one side and plain on other side

MAKTUDA 120 mg: White to off white, oval, biconvex, film coated tablets, debossed with “F7” on one side and plain on other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MAKTUDA is indicated for:

- Treatment of adult and adolescent patient’s age 13 and older with schizophrenia.
- Monotherapy treatment of adult patients with major depressive episodes associated with bipolar disorder (bipolar depression).

4.2 Posology and method of administration

Posology

Schizophrenia

Adults

The recommended starting dose of **MAKTUDA** is 40 mg once daily. Initial dose titration is not required. **MAKTUDA** has been shown to be effective in a dose range of 40 mg per day to 160 mg per day. The maximum recommended dose is 160 mg per day.

Adolescents

The recommended starting dose of **MAKTUDA** is 40 mg once daily. Initial dose titration is not required. **MAKTUDA** has been shown to be effective in a dose range of 40 mg per day to 80 mg per day. The maximum recommended dose is 80 mg per day.

Depressive Episodes Associated with Bipolar I Disorder

The recommended starting dose of **MAKTUDA** in adults is 20 mg given once daily as monotherapy or as adjunctive therapy with lithium or valproate. Initial dose titration is not required. **MAKTUDA** has been shown to be effective in a dose range of 20 mg per day to 120 mg per day as monotherapy or as

adjunctive therapy with lithium or valproate. The maximum recommended dose, as monotherapy or as adjunctive therapy with lithium or valproate, is 120 mg per day. In the monotherapy study, the higher dose range (80 mg to 120 mg per day) did not provide additional efficacy, on average, compared to the lower dose range (20 to 60 mg per day).

The efficacy of **MAKTUDA** in the treatment of mania associated with bipolar disorder has not been established.

Special populations

Renal impairment

Dose adjustment is recommended in moderate (creatinine clearance: 30 to <50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min) patients. The recommended starting dose is 20 mg per day. The dose in these patients should not exceed 80 mg per day.

Hepatic impairment

Dose adjustment is recommended in moderate (Child-Pugh Score = 7 to 9) and severe hepatic impairment (Child-Pugh Score = 10 to 15) patients. The recommended starting dose is 20 mg per day. The dose in moderate hepatic impairment patients should not exceed 80 mg per day and the dose in severe hepatic impairment patients should not exceed 40 mg/day.

Method of administration

For oral use.

MAKTUDA must be taken with food.

4.3 Contraindications

MAKTUDA is contraindicated:

- In patients with a history of hypersensitivity to the active substance or to any of the excipients listed in 6.1.
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.).
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John’s wort, phenytoin, carbamazepine, etc.)

4.4 Special warnings and precautions for use

Risk of suicide

The occurrence of suicidal behaviour is inherent in psychotic illnesses and in some cases has been reported early after initiation or switch of antipsychotic therapy. Close supervision of high-risk patients should accompany anti-psychotic therapy.

Parkinson's disease

If prescribed to patients with Parkinson's disease, **MAKTUDA** exacerbate the underlying parkinsonism symptoms. Physicians should therefore weigh the risks versus the benefits when prescribing **MAKTUDA** to patients with Parkinson's disease.

Extrapyramidal symptoms (EPS)

Medicines such as **MAKTUDA**with dopamine receptor antagonistic properties have been associated with extrapyramidal adverse reactions including rigidity, tremors, mask-like face, dystonias, drooling of saliva, drooped posture and abnormal gait. In placebo controlled clinical studies in adult patients with schizophrenia there was an increased occurrence of EPS following treatment with lurasidone compared to placebo.

Tardive dyskinesia

Medicines such as **MAKTUDA** with dopamine receptor antagonistic properties have been associated with the induction of Tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including lurasidone, should be considered.

Cardiovascular disorders/QT prolongation

Caution should be exercised when **MAKTUDA** is prescribed in patients with known cardiovascular disease or family history of QT prolongation, hypokalaemia, and in concomitant use with other medicines thought to prolong the QT interval.

Seizures

MAKTUDA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Neuroleptic malignant syndrome (NMS)

Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur lurasidone. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, **MAKTUDA**, should be discontinued.

Elderly patients with dementia

MAKTUDA has not been studied in elderly patients with dementia.

Overall mortality

In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotics, including risperidone, aripiprazole, olanzapine, and quetiapine had an increased risk of mortality compared to placebo.

Cerebrovascular accident

An approximately 3-fold increased risk of cerebrovascular adverse reactions has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazoleand olanzapine. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. **MAKTUDA** should be used with caution in elderly patients with dementia who have risk factors for stroke.

Venous thromboembolism

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 **MAKTUDA** and preventive measures undertaken.

Hyperprolactinaemia

MAKTUDA elevates prolactin levels due to antagonism of dopamine D2 receptors. Patients should be counselled on signs and symptoms of elevated prolactin, such as gynaecomastia, galactorrhoea, amenorrhoea and erectile dysfunction. Patients should be advised to seek medical attention if they experience any signs and symptoms.

Weight gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperglycaemia

Rare cases of glucose related adverse reactions, e.g. increase in blood glucose, and have been reported in clinical trials with **MAKTUDA**. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Orthostatic hypotension/syncope

MAKTUDA may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Interaction with grapefruit juice

Grapefruit juice should be avoided during treatment with **MAKTUDA** (see section 4.5).

Serotonin syndrome

Concomitant administration of **MAKTUDA** and other serotonergic agents, such as buprenorphine/opioids, MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Given the primary central nervous system effects of **MAKTUDA**, it should be used with caution in combination with other centrally acting medicines and alcohol.

Caution is advised when prescribing **MAKTUDA** with medicines known to prolong the QT interval, e.g. class I Aantiarrhythmics (e.g. quinidine, disopyramide) and class III antiarrhythmics (e.g. amiodarone, sotalol), someanti - histaminics, some other antipsychotics and some antimalarials (e.g. mefloquine).

MAKTUDA should be used cautiously when co-administered with other serotonergic agents, such as buprenorphine/opioids, MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) ortricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Pharmacokinetic interactions

The concomitant administration of lurasidone and grapefruit juice has not been assessed. Grapefruit juice inhibits CYP3A4 and may increase the serum concentration of lurasidone. Grapefruit juice should be avoided during treatment with MAKTUDA**.**

Potential for other medicines to affect MAKTUDA

MAKTUDA and its active metabolite ID-14283 both contribute to the pharmacodynamic effect at the dopaminergic and serotonergic receptors. **MAKTUDA** and its active metabolite ID-14283 are primarily metabolised by CYP3A4.

CYP3A4 inhibitors

MAKTUDA is contraindicated with strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) (see section 4.3).

Co administration of **MAKTUDA** with the strong CYP3A4 inhibitor ketoconazole resulted in a 9- and 6-fold increase in exposure of **MAKTUDA** and its active metabolite ID-14283 respectively.

Co administration of **MAKTUDA** and posaconazole (strong CYP3A4 inhibitor) resulted in an approximate 4-5 fold increase in lurasidone exposure. A persistent effect of posaconazole on **MAKTUDA** exposure was observed up to 2-3weeks after stop of posaconazole co-administration.

Co administration of **MAKTUDA** with medicines that moderately inhibit CYP3A4 (e.g. diltiazem, erythromycin, fluconazole verapamil) may increase exposure to **MAKTUDA**. Moderate CYP3A4 inhibitors are estimated to result in a 2-5 fold increase in exposure of CYP3A4 substrates.

Co administration of **MAKTUDA** with diltiazem (slow-release formulation), a moderate CYP3A4 inhibitor, resulted in a 2.2and 2.4-fold increase in exposure of lurasidone and ID-14283 respectively (see section 4.2). The use of an immediate release formulation of diltiazem could result in a larger increase in **MAKTUDA** exposure.

CYP3A4 inducers

MAKTUDA is contraindicated with strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St John's wort (*Hypericum perforatum)*) (see section 4.3).

Co administration of **MAKTUDA** with the strong CYP3A4 inducer rifampicin resulted in a 6-fold decrease in exposure of **MAKTUDA**.

Co administration of **MAKTUDA** with mild (e.g. armodafinil, amprenavir, aprepitant, prednisone, rufinamide) or moderate (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin) inducers of CYP3A4 would be expected to give a <2-foldreduction in **MAKTUDA** exposure during co-administration and for up to 2 weeks after discontinuation of mild or moderateCYP3A4 inducers.

When **MAKTUDA** is co-administered with mild or moderate CYP3A4 inducers, the efficacy of **MAKTUDA** needs to be carefully monitored and a dose adjustment may be needed.

Transporters

MAKTUDA is a substrate of P-gp and BCRP *in vitro* and the *in vivo* relevance of this is unclear. Co administration of **MAKTUDA** with P-gp and BCRP inhibitors may increase exposure to **MAKTUDA**.

Potential for MAKTUDA to affect other medicines

Co administration of **MAKTUDA** with midazolam, a sensitive CYP3A4 substrate, resulted in a < 1.5-fold

increase inmidazolam exposure. Monitoring is recommended when **MAKTUDA** and CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine) are co administered.

Co administration of **MAKTUDA** with digoxin (a P-gp substrate) did not increase the exposure to digoxin and only slightly increased C_{max} (1.3 –fold) and therefore, it is considered that **MAKTUDA** can be co-administered with digoxin.**MAKTUDA** is an *in vitro* inhibitor of the efflux transporter P-gp and the clinical relevance of intestinal P-gp inhibition cannot be excluded. Concomitant administration of the P-gp substrate dabigatran etexilate may result in increased dabigatran plasma concentrations.

MAKTUDA is an *in vitro* inhibitor of the efflux transporter BCRP and the clinical relevance of intestinal BCRP inhibition cannot be excluded. Concomitant administration of BCRP substrates may result in increases in the plasma concentrations of these substrates.

Co administration of **MAKTUDA** with lithium indicated that lithium had clinically negligible effects on the pharmacokinetics of lurasidone; therefore no dose adjustment of lurasidone is required when co administered with lithium. **MAKTUDA** does not impact concentrations of lithium.

A clinical drug interaction study investigating the effect of co administration of **MAKTUDA** on patients taking oral combination contraceptives including nor estimate and ethinyl estradiol, indicated that **MAKTUDA** had no clinically or statistically meaningful effects on the pharmacokinetics of the contraceptive or sex hormone binding globulin (SHBG) levels. Therefore, **MAKTUDA** can be co-administered with oral contraceptives.

4.6 Fertility, pregnancy and lactation

Pregnancy

MAKTUDA should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly weighs the potential risk to the foetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Breastfeeding

MAKTUDA was excreted in milk of rats during lactation (see section 5.3). It is not known whether lurasidone or its metabolites are excreted in human milk. Breast feeding in women receiving **MAKTUDA** should be considered only if the potential benefit of treatment justifies the potential risk to the child.

Fertility

Studies in animals have shown a number of effects on fertility, mainly related to prolactin increase, which are not considered to be relevant to human reproduction (see section 5.3).

4.7 Effects on ability to drive and use machines

MAKTUDA has minor influence on the ability to drive and use machines. Patients should be cautioned about operating hazardous machines, including motor vehicles and cycles, until they are reasonably certain that **MAKTUDA** does not affect them adversely (see section 4.8).

Regarding road safety, adolescents who may not be old enough to drive may nevertheless cycle.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were akathisia, nausea, extrapyramidal symptoms and insomnia. They were usually mild to moderate in intensity.

Tabulated summary of adverse reactions

Adverse drug reactions in adults:

System organ class	Frequent	Less frequent	Frequency unknown	
Infections and infestations		Nasopharyngitis		
Blood and lymphatic system disorders		Anaemia, eosinophilia, leukopenia	neutropenia	

Immune system disorders	Hypersensitivity			
Metabolism and nutrition disorders	Weight increased, decreased appetite	Blood glucose increased Hyponatraemia		
Psychiatric disorders	Insomnia, Agitation, anxiety, restlessness	Nightmare, catatonia, panic attack, suicidal behaviour	Sleep disorder	
Nervous system disorders	Akathisia, somnolence, parkinsonism, dizziness, dystonia, dyskinesia	Lethargy, dysarthria, tardive dyskinesia, syncope, convulsion, neuroleptic malignant syndrome (NMS), cerebrovascular accident		
Eye disorders		Blurred vision		
Cardiac disorders	Tachycardia	Angina pectoris, atrioventricular block first degree, bradycardia		
Vascular disorders	Hypertension	Hypotension, orthostatic hypotension, hot flush, blood pressure increased		

Gastrointestinal disorders	Nausea, diarrhoea, vomiting, dyspepsia, salivary hypersecretion, dry mouth, upper abdominal pain, stomach discomfort	Flatulence, dysphagia, gastritis		
Hepatobiliary disorders		Alanine aminotransferase increased		
Skin and subcutaneous tissue disorders	Rash, pruritis	Hyperhidrosis, angioedema	Stevens-Johnson syndrome	
Musculoskeletal and connective tissue disorders	Back pain, musculoskeletal stiffness	Joint stiffness, myalgia, neck pain, rhabdomyolysis		
Renal and urinary disorders	Serum creatinine increased	Dysuria, renal failure		
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal	

			(see section 4.6)	
Reproductive system and breast disorders		Blood prolactin increased, erectile dysfunction, amenorrhoea, dysmenorrhoea, breast pain, galactorrhoea	Breast enlargement	
General disorders and administration site conditions	Fatigue,	Gait disturbance, sudden death		
Investigations	Blood creatinine phosphokinase increased			
Adverse drug reactions in adolescents:				
System organ class	Frequent	Less frequent	Frequency unknown	
Infections and infestations		Nasopharyngitis, rhinitis, upper respiratory tract infection		
Blood and lymphatic system		neutropenia		

disorders				
Immune system disorders		Hypersensitivity		
Endocrine disorders	Hyperprolactinaemia (including blood prolactin increased)	Autoimmune thyroiditis, hyperandrogenism, hypothyroidism		
Metabolism and nutrition disorders	Decreased appetite, Increased appetite	Hyperinsulinaemia		
Psychiatric disorders	Abnormal dreams Agitation Anxiety Depression Insomnia Psychotic disorder Schizophrenia Tension	Aggression Apathy Confusional state Depressed mood Dissociation Hallucination(auditory) Hallucination (visual) Homicidal ideation Impulsive behaviour Initial insomnia Libido decreased Libido increased Listless Mental status		

		changes Obsessive thoughts Panic Attack Psychomotor hyperactivity Restlessness Sleep disorder Suicidal ideation Terminal insomnia Thinking abnormal		
Nervous system disorders	Akathisia, Headache, somnolence, Disturbance in attention Dizziness Dyskinesia Dystonia*** Parkinsonism**	Dizziness postural Dysgeusia Hyperkinesia Memory impairment Migraine Paraesthesia Psychomotor hyperactivity Restless legs syndrome Tardive dyskinesia Tension headache		
Eye disorders		Accommodation disorders, Blurred vision		
Ear and labyrinth disorders		Hyperacusis		

Cardiac disorders	Tachycardia	Palpitations, supraventricular extra systoles		
Vascular disorders	Hypertension	Hypotension, orthostatic hypertension		
Respiratory, thoracic and mediastinal disorders		Or pharyngeal pain, dyspnoea		
Gastrointestinal disorders	Nausea, vomiting, dry mouth, salivary hypersecretion	Abdominal discomfort Abdominal pain upper Aptyalism Diarrhoea Dyspepsia, Lip dry Toothache		
Skin and subcutaneous tissue disorders	Hyperhidrosis	Alopecia, hair growth abnormal, rash, urticaria		
Musculoskeletal and connective tissue disorders	Muscle rigidity	Arthalagia Muscle tightness Musculoskeletal stiffness Myalgia Pain in extremity Pain in jaw		

Renal and urinary disorders		Bilirubinuria Dysuria Micturition disorder Polyuria Proteinuria Renal disorder		
Reproductive system and breast disorders	Erectile dysfunction	Amenorrhoea Breast pain Ejaculation disorder Galactorrhoea Gynaecomastia Menstruation irregular Oligomenorrhoea Sexual dysfunction		
Congenital, familial and genetic disorders		Tourette's disorder		
General disorders and administration site conditions	Asthenia, Fatigue, irritability	Chills Gait disturbance Malaise Non- cardiac chest pain Pyrexia		
Investigations	Blood creatinine phosphokinase increased C-reactive protein increased	Alanine aminotransferase increased Anti-thyroid antibody positive		

	Weight decreased Weight increased	Aspartate aminotransferase increased Blood alkaline phosphatise decreased Blood alkaline phosphokinase increased Blood cholesterol increased Blood glucose increased Blood insulin increased Blood testosterone decreased Blood thyroid stimulating hormone increased Blood triglycerides increased Electrocardiogram PR shortened Haemoglobin decreased High density lipoprotein decreased Low density lipoprotein decreased		

Injury, poisoning and procedural complications		Intentional overdose		

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 SAHPRA website.

4.9 Overdose

Management of overdose

There is no specific antidote to **MAKTUDA**, therefore, appropriate supportive measures should be instituted, and close medical supervision and monitoring should continue until the patient recovers.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible dysrhythmias. If antidysrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects when administered in patients with an acute overdose of **MAKTUDA**.Similarly, the alpha-blocking properties of bretylium might be additive to those of **MAKTUDA**, resulting in problematic potension.

Hypotension and circulatory collapse should be treated with appropriate measures. Adrenaline and dopamine should not be used or other sympathomimetics with beta agonist activity, since beta stimulation may worsen hypotension in the setting of lurasidone-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medicines should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A1.2. Psycholeptics (antidepressants)

Pharmacotherapeutic group: Psycholeptics, antipsychotics. ATC code: N05AE05

Mechanism of action

Lurasidone is a selective blocking agent of dopamine and monoamine effects. Lurasidone binds strongly to dopaminergicD2- and to serotonergic 5-HT2A and 5-HT7- receptors with high binding affinity of 0.994, 0.47 and 0.495 nm, respectively. It also blocks α2c-adrenergic receptors and α2a-adrenergic receptors with a binding affinity of 10.8 and 40.7nM respectively. Lurasidone also exhibits partial agonism at the 5HT-1A receptor with a binding affinity of 6.38 nm. Lurasidone does not bind to histaminergic or muscarinic receptors.

The mechanism of action of the minor active metabolite of lurasidone ID-14283 is similar to that of lurasidone.

Lurasidone doses ranging from 9 to 74 mg administered to healthy subjects produced a dose-dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, in the caudate, putamen and ventral striatum detected by positron emission tomography.

5.2 Pharmacokinetic properties

Absorption

Lurasidone reaches peak serum concentrations in approximately 1-3 hours.

In a food effect study, lurasidone mean Cmax and AUC increased approximately by 2-3-times and 1.5-2-times, respectively, when administered with food compared to the levels observed under fasting conditions.

Distribution

Following administration of 37 mg of lurasidone, the mean approximate apparent volume of distribution was 6000 .Lurasidone is highly bound (~99%) to serum proteins.

Biotransformation

Lurasidone is metabolised mainly via CYP3A4. The major biotransformation pathways are oxidative N-dealkylation hydroxylation of norbornane ring, and S-oxidation.

Lurasidone is metabolised into two active metabolites (ID-14283 and ID-14326) and two non-active metabolites (ID-20219 and ID-20220). Lurasidone and its metabolites ID-14283, ID-14326, ID-20219 and ID-20220 correspond to approximately 11.4, 4.1, 0.4, 24 and 11% respectively, of serum radioactivity respectively.

CYP3A4 is the major enzyme responsible for metabolism of the active metabolite ID-14283.

Lurasidone and its active metabolite ID-14283 both contribute to the pharmacodynamic effect at the dopaminergic and serotonergic receptors.

Based on in vitro studies lurasidone is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes.

In vitro, lurasidone demonstrated no direct, or weak inhibition (direct or time-dependent) (IC50>5.9 µm) of the enzymes cytochrome P450 (CYP) 1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Based on this data, lurasidone is not expected to affect the pharmacokinetics of medicinal products that are substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. For administration of medicinal products that are substrates of CYP3A4 with a narrow therapeutic range, see section 4.5.

Lurasidone is an *in vitro* substrate of the efflux transporters P-gp and BCRP. Lurasidone is not subject to active uptake transport by OATP1B1 or OATP1B3.

Lurasidone is an inhibitor of P-gp, BCRP and OCT1 in vitro (see section 4.5). Lurasidone is not expected to have a clinically relevant inhibitory potential on transporters OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, MATE2K or BSEP based on *in vitro* data.

Elimination:

Following administration of lurasidone, the elimination half-life was 20-40 hours. Following oral administration of aradio labelled dose, approximately 67% dose was recovered in faeces and 19% in urine. Urine comprised mostly of a number of metabolites with minimal renal excretion of parent compound.

Linearity/non-linearity:

The pharmacokinetics of lurasidone is dose-proportional within a total daily dose range of 18.5 mg to 148 mg. Steady-state concentrations of lurasidone are reached within 7 days of starting lurasidone.

Special populations:

Elderly:

Limited data have been collected in healthy subject's ≥ 65 years. Of the data collected, similar exposure was obtained compared with subjects < 65 years. However, an increase in exposure in elderly subjects may be expected for patients if they have impaired renal or hepatic function.

Hepatic impairment:

The serum concentrations of lurasidone are increased in healthy subjects with Child-Pugh Class A, B and C hepatic impairment with an increased exposure of 1.5-, 1.7- and 3-fold respectively.

Renal impairment

The serum concentrations of lurasidone are increased in healthy subjects with mild, moderate and severe renal impairment with an increased exposure of 1.5, 1.9 and 2.0-fold respectively. Subjects with ESRD (CrCl<15 ml/min) have not been investigated.

Sex

There were no clinically relevant differences between sex in the pharmacokinetics of lurasidone in a population pharmacokinetic analysis in patients with schizophrenia.

Race

There were no clinically relevant differences in the pharmacokinetics of lurasidone in a population pharmacokinetic analysis in patients with schizophrenia. It was noted that Asian subjects had 1.5-fold increased exposure to lurasidone compared to Caucasian subjects.

Smoking

Based on *in vitro* studies utilising human liver enzymes, lurasidone is not a substrate for CYP1A2; smoking should therefore, not have an effect on the pharmacokinetics of lurasidone.

Paediatric population

The pharmacokinetics of lurasidone in paediatric patients was evaluated in 47 children aged 6-12 years and 234adolescents aged 13-17 years. Lurasidone was administered as lurasidone hydrochloride at daily doses of 20, 40, 80, 120 mg (6-17 years) or 160 mg (10-17 years only) up to 42 days. There was no clear correlation between obtained serum exposure and age or body weight. The pharmacokinetics of lurasidone in paediatric patients aged 6–17 years was generally comparable to those observed in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Croscarmellose sodium

Hydroxypropyl methylcellulose

Colloidal silicon dioxide

Magnesium stearate

Instacoat Universal green and white which contains:

- Hypromellose
- Polyethylene glycol
- Titanium dioxide
- Yellow iron oxide
- FD and C Blue No. 2 Al lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months for blister pack.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blisters in the carton until required for use.

Do not store in a refrigerator.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Blister pack :

Tablets are packed in a blister containing plain aluminium foil with heat seal lacquered as the lidding material and clear PVC/PVDC as the forming material. The blister is packed in an outer carton.

Blister pack cold form:

Tablets are packed in a blister containing plain aluminium foil with heat seal lacquered as the lidding material and cold form laminate as the forming material. The blister is packed in an outer carton.

Pack sizes include 14, 28, 56, 84, 90, &100

HDPE container:

Tablets are packed in Container, round, white, HDPE, 60 cc HW, 33mm neck finish with 33 mm Closure, child resistant, with pulp and white printed Heat Seal Liner.

Tablets are packed in Container, round, white, HDPE,75 cc HW, 38-400 neck finish with 38 mm Closure, child resistant, with pulp and white printed Heat Seal Liner

Pack size include 30, 90

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBERS

MAKTUDA 20 mg: 57/1.2/0772.767

MAKTUDA 40 mg: 57/1.2/0773.768

MAKTUDA 60 mg: 57/1.2/0774.769

MAKTUDA 80 mg: 57/1.2/0775.770

MAKTUDA 120 mg: 57/1.2/0776.771

9. DATE OF FIRST AUTHORISATION

September 2024

10. DATE OF REVISION OF THE TEXT

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