SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lurasidone 74 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lurasidone hydrochloride equivalent to 74.49 mg lurasidone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pale green to green, oval film coated round tablets, debossed with “LH”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lurasidone is indicated for the treatment of schizophrenia in adults and adolescent aged 13 years and over.

4.2 Posology and method of administration

Posology

Adult population

The recommended starting dose is 37 mg of lurasidone once daily. No initial dose titration is required. It is effective in a dose range of 37 to 148 mg once daily. Dose increase should be based on physician judgement and observed clinical response. The maximum daily dose should not exceed 148 mg.

Patients on doses higher than 111 mg once daily who discontinue their treatment for longer than 3 days should be restarted on 111 mg once daily and up-titrated to their optimal dose. For all other doses patients can be restarted on their previous dose without need for up-titration.

Paediatric population

The recommended starting dose is 37 mg of lurasidone once daily. No initial dose titration is required. It is effective in a dose range of 37 to 74 mg once daily. Dose increase should be based on physician judgement and observed clinical response. The maximum daily dose should not exceed 74 mg. In children, lurasidone should be prescribed by an expert in paediatric psychiatry.

Dose adjustment due to interactions

A starting dose of 18.5 mg is recommended and the maximum dose of lurasidone should not exceed 74 mg once daily in combination with moderate CYP3A4 inhibitors. Dose adjustment of lurasidone may be necessary in combination with mild and moderate CYP3A4 inducers (see section 4.5). For strong CYP3A4 inhibitors and inducers see section 4.3.

Switching between antipsychotic medicinal products

Due to different pharmacodynamic and pharmacokinetic profiles among antipsychotic medicinal products, supervision by a clinician is needed when switching to another antipsychotic product is considered medically appropriate.

Elderly people

Dosing recommendations for elderly patients with normal renal function (CrCl ≥ 80 ml/min) are the same as for adults with normal renal function. However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see "Renal impairment" below).

Limited data are available in elderly people treated with higher doses of lurasidone. No data are available in elderly people treated with 148 mg of lurasidone. Caution should be exercised when treating patients ≥65 years of age with higher doses of lurasidone.

Renal impairment

No dose adjustment of lurasidone is required in patients with mild renal impairment. In patients with moderate (Creatinine Clearance (CrCl) ≥ 30 and < 50 ml/min), severe renal impairment (CrCL >15 and < 30 ml/min) and End Stage Renal Disease (ESRD) patients (CrCl < 15 ml/min), the recommended starting dose is 18.5 mg and the maximum dose should not exceed 74 mg once daily. Lurasidone should not be used in patients with ESRD unless the potential benefits outweigh the potential risks. If used in ESRD, clinical monitoring is advised.

Hepatic impairment

No dose adjustment of lurasidone is required in patients with mild hepatic impairment.

Dose adjustment is recommended in moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) patients. The recommended starting dose is 18.5 mg. The maximum daily dose in moderate hepatic impairment patients should not exceed 74 mg and in severe hepatic impairment patients should not exceed 37 mg once daily.

Method of administration

Lurasidone film-coated tablets are for oral use, to be taken once daily together with a meal. If taken without food, it is anticipated that lurasidone exposure will be significantly lower as compared to when taken with food (see section 5.2).

Lurasidone tablets should be swallowed whole, in order to mask the bitter taste. Lurasidone tablets should be taken at the same time every day to aid compliance.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant administration of strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) and strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St John's wort (Hypericum perforatum) (see section 4.5).

4.4 Special warnings and precautions for use

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

Suicidality

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 antipsychotic therapy.

Parkinson's disease

If prescribed to patients with Parkinson's disease, antipsychotic medicinal products may exacerbate the underlying parkinsonism symptoms. Physicians should therefore weigh the risks versus the benefits when prescribing lurasidone to patients with Parkinson's disease.

Extrapyramidal symptoms (EPS)

Medicinal products 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

Medicinal products 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 lurasidone is prescribed in patients with known cardiovascular disease or family history of QT prolongation, hypokalaemia, and in concomitant use with other medicinal products thought to prolong the QT interval.

Seizures

Lurasidone 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 with lurasidone. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, lurasidone should be discontinued.

Elderly patients with dementia

Lurasidone 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, aripiprazole and olanzapine. The mechanism for this increased risk is not known. An increased risk cannot be excluded

for other antipsychotics or other patient populations. Lurasidone 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 medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with lurasidone and preventive measures undertaken.

Hyperprolactinaemia

Lurasidone elevates prolactin levels due to antagonism of dopamine D2 receptors. Patients should be counselled on signs and symptoms of elevated prolactin, such as gynecomastia, galactorrhoea, amenorrhoea and erectile dysfunction. Patient 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, have been reported in clinical trials with lurasidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Orthostatic hypotension/syncope

Lurasidone 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 lurasidone (see section 4.5).

Serotonin syndrome

Concomitant administration of Lurasidone 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.

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Given the primary central nervous system effects of lurasidone, lurasidone should be used with caution in combination with other centrally acting medicinal products and alcohol.

Caution is advised when prescribing lurasidone with medicinal products known to prolong the QT interval, e.g. class IA antiarrhythmics (e.g. quinidine, disopyramide) and class III antiarrhythmics (e.g. amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g. mefloquine).

Lurasidone 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) or tricyclic 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 lurasidone.

Potential for other medicinal products to affect lurasidone

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

CYP3A4 inhibitors

Lurasidone 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).

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

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

Coadministration of lurasidone with medicinal products that moderately inhibit CYP3A4 (e.g. diltiazem, erythromycin, fluconazole verapamil) may increase exposure to lurasidone. Moderate CYP3A4 inhibitors are estimated to result in a 2-5 fold increase in exposure of CYP3A4 substrates.

Coadministration of lurasidone with diltiazem (slow-release formulation), a moderate CYP3A4 inhibitor, resulted in a 2.2 and 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 lurasidone exposure.

CYP3A4 inducers

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

Coadministration of lurasidone with the strong CYP3A4 inducer rifampicin resulted in a 6-fold decrease in exposure of lurasidone.

Coadministration of lurasidone 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-fold reduction in lurasidone exposure during co-administration and for up to 2 weeks after discontinuation of mild or moderate CYP3A4 inducers.

When lurasidone is coadministered with mild or moderate CYP3A4 inducers, the efficacy of lurasidone needs to be carefully monitored and a dose adjustment may be needed.

Transporters

Lurasidone is a substrate of P-gp and BCRP in vitro and the in vivo relevance of this is unclear. Coadministration of lurasidone with P-gp and BCRP inhibitors may increase exposure to lurasidone.

Potential for lurasidone to affect other medicinal products

Coadministration of lurasidone with midazolam, a sensitive CYP3A4 substrate, resulted in a < 1.5-fold increase in midazolam exposure. Monitoring is recommended

when lurasidone and CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine]) are coadministered.

Coadministration of lurasidone with digoxin (a P-gp substrate) did not increase the exposure to digoxin and only slightly increased Cmax (1.3 –fold) and therefore, it is considered that lurasidone can be coadministered with digoxin. Lurasidone 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.

Lurasidone 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.

Coadministration of lurasidone with lithium indicated that lithium had clinically negligible effects on the pharmacokinetics of lurasidone, therefore no dose adjustment of lurasidone is required when coadministered with lithium. Lurasidone does not impact concentrations of lithium.

A clinical drug interaction study investigating the effect of coadministration of lurasidone on patients taking oral combination contraceptives including norgestimate and ethinyl estradiol, indicated that lurasidone had no clinically or statistically meaningful effects on the pharmacokinetics of the contraceptive or sex hormone binding globulin (SHBG) levels. Therefore, lurasidone can be coadministered with oral contraceptives.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of lurasidone in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown. Lurasidone should not be used during pregnancy unless clearly necessary.

Neonates exposed to antipsychotics (including lurasidone) during the third trimester 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.

Breast-feeding

Lurasidone 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 lurasidone 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

Lurasidone 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 lurasidone 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 safety of lurasidone has been evaluated at doses of 18.5 -148 mg in clinical studies in patients with schizophrenia treated for up to 52 weeks and in the post-marketing setting. The most common adverse drug reactions (ADRs) (≥ 10%) were akathisia, nausea and insomnia.

Tabulated summary of adverse reactions

Adverse drug reactions (ADRs) based upon pooled data are shown by system, organ class and by preferred term are listed in Table 1 below. The incidence of ADRs reported in clinical trials is tabulated by frequency category. The following terms and frequencies are applied: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1 /10,000) and not known (cannot be estimated from the available data).

Table 1: Adverse drug reactions (ADRs) Based Upon Pooled Data for Adults

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
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		
Ear and labyrinth disorders			Vertigo		
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 Pruritus	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 4.6)
Reproductive system and breast disorders			Blood prolactin increased Erectile dysfunction Amenorrhoea Dysmenorrhea	Breast pain Galactorrhoea	Breast enlargement*** *
General disorders and administration site conditions		Fatigue	Gait disturbance	Sudden death	
Investigations		Blood creatinine phosphokinase increased			

*Somnolence includes adverse reaction terms: hypersomnia, hypersomnolence, sedation, and somnolence.
**Parkinsonism includes adverse reaction terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor.
***Dystonia includes adverse reaction terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus.
****ADRs noted in Phase 2 and 3 controlled and uncontrolled studies; however, the incidence of occurrence for these are too low to estimate frequencies.

Table 2: Adverse Drug Reactions (ADRs) for Adolescents

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Infections and infestations			Nasopharyngitis Rhinitis Upper respiratory tract infection		
Blood and lymphatic system disorders			Neutropenia		
Immune System Disorders			Hypersensitivity		
Endocrine disorders		Hyperprolactinaemia (including blood prolactin increased)	Autoimmune thyroiditis Hyperandrogenism Hypothyroidism		
Metabolism and nutrition disorders		Decreased appetite Increased appetite	Hyperinsulinemia		
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 disorder Vision blurred		
Ear and labyrinth disorders			Hyperacusis		
Cardiac disorders		Tachycardia	Palpitations Supraventricular extrasystoles		
Vascular disorders			Orthostatic hypotension Hypertension		
Respiratory, thoracic and mediastinal disorders			Oropharyngeal pain Dyspnoea		

Gastrointestinal disorders	Nausea	Constipation Dry mouth Salivary hypersecretion Vomiting	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	Arthralgia 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 creatine phosphokinase increased C-reactive protein increased Weight decreased Weight increased	Alanine aminotransferase increased Anti-thyroid antibody positive Aspartate aminotransferase increased Blood alkaline phosphatase 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		

*Somnolence includes the following adverse reactions observed in adolescents: hypersomnia, sedation, and somnolence.
**Parkinsonism includes the following adverse reactions observed in adolescents: cogwheel rigidity, extrapyramidal disorder, hypokinesia, parkinsonism, and tremor.
*** Dystonia includes the following adverse reactions observed in adolescents: dystonia, oculogyric crisis and torticollis.

Description of selected adverse reactions

Post marketing reports of clinically serious cases of skin and other hypersensitivity reactions have been reported in association with lurasidone treatment, including some reports of Stevens-Johnson syndrome.

Events of interest to the class
Extrapyramidal symptoms (EPS): In the adult short-term placebo-controlled studies, the incidence of reported events related to EPS, excluding akathisia and restlessness, was 13.5% for lurasidone-treated subjects versus 5.8% for placebo-treated subjects. The incidence of akathisia for lurasidone-treated subjects was 12.9% versus 3.0% for placebo-treated subjects. In the adolescent short-term placebo- controlled study, the incidence of reported events related to EPS, excluding akathisia, was 5.1% for lurasidone-treated subjects versus 1.8% for placebo-treated subjects. The incidence of akathisia for lurasidone-treated subjects was 8.9% versus 1.8% for placebo-treated subjects.

Dystonia: 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, difficulty swallowing, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity, higher potency and at higher doses of first generation antipsychotic medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

Venous thromboembolism: Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs -Frequency unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store).

4.9 Overdose

Management of overdose

There is no specific antidote to lurasidone, 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 arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects when administered in patients with an acute overdose of lurasidone. Similarly, the alpha-blocking properties of bretylium might be additive to those of lurasidone, resulting in problematic hypotension.

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 medicinal products 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

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 dopaminergic D2- 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 40.7 nM 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.

Pharmacodynamic effects

In the main clinical efficacy studies, lurasidone was administered at doses of 37-148 mg lurasidone.

Clinical efficacy

The efficacy of lurasidone in the treatment of schizophrenia was demonstrated in five multi-centre, placebo-controlled, double-blind, 6-week trials in subjects who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia. Lurasidone doses, which varied across the five trials, ranged from 37 to 148 mg lurasidone once daily. In the short-term trials, the primary efficacy endpoint was defined as the mean change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) total scores, a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression. Lurasidone demonstrated superior efficacy compared with placebo across Phase 3 studies (see Table 2). Lurasidone showed significant separation from placebo from as early as Day 4. Additionally, lurasidone was superior to placebo on the predefined secondary endpoint Clinical Global Impression – Severity (CGI-S) scale. Efficacy was also confirmed in a secondary analysis of treatment response (defined as ≥ 30% decrease from Baseline in PANSS total score).

Table 3: Schizophrenia Adult Studies: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change from Baseline to Week 6-MMRM for Studies D1050229, D1050231, and D1050233: Intent-to-Treat Analysis Set

Study Statistic	Placebo	Lurasidone dose (b)				Active Control (a)
		37 mg	74 mg	111 mg	148 mg	

Study D1050229	N=124	N=121	N=118	N=123	--	--
Baseline Mean (SD)	96.8 (11.1)	96.5 (11.6)	96.0 (10.8)	96.0 (9.7)	--	--
LS Mean Change (SE)	-17.0 (1.8)	-19.2 (1.7)	-23.4 (1.8)	-20.5 (1.8)	--	--
Treatment Difference vs. placebo						
Estimate (SE)	--	-2.1 (2.5)	-6.4 (2.5)	-3.5 (2.5)	--	--
p-value	--	0.591	0.034	0.391	--	--
Study D1050231	N=114	N=118	--	N=118	--	N=121
Baseline Mean (SD)	95.8 (10.8)	96.6 (10.7)	--	97.9 (11.3)	--	96.3 (12.2)
LS Mean Change (SE)	-16.0 (2.1)	-25.7 (2.0)	--	-23.6 (2.1)	--	-28.7 (1.9)
Treatment Difference vs. placebo						
Estimate (SE)	--	-9.7 (2.9)	--	-7.5 (3.0)	--	-12.6 (2.8)
p-value	--	0.002	--	0.022	--	<0.001
Study D1050233	N=120	--	N=125	--	N=121	N=116
Baseline Mean (SD)	96.6 (10.2)	--	97.7 (9.7)	--	97.9 (11.8)	97.7 (10.2)
LS Mean Change (SE)	-10.3 (1.8)	--	-22.2 (1.8)	--	-26.5 (1.8)	-27.8 (1.8)
Treatment Difference vs. placebo						
Estimate (SE)	--	--	-11.9 (2.6)	--	-16.2 (2.5)	-17.5 (2.6)
p-value	--	--	<0.001	--	<0.001	<0.001

(a) Olanzapine 15 mg in Study D1050231, quetiapine extended-release (XR) 600 mg in Study D1050233. N is number of subjects per model estimate.

(b) p-values for lurasidone vs. placebo were adjusted for multiple comparisons. P-values for olanzapine and quetiapine XR vs. placebo were unadjusted.

In the short-term studies there was no consistent dose-response correlation observed.

Long-term maintenance efficacy of lurasidone (37 to 148 mg lurasidone once daily) was demonstrated in a 12 month non-inferiority trial with quetiapine extended release (200 to 800 mg once daily). Lurasidone was non-inferior to quetiapine extended release in time to relapse of schizophrenia. Lurasidone had a small increase from baseline to Month 12 in body weight and body mass index (Mean (SD): 0.73 (3.36) kg and 0.28 (1.17) kg/m2, respectively) compared to quetiapine extended release (1.23 (4.56) kg and 0.45 (1.63) kg/m2, respectively). Overall, lurasidone had a negligible effect on weight and other metabolic parameters including total cholesterol, triglycerides, and glucose levels.

In a long-term safety study clinically stable patients were treated using 37 – 111 mg lurasidone or risperidone 2 – 6 mg. In that study the rate of relapse over a 12-month period was 20% for lurasidone and 16% for risperidone. This difference neared, but did not reach, statistical significance.

In a long-term trial designed to assess the maintenance of effect, lurasidone was more effective than placebo in maintaining symptom control and delaying relapse of schizophrenia. After having been treated for an acute episode and stabilized for a

minimum of 12 weeks with lurasidone, patients were then randomised in a double-blind manner to either continue on lurasidone or on placebo until they experienced a relapse in schizophrenia symptoms. In the primary analysis of time to relapse in which patients that withdrew without relapse were censored at the time of withdrawal, patients on lurasidone showed a significantly longer time to relapse compared with patients on placebo (p=0.039). The Kaplan-Meier estimates of the probability of relapse at Week 28 were 42.2% for lurasidone and 51.2% for placebo. The probability of all-cause discontinuation at Week 28 were 58.2% for lurasidone and 69.9% for placebo (p=0.072).

Paediatric population

Schizophrenia

The efficacy of lurasidone, was established in a 6-week, randomized, double-blind, placebo-controlled study of adolescents (13 to 17 years) who met DSM-IV-TR criteria for schizophrenia (N=326). Patients were randomized to one of two fixed-doses of Lurasidone (37 or 74 mg/day) or placebo.

The primary rating instrument used to assess psychiatric signs and symptoms was the PANSS. The key secondary instrument was the CGI-S.

For both dose groups, Lurasidone was superior to placebo in reduction of PANSS and CGI-S scores at Week 6. On average, the 74 mg/day dose did not provide additional benefit compared to the 37 mg/day dose.

The primary efficacy results are provided in Table 4.

Table - 4 Primary Efficacy Results (PANSS Total Score) - Change From Baseline to Week 6- MMRM for the Adolescent Schizophrenia Study D1050301: Intent-to-Treat Analysis Set

Study Statistic	Placebo	Lurasidone dose (a)	
		37 mg	74 mg
Study D1050301	N=112	N=108	N=106
Baseline Mean (SD)	92.8 (11.08)	94.5 (10.97)	94.0 (11.12)
LS Mean Change (SE)	-10.5 (1.59)	-18.6 (1.59)	-18.3 (1.60)
Treatment Difference vs. placebo			
Estimate (SE)	--	-8.0 (2.21)	-7.7 (2.22)
p-value	--	0.0006	0.0008

N is number of subjects per model estimate.
(a) p-values for lurasidone vs. placebo were adjusted for multiple comparisons.

The improvements in the CGI-S scores at Week 6 were significantly different from placebo for both the lurasidone 74 mg/day (-0.42 ± 0.130, adjusted p = 0.0015) and lurasidone 37 mg/day (-0.47 ± 0.130, adjusted p = 0.0008) treatment groups.

A 104-week extension study (Study D1050302) was designed to evaluate the long-term safety, tolerability, and effectiveness of flexibly dosed lurasidone (18.5, 37, 55.5, or 74 mg/day) in paediatric subjects who completed a 6-week treatment period

in three preceding studies of various indications. Only results for 271 subjects with schizophrenia who enrolled from Study D1050301 are hereinafter presented. Of these, 186 subjects (68.6%) completed through 52 weeks and 156 (57.6%) subjects completed 104 weeks of flexible dosing with lurasidone 18.5 to 74 mg/day.

For subjects who continued from D1050301, the mean (95% CI) in PANSS total score from DB Baseline was -26.5 (-28.5, -24.5) at Week 28 LOCF, -28.2 (-30.2, -26.2) at Week 52 LOCF, and -29.5 (-31.8, -27.3) at Week 104 LOCF/post-OL Endpoint, and mean change (95% CI) from OL Baseline was -9.2 (-11.1, -7.2) at Week 28 LOCF, -10.8 (-13.0, -8.7) at Week 52 LOCF, and -12.2 (-14.5, -9.8) at Week 104 LOCF/post-OL Endpoint.

Bipolar Depression

The short-term efficacy of lurasidone was studied in a 6-week multicentre, randomized, double-blind, placebo-controlled, study of children and adolescent patients (10-17 years of age) who met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria for a major depressive episode associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=350). Patients were randomized to flexibly dosed lurasidone 18-74 mg once daily or placebo.

The primary efficacy endpoint was defined as the mean change from baseline to Week 6 in Children's Depression Rating Scale, Revised (CDRS-R) Total Score. The key secondary endpoint was Clinical Global Impression – Bipolar Version, Severity of Illness (CGI-BP-S) Depression Score. Statistically significant differences favouring lurasidone over placebo were shown for these endpoints for the total population studied, beginning at Week 2 and were maintained at each study visit through to the end of the study. However, the primary and key secondary efficacy endpoints were not met in younger patients (below 15 years of age). Placebo-adjusted LS mean change (95% CI) from Baseline to Week 6 LOCF in CDRS-R total score for the lurasidone group was -1.8 (-5.6, 2.0) for subjects in the 10- to 14-year-old age patients and was -8.6 (-12.4, -4.8) for subjects in the 15- to 17-year-old age patients (Table 5).

The safety profile of lurasidone in children included in this short-term study is in general consistent with that observed when treated within the approved indication in adults, however, differences in frequency of the most commonly occurred adverse reactions have been observed in paediatric patients for nausea (very common), diarrhoea (common) and decreased appetite (common), compared with adults (common, unknown, and uncommon, respectively).

Table - 5 Bipolar Depression Paediatric Study: Children's Depression Rating Scale, Revised (CDRS-R) Total Score and Clinical Global Impression-Bipolar Version, Severity of Illness (CGI-BP-S) Depression Score (Depression) - Change From Baseline to Week 6 - MMRM for Study D1050326: Intent-to-Treat Analysis Set

Parameters	Study Statistic	Placebo	Lurasidone dose 18.5-74 mg (a) (b)
Primary Endpoint:		N=170	N=173

CDRS-R Total Score	Baseline Mean (SD)	58.6 (8.26)	59.2 (8.24)
	LS Mean Change (SE)	-15.3 (1.08)	-21.0 (1.06)
	Treatment Difference vs. placebo		
	Estimate (SE; 95% CI)	--	-5.7 (1.39; -8.4 to -3.0)
	p-value	--	<0.0001
Key Secondary Endpoint: CGI-BP-S Depression Score		N=170	N=173
	Baseline Mean (SD)	4.5	4.6
	LS Mean Change (SE)	-1.05 (0.087)	-1.49 (0.085)
	Treatment Difference vs. placebo		
	Estimate (SE; 95% CI)	--	-0.44 (0.112; -0.66 to -0.22)
	p-value	--	<0.0001

N is number of subjects.

(a) p-values for lurasidone vs. placebo were adjusted for multiple comparisons.

(b) Lurasidone doses of 18.5, 37, 55.5, 74 mg are equivalent to 20, 40, 60 and 80 amounts of lurasidone hydrochloride.

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 L. 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 a radiolabelled 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.

Pharmacokinetics in special patient groups

Elderly people

Limited data have been collected in healthy subjects ≥ 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.

Gender

There were no clinically relevant differences between genders 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 234 adolescents aged 13-17 years. Lurasidone was administered as lurasidone hydrochloride at daily doses of either 20, 40, 80, 120 mg (6-17 years) or 160 mg (10-17 years only) for 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.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic

potential. Major findings in repeat-dose toxicity studies of lurasidone were centrally mediated endocrine changes resulting from serum prolactin elevations in rats, dogs and monkeys. High serum prolactin levels in long-term repeat-dose studies in female rats were associated with effects on bones, adrenal glands, and reproductive tissues. In a long-term dog repeat-dose study, high serum prolactin levels were associated with effects on male and female reproductive tissues.

In rats, lurasidone had no effect on male and female reproduction at oral doses of 150 and 0.1 mg/kg/day lurasidone hydrochloride, respectively, or on early embryonic development at an oral dose of 15 mg/kg/day lurasidone hydrochloride.

A fertility study in female rats resulted in prolonged oestrous cycle and delayed copulation at ≥1.5 mg/kg/day lurasidone hydrochloride, whilst the copulation and fertility indices, and the numbers of corpora lutea, implantations and live foetuses were decreased at 150 mg/kg/day lurasidone hydrochloride. These effects were due to the hyperprolactinemia following lurasidone treatment, affecting the oestrous cycle and copulatory behaviour as well as the maintenance of corpus luteum of the female rats, resulting in a decrease in implantation and the number of live foetuses. These prolactin-related effects are not considered to be relevant to human reproduction.

A single dose of 10 mg/kg lurasidone hydrochloride to pregnant rats resulted in fetal exposure. In a dose range finding study in pregnant rats, 150 mg/kg/day lurasidone hydrochloride caused fetal growth retardation without signs of teratogenicity. Lurasidone was not teratogenic in rats or rabbits at an exposure similar to or below the maximum recommended human dose (148 mg lurasidone).

In the definitive juvenile rat toxicity study, no increased sensitivity of juvenile animals to lurasidone-related effects on body weight, food consumption, and clinical observations were apparent, but similar effects as in adult rat were noted (delays in growth and development and hyperprolactinaemia). Hyperactivity that was evident at ≥3 mg/kg/day during the post-treatment period has also been reported for other D2 receptor antagonists. Slightly lower birth weights and body weights/body weight gains during the postnatal period were noted in the offspring of juvenile rats previously treated with ≥30 mg/kg/day. At the NOAEL of 3 mg/kg/day, the exposures of lurasidone and most metabolites were lower than that achieved at the recommended clinical dose in adolescents aged 13 years or above.

Lurasidone was excreted in milk of rats during lactation.

Lurasidone was not genotoxic in a battery of tests. Mammary gland and/or pituitary gland tumours were observed in the mouse and rat carcinogenicity studies and are most likely due to the increased blood prolactin levels. These findings are common in rodents treated with antipsychotic medicinal products with dopamine D2 blocking activity and are considered to be rodent-specific.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Cellulose, microcrystalline (E460)
Mannitol (E421)
Hypromellose 2910 (E464)
Croscarmellose sodium (E468)
Magnesium stearate (E572)

Tablet Coating
Hypromellose 2910 (E464)

Titanium dioxide (E171)
Macrogol MW 8000 (E1521)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Cartons contain 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 90 x 1 or 98 x 1 tablets in OPA/AI/PVC/AI blister comprising of – Aluminium forming foil and Aluminium sealing foil.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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