**SUMMARY OF PRODUCT CHARACTERISTICS**

**1.Name of the medicinal product**

Lurasidone Hydrochloride Tablets 40 mg (LURATA 40)

**2.Qualitative and quantitative composition**

Each film-coated tablet contains
Lurasidone hydrochloride 40 mg
**Excipients of known effect:** Lactose monohydrate

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

**3.Pharmaceutical form**

Film-coated tablet .

White colored, round shaped biconvex, film coated tablets, debossed with "40" on one side and "ML" on other side.

**4. Clinical particulars**

**4.1 Therapeutic indications**

Lurasidone hydrochloride 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 hydrochloride is 40 mg once daily. No initial dose titration is required. It is effective in a dose range of 40 to 160 mg once daily. Dose increase should be based on physician judgement and observed clinical response. The maximum daily dose should not exceed 160 mg.

Patients on doses higher than 120 mg once daily who discontinue their treatment for longer than 3 days should be restarted on 120 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 hydrochloride . No data are available in elderly people treated with lurasidone hydrochloride 160 mg. Caution should be exercised when treating patients ≥65 years of age with higher doses of lurasidone hydrochloride .

*Renal impairment*

No dose adjustment of lurasidone hydrochloride 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 20 mg and the maximum dose should not exceed 80 mg once daily. lurasidone hydrochloride 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 hydrochloride 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 20 mg. The maximum daily dose in moderate hepatic impairment patients should not exceed 80 mg and in severe hepatic impairment patients should not exceed 40 mg once daily.

*Paediatric population*

The safety and efficacy of lurasidone hydrochloride 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 20 mg is recommended and the maximum dose of lurasidone hydrochloride should not exceed 80 mg once daily in combination with moderate CYP3A4 inhibitors. Dose adjustment of lurasidone hydrochloride 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

lurasidone hydrochloride 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 hydrochloride exposure will be significantly lower as compared to when taken with food (see section 5.2).

lurasidone hydrochloride tablets should be swallowed whole, in order to mask the bitter taste. lurasidone hydrochloride 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 exacerbatethe underlying parkinsonism symptoms. Physicians should therefore weigh the risks versus the benefits when prescribing lurasidone hydrochloride 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 hydrochloride 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 hydrochloride , should be considered.

Cardiovascular disorders/QT prolongation

Caution should be exercised when lurasidone hydrochloride 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 hydrochloride 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 hydrochloride . Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics,

including lurasidone hydrochloride , should be discontinued.

Elderly patients with dementia

lurasidone hydrochloride 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 hydrochloride 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 hydrochloride and preventive measures undertaken.

Hyperprolactinaemia

lurasidone hydrochloride 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 hydrochloride . Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Orthostatic hypotension/syncope

lurasidone hydrochloride 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 hydrochloride 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 hydrochloride (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 hydrochloride , lurasidone hydrochloride should be used with caution in combination with other centrally acting medicinal products and alcohol.

Caution is advised when prescribing lurasidone hydrochloride 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 hydrochloride and grapefruit juice has not been assessed. Grapefruit juice inhibits CYP 3A4 and may increase the serum concentration of lurasidone hydrochloride . Grapefruit juice should be avoided during treatment with lurasidone hydrochloride .

Potential for other medicinal products to affect lurasidone hydrochloride

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

*CYP3A4 inhibitors*

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

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

Coadministration of lurasidone hydrochloride with diltiazem (slow-release formulation), a moderate CYP3A4 inhibitor, resulted in a 2.2 and 2.4-fold increase in exposure of lurasidone hydrochloride 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 hydrochloride exposure.

*CYP3A4 inducers*

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

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

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

*Transporters*

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

Potential for lurasidone hydrochloride to affect other medicinal products

Coadministration of lurasidone hydrochloride with midazolam, a sensitive CYP3A4 substrate, resulted in a < 1.5-fold increase in midazolam exposure. Monitoring is recommended when lurasidone hydrochloride 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 hydrochloride with digoxin (a P-gp substrate) did not increase the exposure to digoxin and only slightly increased Cmax (1.3 –fold) and therefore, it is considered that lurasidone hydrochloride can be coadministered with digoxin. lurasidone hydrochloride 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 hydrochloride 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 hydrochloride with lithium indicated that lithium had clinically negligible effects on the pharmacokinetics of lurasidone hydrochloride , therefore no dose adjustment of lurasidone hydrochloride is required when coadministered with lithium. lurasidone hydrochloride does not impact concentrations of lithium.

A clinical drug interaction study investigating the effect of coadministration of

lurasidone hydrochloride on patients taking oral combination contraceptives including norgestimate and ethinyl estradiol, indicated that lurasidone hydrochloride had no clinically or statistically meaningful effects on the pharmacokinetics of the contraceptive or sex hormone binding globulin (SHBG) levels. Therefore, lurasidone hydrochloride 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 hydrochloride 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 hydrochloride should not be used during pregnancy unless clearly necessary.

Neonates exposed to antipsychotics (including lurasidone hydrochloride ) 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 hydrochloride was excreted in milk of rats during lactation (see section 5.3). It is not known whether lurasidone hydrochloride or its metabolites are excreted in human milk. Breast feeding in women receiving lurasidone hydrochloride 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 hydrochloride 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 hydrochloride does not affect them adversely (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile

The safety of lurasidone hydrochloride has been evaluated at doses of 20 -160 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 120 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****<br>AV block first degree****<br>Bradycardia**** |
| Vascular disorders | | | Hypertension<br>Hypotension<br>Orthostatic hypotension<br>Hot flush<br>Blood pressure increased | | |
| Gastrointestinal disorders | | Nausea<br>Vomiting<br>Dyspepsia<br>Salivary hypersecretion<br>Dry mouth<br>Upper abdominal pain<br>Stomach discomfort | Flatulence | | Diarrhoea***<br>Dysphagia****<br>Gastritis**** |
| Hepatobiliary disorders | | | Alanine aminotransferase increased | | |
| Skin and subcutaneous tissue disorders | | | Hyperhidrosis | | Rash****<br>Pruritus****<br>Angioedema***<br>Stevens-Johnson syndrome |

| | | | | | |
|---|---|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | Musculoskeletal stiffness<br>Blood creatine phosphokinase increase | Joint stiffness<br>Myalgia<br>Neck pain<br>Back pain<br>Dysuria | Rhabdomyolysis | Renal failure**** |
| Renal and urinary disorders | | Serum creatinine increased | | | |
| 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****<br>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 hydrochloride 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 hydrochloride -treated subjects versus 5.8% for placebo- treated subjects. The incidence of akathisia for lurasidone hydrochloride -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:** Healthcare professionals are asked to report any suspected adverse reactions via the relevant national regulatory authority pharmacovigilance.

## 4.9 Overdose

Management of overdose

There is no specific antidote to lurasidone hydrochloride , 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 hydrochloride . Similarly the alpha-blocking properties of bretylium might be additive to those of lurasidone hydrochloride , 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 hydrochloride -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 hydrochloride is a selective blocking agent of dopamine and monoamine effects. lurasidone hydrochloride 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 hydrochloride also exhibits partial agonism at the 5HT-1A receptor with a binding affinity of 6.38 nM. lurasidone hydrochloride does not bind to cholinergic or muscarinic receptors.

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

lurasidone hydrochloride doses ranging from 10 to 80 mg administered to healthy subjects produced a dose-dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, in the caudate, putamen and ventral striatum detected by positron emission tomography.

Pharmacodynamic effects

In the main clinical efficacy studies, lurasidone hydrochloride was administered at doses of 40-160 mg.

*Clinical efficacy*

The efficacy of lurasidone hydrochloride 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 hydrochloride doses, which varied across the five trials, ranged from 40 to 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 hydrochloride

demonstrated superior efficacy compared with placebo across Phase 3 studies (see Table 2). lurasidone hydrochloride showed significant separation from placebo from as early as Day 4. Additionally, lurasidone hydrochloride 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 hydrochloride dose (b) (c)** | | | | **Active Control (a)** |
|---|---|---|---|---|---|---|
| | | **40 mg** | **80 mg** | **120 mg** | **160 mg** | |
| Study D1050229<br>Baseline Mean (SD)<br>LS Mean Change (SE) Treatment Difference vs. placebo<br>Estimate (SE) p-value | N=124<br>96.8 (11.1)<br>-17.0 (1.8)<br>–<br>-- | N=121<br>96.5 (11.6)<br>-19.2 (1.7)<br>-2.1(2.5)<br>0.591 | N=118<br>96.0 (10.8)<br>-23.4 (1.8)<br>-6.4(2.5)<br>0.034 | N=123<br>96.0(9.7)<br>-20.5(1.8)<br>-3.5(2.5)<br>0.391 | –<br>–<br>–<br>–<br>-- | –<br>–<br>–<br>–<br>-- |
| Study D1050231<br>Baseline Mean (SD)<br>LS Mean Change (SE) Treatment | N=114<br>95.8 (10.8)<br>-16.0 (2.1)<br>– | N=118<br>96.6(10.7)<br>-25.7(2.0)<br>-9.7(2.9) | –<br>–<br>–<br>– | N=118<br>97.9(11.3)<br>-23.6(2.1)<br>-7.5(3.0) | –<br>–<br>–<br>– | N=121<br>96.3(12.2)<br>-28.7(1.9)<br>-12.6(2.8) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Difference vs. placebo<br>Estimate (SE)<br>p-value | -- | 0.002 | -- | 0.022 | -- | <0.001 |
| Study D1050233<br>Baseline Mean (SD)<br>LS Mean Change (SE) Treatment<br>Difference vs.<br>placebo<br>Estimate (SE)<br>p-value | N=120<br>96.6(10.2)<br>-10.3(1.8)<br>–<br><br>--<br> | –<br>–<br>–<br>–<br><br>-- | N=125<br>97.7(9.7)<br>-22.2(1.8)<br>-11.9(2.6)<br><0.001 | –<br>–<br>–<br>–<br>– | N=121<br>97.9(11.8)<br>-26.5(1.8)<br>-16.2(2.5)<br><0.001 | N=116<br>97.7(10.2)<br>-27.8(1.8)<br>-17.5(2.6)<br><br><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 hydrochloride vs. placebo were adjusted for multiple comparisons. P-values for olanzapine and quetiapine XR vs. placebo were unadjusted.

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

Long-term maintenance efficacy of lurasidone hydrochloride 40 to 160 mg once daily was demonstrated in a 12 month non-inferiority trial with quetiapine extended release (XR) (200 to 800 mg once daily). lurasidone hydrochloride was non-inferior to quetiapine XR in time to relapse of schizophrenia. lurasidone hydrochloride 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 hydrochloride 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 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 hydrochloride 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 hydrochloride 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 hydrochloride , patients were then randomised in a double-blind manner to either continue on lurasidone hydrochloride 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 hydrochloride 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 hydrochloride and 51.2% for placebo. The probability of all-cause discontinuation at Week 28 were 58.2% for lurasidone hydrochloride 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 hydrochloride 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 hydrochloride reaches peak serum concentrations in approximately 1-3 hours.

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

Distribution

Following administration of 40 mg of lurasidone hydrochloride hydrochloride, the mean approximate apparent volume of distribution was 6000 L. lurasidone hydrochloride is highly bound (~99%) to serum proteins.

Biotransformation

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

lurasidone hydrochloride is metabolised into two active metabolites (ID-14283 and ID-14326) and two non-active metabolites (ID- 20219 and ID-20220). lurasidone hydrochloride 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 hydrochloride and its active metabolite ID-14283 both contribute to the pharmacodynamic effect at the dopaminergic and serotonergic receptors.

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

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

lurasidone hydrochloride is an inhibitor of P-gp, BCRP and OCT1 *in vitro* (see section 4.5). lurasidone hydrochloride 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 hydrochloride , 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 hydrochloride is dose-proportional within a total daily dose range of 20 mg to 160 mg lurasidone hydrochloride. Steady-state concentrations of lurasidone hydrochloride are reached within 7 days of starting.

Pharmacokinetics in special patient groups:

*Elderly people*

Limited data have been collected in healthy subjects ≥ 65years. 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 hydrochloride 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 hydrochloride 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 hydrochloride in a population pharmacokinetic analysis in patients with schizophrenia.

*Race*

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

*Smoking*

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

*Paediatric population*

The pharmacokinetics of lurasidone hydrochloride in paediatric patients was investigated in 49 children aged 6-12 years and 56 adolescents aged 13-17 years. lurasidone hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride was not teratogenic in rats or rabbits at an exposure similar to or below the maximum recommended human dose (160 mg lurasidone hydrochloride).

lurasidone hydrochloride was excreted in milk of rats during lactation.

lurasidone hydrochloride 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

Lactose monohydrate, Mannitol 60, Pregelatinized Starch,
Croscarmellose sodium, Povidone K30, Citric acid anhydrous powder,
Magnesium stearate.

Tablet coating

HPMC 2910/ Hypromellose,Titanium Dioxide, Macrogol / PEG, Carnauba wax.

**6.2 Incompatibilities :** Not applicable.

**6.3 Shelf life:** 3 years

**6.4 Special precautions for storage:** Do not store above $30^0$C.

## 6.5 Nature and contents of container

Alu-Alu Blister pack of 10's

Presented packs as 1x10's/ 3x10's /10x10's Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

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

## 7. Marketing authorisation holder

MSN LABORATORIES PRIVATE LIMITED,

MSN House, Plot No. : C-24,
Anrich Industrial Estate,
Sanath Nagar, Hyderabad - 500 018
Telangana, India.

## 8. Marketing Authorization Number

H2020/CTD7469/1404ER/R1

## 9. Date of first authorization/renewal of the authorization

2025 September 15

## 10. Date of revision of the text

2025 September 15