ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Latuda 18.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lurasidone hydrochloride equivalent to18.6 mg lurasidone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Latuda 18.5 mg film-coated tablets: white to off-white, film-coated round tablets of 6 mm debossed with 'LA'

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Latuda is indicated for the treatment of schizophrenia in adults aged 18 years and over.

4.2 Posology and method of administration

Posology

The recommended starting dose of lurasidone is 37 mg 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.

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 Latuda 148 mg. Caution should be exercised when treating patients ≥65 years of age with higher doses of Latuda.

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. Latuda 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.

Paediatric population
The safety and efficacy of lurasidone in children aged less than 18 years have not been established. Current available data are described in section 5.2, but no recommendation on a posology can be made.

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.

Method of administration

Latuda 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).

Latuda tablets should be swallowed whole, in order to mask the bitter taste. Latuda 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 Latuda 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 antipsychotics including lurasidone. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including 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.

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.

Renal impairment
Dose adjustment is recommended for patients with moderate and severely impaired renal function and in patients with ESRD. Use in patients with ESRD has not been investigated and therefore lurasidone should not be used in patients with ESRD unless the potential benefits outweigh the potential risks. If used in patients with ESRD, clinical monitoring is advised (see sections 4.2 and 5.2).

Hepatic impairment
Dose adjustment is recommended for patients with moderate and severely impaired hepatic function (Child-Pugh Class B and C) (see sections 4.2 and 5.2). Caution is recommended in patients with severely impaired hepatic function.

Interaction with Grapefruit juice
Grapefruit juice should be avoided during treatment with lurasidone (see section 4.5).

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).

Pharmacokinetic interactions

The concomitant administration of lurasidone and grapefruit juice has not been assessed. Grapefruit juice inhibits CYP 3A4 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.

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.

<u>Potential for lurasidone to affect other medicinal products</u>

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 C_{max} (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/fetal 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 Latuda 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, until they are reasonably certain that lurasidone does not affect them adversely (see section 4.8).

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 and somnolence, which were dose-related up to 111 mg daily.

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 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 (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (<1 /10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Infections and infestations			Nasopharyngitis		
Blood and lymphatic system disorders				Eosinophilia	Leukopenia**** Neutropenia**** Anemia****
Immune system disorders					Hypersensitivity#
Metabolism and nutrition disorders		Weight increased	Decreased appetite Blood glucose increased		
Psychiatric disorders		Insomnia Agitation Anxiety Restlessness	Nightmare Catatonia		Suicidal behaviour**** Panic attack**** Sleep disorder****
Nervous system disorders	Akathisia Somnolence*	Parkinsonism** Dizziness Dystonia*** Dyskinesia	Lethargy Dysarthria Tardive dyskinesia	Neuroleptic malignant syndrome (NMS)	Convulsion****
Eye disorders			Blurred vision		
Ear and labyrinth disorders					Vertigo****
Cardiac disorders			Tachycardia		Angina**** AV block first degree**** Bradycardia****
Vascular disorders			Hypertension Hypotension Orthostatic hypotension Hot flush Blood pressure increased		
Gastrointestinal disorders		Nausea Vomiting Dyspepsia Salivary hypersecretion Dry mouth Upper abdominal pain Stomach discomfort	Flatulence		Diarrhoea**** Dysphagia**** Gastritis****
Hepatobiliary disorders			Alanine aminotransferase increased		

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Skin and subcutaneous tissue disorders			Hyperhidrosis		Rash**** Pruritus**** Angioedema**** Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders		Musculoskeletal stiffness Blood creatine phosphokinase increase	Joint stiffness Myalgia Neck pain Back 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		Breast enlargement**** Breast pain**** Galactorrhoea**** Erectile dysfunction**** Amenorrhoea**** Dysmenorrhoea****
General disorders and administration site conditions		Fatigue	Gait disturbance		Sudden death attributable to underlying cardiovascular disease observed during the clinical development programme****

*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.
Hypersensitivity may include symptoms such as throat swelling, tongue swelling, urticaria, or symptoms of angioedema, rash or pruritus (grouped under Skin and subcutaneous tissue disorders in Table 1).

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 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.

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 national reporting system listed in Appendix V.

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 (10-80 mg lurasidone hydrochloride) 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 (equivalent to 40-160 mg lurasidone hydrochloride).

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 (equivalent to 40-160 mg lurasidone hydrochloride) 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 2
Schizophrenia 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) (c)				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.
(c) Lurasidone doses of 37, 74, 111 and 148 mg are equivalent to 40, 80, 120 and 160 mg amounts of lurasidone hydrochloride.

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 (equivalent to 40 -160 mg lurasidone hydrochloride)) was demonstrated in a 12 month non-inferiority trial with quetiapine extended release (XR) (200 to 800 mg once daily). Lurasidone was non-inferior to quetiapine XR 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/m^2, respectively) compared to quetiapine XR (1.23 (4.56) kg and 0.45 (1.63) kg/m^2, 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 (equivalent to 40 – 120 mg lurasidone hydrochloride) 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

The European Medicines Agency has deferred the obligation to submit the results of studies with lurasidone in one or more subsets of the paediatric population in schizophrenia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

In a food effect study, lurasidone mean C_{max} 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 (equivalent to 40 mg lurasidone hydrochloride), 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 (equivalent to 20 to 160 mg lurasidone hydrochloride). 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 investigated in 49 children aged 6-12 years and 56 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 7 days. There was no clear correlation between obtained plasma 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 estrous 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 fetuses were decreased at 150 mg/kg/day lurasidone hydrochloride. These effects were due to the hyperprolactinemia following lurasidone treatment, affecting the estrous 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 equivalent to 160 mg lurasidone hydrochloride).

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

Core
Mannitol (E 421)
Starch, pregelatinised
Croscarmellose sodium (E468)
Hypromellose 2910 (E 464)
Magnesium stearate (E 470b)

Tablet coating
Hypromellose 2910 (E 464)
Titanium dioxide (E 171)
Macrogol 8000
Carnauba wax (E 903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

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 aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

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

Sunovion Pharmaceuticals Europe Ltd.
First Floor
Southside
97-105 Victoria Street
London
SW1E 6QT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/913/001-007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Latuda 37 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lurasidone hydrochloride equivalent to 37.2 mg lurasidone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Latuda 37 mg: film-coated tablets: white to off-white, film-coated round tablets of 8 mm debossed with 'LB'

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Latuda is indicated for the treatment of schizophrenia in adults aged 18 years and over.

4.2 Posology and method of administration

Posology

The recommended starting dose of lurasidone is 37 mg 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.

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 Latuda 148 mg. Caution should be exercised when treating patients ≥65 years of age with higher doses of Latuda.

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. Latuda 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.

Paediatric population
The safety and efficacy of lurasidone in children aged less than 18 years have not been established. Current available data are described in section 5.2, but no recommendation on a posology can be made.

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.

Method of administration

Latuda 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).

Latuda tablets should be swallowed whole, in order to mask the bitter taste. Latuda 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 Latuda 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 antipsychotics including lurasidone. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including 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.

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.

Renal impairment
Dose adjustment is recommended for patients with moderate and severely impaired renal function and in patients with ESRD. Use in patients with ESRD has not been investigated and therefore lurasidone should not be used in patients with ESRD unless the potential benefits outweigh the potential risks. If used in patients with ESRD, clinical monitoring is advised (see sections 4.2 and 5.2).

Hepatic impairment
Dose adjustment is recommended for patients with moderate and severely impaired hepatic function (Child-Pugh Class B and C) (see sections 4.2 and 5.2). Caution is recommended in patients with severely impaired hepatic function.

Interaction with Grapefruit juice
Grapefruit juice should be avoided during treatment with lurasidone (see section 4.5).

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).

Pharmacokinetic interactions

The concomitant administration of lurasidone and grapefruit juice has not been assessed. Grapefruit juice inhibits CYP 3A4 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.

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.

<u>Potential for lurasidone to affect other medicinal products</u>

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 C_{max} (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/fetal 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 Latuda 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, until they are reasonably certain that lurasidone does not affect them adversely (see section 4.8).

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 and somnolence, which were dose-related up to 111 mg daily.

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 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 (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (<1 /10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Infections and infestations			Nasopharyngitis		
Blood and lymphatic system disorders				Eosinophilia	Leukopenia**** Neutropenia**** Anemia****
Immune system disorders					Hypersensitivity#
Metabolism and nutrition disorders		Weight increased	Decreased appetite Blood glucose increased		
Psychiatric disorders		Insomnia Agitation Anxiety Restlessness	Nightmare Catatonia		Suicidal behaviour**** Panic attack**** Sleep disorder****
Nervous system disorders	Akathisia Somnolence*	Parkinsonism** Dizziness Dystonia*** Dyskinesia	Lethargy Dysarthria Tardive dyskinesia	Neuroleptic malignant syndrome (NMS)	Convulsion****
Eye disorders			Blurred vision		
Ear and labyrinth disorders					Vertigo****
Cardiac disorders			Tachycardia		Angina**** AV block first degree**** Bradycardia****
Vascular disorders			Hypertension Hypotension Orthostatic hypotension Hot flush Blood pressure increased		
Gastrointestinal disorders		Nausea Vomiting Dyspepsia Salivary hypersecretion Dry mouth Upper abdominal pain Stomach discomfort	Flatulence		Diarrhoea**** Dysphagia**** Gastritis****
Hepatobiliary disorders			Alanine aminotransferase increased		

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Skin and subcutaneous tissue disorders			Hyperhidrosis		Rash**** Pruritus**** Angioedema**** Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders		Musculoskeletal stiffness Blood creatine phosphokinase increase	Joint stiffness Myalgia Neck pain Back 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		Breast enlargement**** Breast pain**** Galactorrhoea**** Erectile dysfunction**** Amenorrhoea**** Dysmenorrhoea****
General disorders and administration site conditions		Fatigue	Gait disturbance		Sudden death attributable to underlying cardiovascular disease observed during the clinical development programme****

*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.
Hypersensitivity may include symptoms such as throat swelling, tongue swelling, urticaria, or symptoms of angioedema, rash or pruritus (grouped under Skin and subcutaneous tissue disorders in Table 1).

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 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.

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 national reporting system listed in Appendix V.

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 (10-80 mg lurasidone hydrochloride) 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 (equivalent to 40-160 mg lurasidone hydrochloride).

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 (equivalent to 40-160 mg lurasidone hydrochloride) 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 2
Schizophrenia 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) (c)				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.
(c) Lurasidone doses of 37, 74, 111 and 148 mg are equivalent to 40, 80, 120 and 160 mg amounts of lurasidone hydrochloride.

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 (equivalent to 40 -160 mg lurasidone hydrochloride)) was demonstrated in a 12 month non-inferiority trial with quetiapine extended release (XR) (200 to 800 mg once daily). Lurasidone was non-inferior to quetiapine XR 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/m^2, respectively) compared to quetiapine XR (1.23 (4.56) kg and 0.45 (1.63) kg/m^2, 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 (equivalent to 40 – 120 mg lurasidone hydrochloride) 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

The European Medicines Agency has deferred the obligation to submit the results of studies with lurasidone in one or more subsets of the paediatric population in schizophrenia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

In a food effect study, lurasidone mean C_{max} 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 (equivalent to 40 mg lurasidone hydrochloride), 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 (equivalent to 20 to 160 mg lurasidone hydrochloride). 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 investigated in 49 children aged 6-12 years and 56 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 7 days. There was no clear correlation between obtained plasma 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 estrous 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 fetuses were decreased at 150 mg/kg/day lurasidone hydrochloride. These effects were due to the hyperprolactinemia following lurasidone treatment, affecting the estrous 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 equivalent to 160 mg lurasidone hydrochloride).

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

Core
Mannitol (E 421)
Starch, pregelatinised
Croscarmellose sodium (E468)
Hypromellose 2910 (E 464)
Magnesium stearate (E 470b)

Tablet coating
Hypromellose 2910 (E 464)
Titanium dioxide (E 171)
Macrogol 8000
Carnauba wax (E 903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

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 aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

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

Sunovion Pharmaceuticals Europe Ltd.
First Floor
Southside
97-105 Victoria Street
London
SW1E 6QT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/913/008-014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Latuda 74 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lurasidone hydrochloride equivalent to 74.5 mg lurasidone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Latuda 74 mg film-coated tablets: pale green, film-coated oval tablets of 12 mm x 7 mm debossed with 'LD'

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Latuda is indicated for the treatment of schizophrenia in adults aged 18 years and over.

4.2 Posology and method of administration

Posology

The recommended starting dose of lurasidone is 37 mg 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.

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 Latuda 148 mg. Caution should be exercised when treating patients ≥65 years of age with higher doses of Latuda.

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. Latuda 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.

Paediatric population
The safety and efficacy of lurasidone in children aged less than 18 years have not been established. Current available data are described in section 5.2, but no recommendation on a posology can be made.

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.

Method of administration

Latuda 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).

Latuda tablets should be swallowed whole, in order to mask the bitter taste. Latuda 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 Latuda 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 antipsychotics including lurasidone. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including 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.

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.

Renal impairment
Dose adjustment is recommended for patients with moderate and severely impaired renal function and in patients with ESRD. Use in patients with ESRD has not been investigated and therefore lurasidone should not be used in patients with ESRD unless the potential benefits outweigh the potential risks. If used in patients with ESRD, clinical monitoring is advised (see sections 4.2 and 5.2).

Hepatic impairment
Dose adjustment is recommended for patients with moderate and severely impaired hepatic function (Child-Pugh Class B and C) (see sections 4.2 and 5.2). Caution is recommended in patients with severely impaired hepatic function.

Interaction with Grapefruit juice
Grapefruit juice should be avoided during treatment with lurasidone (see section 4.5).

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).

Pharmacokinetic interactions

The concomitant administration of lurasidone and grapefruit juice has not been assessed. Grapefruit juice inhibits CYP 3A4 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.

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.

<u>Potential for lurasidone to affect other medicinal products</u>

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 C_{max} (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/fetal 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 Latuda 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, until they are reasonably certain that lurasidone does not affect them adversely (see section 4.8).

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 and somnolence, which were dose-related up to 111 mg daily.

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 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 (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (<1 /10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Infections and infestations			Nasopharyngitis		
Blood and lymphatic system disorders				Eosinophilia	Leukopenia**** Neutropenia**** Anemia****
Immune system disorders					Hypersensitivity#
Metabolism and nutrition disorders		Weight increased	Decreased appetite Blood glucose increased		
Psychiatric disorders		Insomnia Agitation Anxiety Restlessness	Nightmare Catatonia		Suicidal behaviour**** Panic attack**** Sleep disorder****
Nervous system disorders	Akathisia Somnolence*	Parkinsonism** Dizziness Dystonia*** Dyskinesia	Lethargy Dysarthria Tardive dyskinesia	Neuroleptic malignant syndrome (NMS)	Convulsion****
Eye disorders			Blurred vision		
Ear and labyrinth disorders					Vertigo****
Cardiac disorders			Tachycardia		Angina**** AV block first degree**** Bradycardia****
Vascular disorders			Hypertension Hypotension Orthostatic hypotension Hot flush Blood pressure increased		
Gastrointestinal disorders		Nausea Vomiting Dyspepsia Salivary hypersecretion Dry mouth Upper abdominal pain Stomach discomfort	Flatulence		Diarrhoea**** Dysphagia**** Gastritis****
Hepatobiliary disorders			Alanine aminotransferase increased		

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Skin and subcutaneous tissue disorders			Hyperhidrosis		Rash**** Pruritus**** Angioedema**** Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders		Musculoskeletal stiffness Blood creatine phosphokinase increase	Joint stiffness Myalgia Neck pain Back 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		Breast enlargement**** Breast pain**** Galactorrhoea**** Erectile dysfunction**** Amenorrhoea**** Dysmenorrhoea****
General disorders and administration site conditions		Fatigue	Gait disturbance		Sudden death attributable to underlying cardiovascular disease observed during the clinical development programme****

*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.
Hypersensitivity may include symptoms such as throat swelling, tongue swelling, urticaria, or symptoms of angioedema, rash or pruritus (grouped under Skin and subcutaneous tissue disorders in Table 1).

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 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.

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 national reporting system listed in Appendix V.

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 (10-80 mg lurasidone hydrochloride) 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 (equivalent to 40-160 mg lurasidone hydrochloride).

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 (equivalent to 40-160 mg lurasidone hydrochloride) 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 2
Schizophrenia 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) (c)				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.
(c) Lurasidone doses of 37, 74, 111 and 148 mg are equivalent to 40, 80, 120 and 160 mg amounts of lurasidone hydrochloride.

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 (equivalent to 40 -160 mg lurasidone hydrochloride)) was demonstrated in a 12 month non-inferiority trial with quetiapine extended release (XR) (200 to 800 mg once daily). Lurasidone was non-inferior to quetiapine XR 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/m^2, respectively) compared to quetiapine XR (1.23 (4.56) kg and 0.45 (1.63) kg/m^2, 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 (equivalent to 40 – 120 mg lurasidone hydrochloride) 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

The European Medicines Agency has deferred the obligation to submit the results of studies with lurasidone in one or more subsets of the paediatric population in schizophrenia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

In a food effect study, lurasidone mean C_{max} 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 (equivalent to 40 mg lurasidone hydrochloride), 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 (equivalent to 20 to 160 mg lurasidone hydrochloride). 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 investigated in 49 children aged 6-12 years and 56 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 7 days. There was no clear correlation between obtained plasma 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 estrous 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 fetuses were decreased at 150 mg/kg/day lurasidone hydrochloride. These effects were due to the hyperprolactinemia following lurasidone treatment, affecting the estrous 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 equivalent to 160 mg lurasidone hydrochloride).

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

Core
Mannitol (E 421)
Starch, pregelatinised
Croscarmellose sodium (E468)
Hypromellose 2910 (E 464)
Magnesium stearate (E 470b)

Tablet coating
Hypromellose 2910 (E 464)
Titanium dioxide (E 171)
Macrogol 8000
Iron oxide, Yellow (E 172)
Indigotine (E 132)
Carnauba wax (E 903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

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 aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

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

Sunovion Pharmaceuticals Europe Ltd.
First Floor
Southside
97-105 Victoria Street
London
SW1E 6QT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/913/015-021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AndersonBrecon (UK) Ltd.
Units 2-7
Wye Valley Business Park
Brecon Road
Hay-on-Wye
Hereford
HR3 5PG
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Latuda 18.5 mg film-coated tablets
lurasidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains lurasidone hydrochloride equivalent to18.6 mg lurasidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
56 x 1 film-coated tablets
60 x 1 film-coated tablets
90 x 1 film-coated tablets
98 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sunovion Pharmaceuticals Europe Ltd.
First Floor
Southside
97-105 Victoria Street
London
SW1E 6QT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/913/001 14 x 1 film-coated tablets
EU/1/14/913/002 28 x 1 film-coated tablets
EU/1/14/913/003 30 x 1 film-coated tablets
EU/1/14/913/004 56 x 1 film-coated tablets
EU/1/14/913/005 60 x 1 film-coated tablets
EU/1/14/913/006 90 x 1 film-coated tablets
EU/1/14/913/007 98 x 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Latuda 18.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Latuda 18.5 mg tablets
lurasidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sunovion logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Latuda 37 mg film-coated tablets
lurasidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains lurasidone hydrochloride equivalent to 37.2 mg lurasidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
56 x 1 film-coated tablets
60 x 1 film-coated tablets
90 x 1 film-coated tablets
98 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sunovion Pharmaceuticals Europe Ltd.
First Floor
Southside
97-105 Victoria Street
London
SW1E 6QT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/913/008 14 x 1 film-coated tablets
EU/1/14/913/009 28 x 1 film-coated tablets
EU/1/14/913/010 30 x 1 film-coated tablets
EU/1/14/913/011 56 x 1 film-coated tablets
EU/1/14/913/012 60 x 1 film-coated tablets
EU/1/14/913/013 90 x 1 film-coated tablets
EU/1/14/913/014 98 x 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Latuda 37 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Latuda 37 mg tablets
lurasidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sunovion logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Latuda 74 mg film-coated tablets
lurasidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains lurasidone hydrochloride equivalent to 74.5 mg lurasidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
56 x 1 film-coated tablets
60 x 1 film-coated tablets
90 x 1 film-coated tablets
98 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sunovion Pharmaceuticals Europe Ltd.
First Floor
Southside
97-105 Victoria Street
London
SW1E 6QT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/913/015 14 x 1 film-coated tablets
EU/1/14/913/016 28 x 1 film-coated tablets
EU/1/14/913/017 30 x 1 film-coated tablets
EU/1/14/913/018 56 x 1 film-coated tablets
EU/1/14/913/019 60 x 1 film-coated tablets
EU/1/14/913/020 90 x 1 film-coated tablets
EU/1/14/913/021 98 x 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Latuda 74 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Latuda 74 mg tablets
lurasidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sunovion logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Latuda 18.5 mg film-coated tablets
Latuda 37 mg film-coated tablets
Latuda 74 mg film-coated tablets
lurasidone

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Latuda is and what it is used for
2. What you need to know before you take Latuda
3. How to take Latuda
4. Possible side effects
5. How to store Latuda
6. Contents of the pack and other information

1. What Latuda is and what it is used for

Latuda contains the active substance lurasidone and belongs to a group of medicines called antipsychotics. It is used to treat symptoms of schizophrenia in adults aged 18 years or over. Lurasidone works by blocking receptors in the brain to which the substances dopamine and serotonin attach. Dopamine and serotonin are neurotransmitters (substances that allow nerve cells to communicate with each other) that are involved in the symptoms of schizophrenia. By blocking their receptors, lurasidone helps to normalise the activity of the brain, reducing the symptoms of schizophrenia.

Schizophrenia is a disorder with symptoms such as hearing things, seeing or sensing things that are not there, mistaken beliefs, unusual suspiciousness, becoming withdrawn, incoherent speech and behaviour and emotional flatness. People with this disorder may also feel depressed, anxious, guilty, or tense. This medicine is used to improve your symptoms of schizophrenia.

2. What you need to know before you take Latuda

Do NOT take Latuda if you:
- are allergic to lurasidone or any of the other ingredients of this medicine (listed in section 6)
- are taking medicines which may affect the level of lurasidone in your blood such as:
  - medicines for fungal infections such as itraconazole, ketoconazole (except as a shampoo), posaconazole or voriconazole
  - medicines for an infection such as the antibiotic clarithromycin or telithromycin
  - medicines for HIV infections such as cobicistat, indinavir, nelfinavir, ritonavir, and saquinavir

- boceprevir, and telaprevir (medicines for chronic hepatitis)
- nefazodone (a medicine for depression)
- rifampicin (a medicine for tuberculosis)
- carbamazepine, phenobarbital and phenytoin (medicines for seizures)
- St John's wort (*Hypericum perforatum*) (herbal medicine for depression).

Warnings and precautions
It may take several days or even weeks before this medicine will have a full effect. Contact your doctor if you have questions on this medicine.

Talk to your doctor or pharmacist before taking this medicine, or during treatment, especially if you have:

- Parkinson's disease or dementia
- ever been diagnosed with a condition whose symptoms include high temperature and muscle stiffness (also known as neuroleptic malignant syndrome) or if you have ever experienced rigidity, tremors or problems moving (extrapyramidal symptoms) or abnormal movements of the tongue or face (tardive dyskinesia). You should be aware that these conditions may be caused by this medicine
- heart disease or heart disease treatment that makes you prone to low blood pressure or have a family history of irregular heart beat (including QT prolongation)
- a history of seizures (fits) or epilepsy
- a history of blood clots, or if someone else in your family has a history of blood clots, as medicines for schizophrenia have been associated with formation of blood clots
- increased levels of the hormone prolactin in your blood
- diabetes or are prone to diabetes
- decreased kidney function
- decreased liver function
- an increase in your weight
- blood pressure dropping upon your standing up which may cause fainting.

If you have any of these conditions, please talk to your doctor as he/she may want to adjust your dose, monitor you more closely or stop treatment with Latuda.

Children and adolescents
This medicine is not recommended for children and adolescents under 18 years due to the lack of data in these patients.

Other medicines and Latuda
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is especially important if you are taking:

- any medicines that also work in the brain, as their effects could be additive in a negative way with the effects of Latuda on your brain
- medicines that lower blood pressure, as this medicine can also lower blood pressure
- medicines for Parkinson's disease and restless legs syndrome (e.g. levodopa) as this medicine can reduce their effects
- medicines containing ergot alkaloid derivatives (used for treating migraines), and other medicines including terfenadine and astemizole (used for treating hay fever and other allergic conditions), cisapride (used for treating digestive problems), pimozide (used to treating psychiatric illnesses), quinidine (used for treating heart conditions), bepridil (used for treating chest pain).

Tell your doctor if you take any of these medicines since your doctor may have to change the dose of that medicine during treatment with Latuda.

The following medicines may increase the level of lurasidone in your blood:
- diltiazem (to treat high blood pressure)
- erythromycin (to treat infections)
- fluconazole (to treat fungal infections)
- verapamil (to treat high blood pressure or chest pain).

The following medicines may decrease the level of lurasidone in your blood:
- amprenavir, efavirenz, etravirine (to treat HIV infection)
- aprepitant (to treat nausea and vomiting)
- armodafinil, modafinil (to treat sleepiness)
- bosentan (to treat high blood pressure or ulcers of the fingers)
- nafcillin (to treat infections)
- prednisone (to treat inflammatory disease)
- rufinamide (to treat seizures).

Tell your doctor if you take any of these medicines since your doctor may change your dose of Latuda.

Latuda with food, drink and alcohol
Alcohol should be avoided when taking this medicine. This is because alcohol will have an additive negative effect.
Do not drink grapefruit juice while you are taking this medicine. Grapefruit can affect the way this medicine works.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or planning to have a baby, ask your doctor for advice before taking this medicine.

You should not take this medicine during pregnancy unless this has been agreed with your doctor.

If your doctor decides that the potential benefit of treatment during pregnancy justifies the potential risk to your unborn baby, your doctor will monitor your baby closely after birth. This is because the following symptoms may occur in newborn babies of mothers that have used lurasidone in the last trimester (last three months) of their pregnancy:
- shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding.

If your baby develops any of these symptoms you should contact your doctor.

It is not known if lurasidone passes into breast milk. Talk to your doctor if you are breast-feeding, or if you plan to breast-feed.

Driving and using machines
Sleepiness, dizziness and vision problems may occur during treatment with this medicine (see section 4, Possible side effects). Do not drive or use any tools or machines until you know that this medicine does not affect you in a negative way.

3. How to take Latuda

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended starting dose is 37 mg once a day.
The dose may be increased or decreased by your doctor within the dose range of 18.5 mg to 148 mg once a day. The maximum dose should not exceed 148 mg once a day.

Your dose will be decided by your doctor and may depend on:
- how well you respond to a dose
- if you are taking some other medicines (see section 2, Other medicines and Latuda)
- if you have kidney or liver problems.

Swallow your tablet(s) whole with water, in order to mask the bitter taste. You should take your dose regularly every day at the same time of the day, so that it is easier to remember it. You must take this medicine with food or just after eating, as this helps the body to take up the medicine and allows it to work better.

If you take more Latuda than you should
If you take more of this medicine than you should, contact your doctor immediately. You may experience sleepiness, tiredness, abnormal body movements, problems with standing and walking, dizziness from low blood pressure, and abnormal heart beats.

If you forget to take Latuda
Do not take a double dose to make up for a forgotten dose. If you miss one dose, take your next dose on the day after the missed dose. If you miss two or more doses, contact your doctor.

If you stop taking Latuda
If you stop taking this medicine you will lose the effects of the medicine. You should not stop this medicine unless told to do so by your doctor as your symptoms may return.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any of the following symptoms **seek medical attention immediately**:
- a severe allergic reaction seen as fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes a drop in blood pressure. These reactions are seen rarely (may affect up to 1 in 1,000 people).

- A serious blistering rash affecting the skin, mouth, eyes and genitals (Stevens-Johnson syndrome)

- Fever, sweating, muscle stiffness, and reduced consciousness. These could be symptoms of a condition known as neuroleptic malignant syndrome. These reactions are seen rarely (may affect up to 1 in 1,000 people).

- Blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.

The following side effects may also happen:

Very common (may affect more than 1 in 10 people):
- feeling of restlessness and inability to sit still
- sleepiness.

Common (may affect up to 1 in 10 people):
- Parkinsonism: This is a medical term that describes many symptoms which include increase in saliva secretion or watery mouth, drooling, jerks when bending the limbs, slow, reduced or

impaired body movements, no expression in the face, muscle tightness, stiff neck, muscle stiffness, small, shuffling, hurried steps and lack of normal arm movements when walking, persistent blinking in response to tapping of the forehead (an abnormal reflex)
- speech problems, unusual muscle movements; a collection of symptoms known as extrapyramidal symptoms (EPS) which typically will involve unusual purposeless involuntary muscle movements.
- dizziness
- muscle spasms and stiffness
- nausea (feeling sick), vomiting (being sick)
- indigestion
- dry mouth or excess saliva
- abdominal pain
- difficulty sleeping, tiredness, agitation and anxiety
- weight gain
- increase in creatine phosphokinase (an enzyme in muscles) seen in blood tests
- increase in creatinine (a marker of kidney function) seen in blood tests.

Uncommon (may affect up to 1 in 100 people):
- slurred speech
- nightmares
- muscle aches
- joint pains
- problems walking
- rigid posture
- increased blood prolactin, increased blood glucose (blood sugar), increase in some liver enzymes, seen in blood tests
- increased blood pressure
- blood pressure dropping upon standing up which may cause fainting
- fast heart beat
- common cold
- hot flush
- blurred vision
- reduced appetite
- sweating
- pain when passing urine.
- uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia).

Rare (may affect up to 1 in 1,000 people):
- Rhabdomyolysis which is the breakdown of muscle fibres that leads to the release of muscle fibre contents (myoglobin) into the bloodstream, seen as muscle pain, being sick, being confused, an abnormal heart rate and rhythm, and possibly dark urine
- increase in eosinophils (a type of white blood cell).

Not known (frequency cannot be estimated from the available data):
- reduced levels of white blood cells (which fight infection) and red blood cells (which carry oxygen around the body)
- deliberate injury to oneself
- sudden feelings of anxiety
- sleep disorder
- spinning sensation
- seizure (fits)
- chest pain
- abnormal nerve impulses in the heart
- slow heart rate
- diarrhoea

- difficulty swallowing
- swelling of the tongue or throat
- irritation to lining of stomach
- rash, which may be itchy and include swelling, blistering or red patches on the skin.
- kidney failure
- newborn babies may show the following: agitation, increase or decreases in muscle tone, tremor, sleepiness, breathing or feeding problems
- abnormal breast enlargement, breast pain, milk secretion from breasts
- problems with erections
- painful or absence of menstrual periods
- sudden death associated with heart disease.

In elderly people with dementia, a small increase in the number of deaths has been reported for patients taking medicines for schizophrenia compared with those not receiving these medicines.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in **Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Latuda

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Latuda contains
- The active substance is lurasidone.
  Each 18.5 mg tablet contains lurasidone hydrochloride equivalent to 18.6 mg lurasidone.
  Each 37 mg tablet contains lurasidone hydrochloride equivalent to 37.2 mg lurasidone.
  Each 74 mg tablet contains lurasidone hydrochloride equivalent to 74.5 mg lurasidone.
- The other ingredients are mannitol, pregelatinised starch, croscarmellose sodium, hypromellose, magnesium stearate (E470b), titanium dioxide (E171), macrogol, yellow iron oxide (E172) (present in 74 mg tablets), indigotine (E132) (present in 74 mg tablets) and carnauba wax (E903).

What Latuda looks like and contents of the pack
- Latuda 18.5 mg film-coated tablets are white to off-white, film-coated round tablets debossed with “LA”
- Latuda 37 mg film-coated tablets are white to off-white, film-coated round tablets debossed with “LB”
- Latuda 74 mg film-coated tablets are pale green, film-coated oval tablets debossed with “LD”.

Latuda film-coated tablets are available in pack sizes containing 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 90 x 1 or 98 x 1 film-coated tablet in aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.