# EU RISK MANAGEMENT PLAN

# LATUDA (lurasidone hydrochloride)

Activity code: 151(Z)PV21372A

| | |
|---|---|
| **RMP Version number** | 9.1 |
| **Date lock point for this RMP** | 05NOV2021 |
| **Date of final sign off** | 08MAR2022 |
| **Rationale for submitting an updated RMP** | Implementation of the PASS outcome and consequent removal of important risks in accordance with GVP guideline Module V – Risk management systems (Rev 2) dated March 28th, 2017<br>Discontinuation of targeted questionnaire for angioedema<br>Implementation of changes recommended in the PRAC Preliminary Assessment Report (EMA/122166/2022) |
| **Summary of significant changes in this RMP** | Removal from the list of safety concerns of important identified risks and important potential risks<br>Discontinuation of targeted questionnaire for angioedema<br>Removal from the list of safety concerns of one missing information.<br>Inclusion of approval date of RMP versions in the *Summary of changes to the risk management plan over time*. |
| **Other RMP version under evaluation** | Not applicable |
| **Details of the currently approved RMP** | Version number 8.1 approved on 25AUG2020 |

**QPPV name:** Paolo DIONISIO

**QPPV signature:**

[redacted]

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# PART I: PRODUCT OVERVIEW

Table Part I.1 – Product Overview

| | |
|---|---|
| **Active substance(s) (INN or common name)** | Lurasidone hydrochloride |
| **Pharmacotherapeutic group(s) (ATC code)** | Psycholeptics, antipsychotics (ATC code: N05AE05) |
| **Marketing Authorisation Holder** | Aziende Chimiche Riunite Angelini Francesco S.p.A. (Angelini S.p.A.) |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name(s) in the European Economic Area (EEA)** | Latuda |
| **Marketing authorisation procedure** | Centralized (EMEA/H/C/2713) |
| **Brief description of the product** | Chemical class<br>Lurasidone hydrochloride (lurasidone) is a novel small molecule atypical antipsychotic. |
| | Summary of mode of action<br>Lurasidone has a unique receptor-binding profile including high affinity for dopamine D(2), serotonin, 5-hydroxytryptamine (5-HT)(2A), 5-HT(7), 5-HT(1A), and noradrenalin alpha(2c) receptors. |
| | Important information about its composition<br>The active substance is: [(3aR,4S,7R,7aS)-2-{(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2H-isoindole-1,3-dione hydrochloride]. |
| **Hyperlink to the Product Information** | Section 1.3.5 of the eCTD |
| **Indication(s) in the EEA** | Current<br>Treatment of schizophrenia in adults and adolescent aged 13 years and over. |
| | Proposed |

| | |
|---|---|
| **Dosage in the EEA** | Current<br>*Adult population*<br>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 judgment and observed clinical response. The maximum daily dose should not exceed 148 mg.<br>*Paediatric population*<br>The recommended starting dose is 37 mg of lurasidone once daily. No initial dose titration is required. It is effective in a dose range of 37 to 74 mg once daily. Dose increase should be based on physician judgement and observed clinical response. The maximum daily dose should not exceed 74 mg. |
| | Proposed<br>Not applicable |
| **Pharmaceutical form(s) and strengths** | Current<br>• Film-coated tablets containing 20 mg lurasidone hydrochloride (equivalent to 18.6 mg lurasidone)<br>• Film-coated tablets containing 40 mg lurasidone hydrochloride (equivalent to 37.2 mg lurasidone)<br>• Film-coated tablets containing 80 mg lurasidone hydrochloride (equivalent to 74.5 mg lurasidone) |
| | Proposed<br>Not applicable |
| **Is the product subject to additional monitoring in the EU?** | No |

# PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

## INDICATION

The indication for Latuda is the treatment of schizophrenia in adults and adolescent aged 13 years and over. The indication in schizophrenic patients aged 18 years and over has been already approved in the EU.

## INCIDENCE

Incidence data from the World Health Organization [WHO 2011] for Europe sub Region A (United Kingdom, Ireland, Croatia, Spain, Holland, Germany, Denmark, Sweden, Norway, Iceland, Czech Republic, and Finland) in 2000 show the male and female data to be 15 per $10^5$ and 13.8 per $10^5$ respectively. Data from McGrath et al. [McGrath 2008], covering the world population with median and mid-range 80 percentiles yields 15.2 (7.2-43.0), indicating the earlier European data coincides with the median estimate.

While the onset of schizophrenia typically occurs in young adulthood (ages 18 to 25), adolescent onset is not uncommon, with an incidence ranging from 0.1% to 1% in individuals aged 13 to 18 years. The initial presentation of schizophrenia in adolescence differs somewhat from adult onset, including a typically more insidious onset, more severe premorbid neuro-developmental abnormalities, and the presence of more frequent visual hallucinations [Bailly 2004, Russell 1994, Werry 1992].

## PREVALENCE

The prevalence of schizophrenia has consistently been reported to be approximately 1% [Schultz 1999]; however, there is much variability between estimates reported in different settings. A review of systematic reviews of schizophrenia prevalence reported a median point prevalence of 4.6 per 1,000 ($10^{th}$-$90^{th}$ percentiles 1.9-10.0), median lifetime prevalence of 4.0 per 1,000 ($10^{th}$-$90^{th}$ percentiles 1.6-12.1), and incidence of 15.2 per 100,000 [WHO 2011].

Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 0.5 to 1% (APA, 2000). Within the paediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents [APA, 1997]. Schizophrenia has also been described in children, but it is thought to be uncommon (0.1 to 1% of schizophrenic psychoses will present prior to age 10) [American Academy of Child and Adolescent Psychiatry 2001, Remschmidt 1996].

## DEMOGRAPHICS OF THE POPULATION IN THE AUTHORISED INDICATION

Age

In a review of the epidemiology of schizophrenia carried out in the late nineties [Schultz 1999] the mean age for first contact or first hospital admission is in the range 25 to 35 years. One study within the review, illustrating the progression of the condition quoted mean ages of 24.0, 25.5, 29.0, 30.1, and 30.3 for first sign, first negative symptom, first positive symptom, first peak positive symptom, and first hospital admission, respectively.

Gender

The lifetime risk for schizophrenia until age 60 appeared to be the same for men and women in the same review [Schultz 1999]. On average women fall ill 3 to 4 years later than men and show a second peak of onset around menopause. Late onset schizophrenia is more frequent and more severe in women than men. Type of onset, and core symptoms do not differ between the sexes. The most pronounced sex difference is the socially negative illness behavior of young men [Schultz 1999] .

There are no clear sex differences in family history, obstetric complications, minor physical anomalies, and neurological soft signs [Leung 2000]. The majority of schizophrenia patients do not marry and most have limited social contacts [NIH 2009]. Schizophrenia patients are disproportionately represented in the prison and homeless populations [NIH 2009].

Risk factors

Schizophrenia is currently recognized as being a neurodevelopmental disorder (typified by abnormal brain development, as described in the section on “Morbidity” above); however, numerous other factors, some of which are environmental in nature, have been associated with the condition. These may not all strictly speaking be risk factors for the disease but may be markers or merely have an association with the condition. The following factors have been found to be associated with schizophrenia [Boydell 2001]:

- A family history of schizophrenia is a strong and well-established risk factor for development of the disease.
- Abnormal neurological development, including brain anomalies as early as the in utero phase. Patients with schizophrenia typically have a larger lateral ventricular volume and reduced cerebral volume, frontal lobes, amygdala/hippocampus and thalamus [Wright 2000].
- Developmental deficits in childhood and adolescence including motor, speech and language, cognitive, attention and social deficits [Boydell 2001, Lewis 2000].
- Low IQ [Boydell 2001, David 1997].
- Urbanization, particularly being born and raised in an urban setting [Boydell 2001].
- Season of birth. Being born in late winter and early spring is associated with an enhanced risk of schizophrenia. The mechanism behind this is unclear, but some have proposed it could potentially be

due to exposure to influenza or other infections in utero [Boydell 2001].

- Pregnancy and obstetric complications have been associated with an enhance risk of schizophrenia, including: bleeding in pregnancy, preeclampsia, and hypoxia during birth.
- Migrant status. Second generation African-Caribbean migrant groups are at enhanced risk of developing schizophrenia. It is second-generation migrant status and not ethnicity per se that is the key factor behind this, since non-migrant African-Caribbean individuals in the relevant countries of origin are not at an enhanced risk of schizophrenia nor are first generation African-Caribbean individuals. The precise mechanisms are not entirely clear; however, greater discrimination and social isolation may be contributing factors.
- Social isolation.
- Cannabis use has been associated with schizophrenia, but it is not clear whether this is a trigger, a causal factor, an outcome of schizophrenia or a spurious factor.

It must be noted that the above constellation of factors has low power for predicting schizophrenia onset, not least because they are not specific to the condition.

**MAIN EXISTING TREATMENT OPTIONS**

The current standard of care in European medical practice consists of pharmacological and nonpharmacological supportive treatment such as standardized psychotherapy, psychoeducation, social support, and counseling (National Institute for Health & Clinical Excellence guidelines; European Medicines Agency guidelines) [NIH 2010, EMA/CHMP/40072/2010 Rev.1].

In adults, treatment options include pharmacological (antipsychotic medications) and nonpharmacological (supportive treatment) [Brenner 2000]. Antipsychotics are the mainstay of pharmacological intervention in the treatment of schizophrenia. As there is large interindividual variability in response to these drugs, several different antipsychotic medications are often tried before the most appropriate one is found.

The different treatment options include typical (first generation) and atypical (second generation) antipsychotics:

1) Typical antipsychotics (primarily dopamine D2 receptor antagonists) include chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, and trifluoperazine. These medications can cause certain side effects (known as extrapyramidal symptoms [EPS]), including rigidity (muscle stiffness), unusual body or facial movements, persistent muscle spasms, tremors, restlessness, or a feeling of internal jitteriness. Some typical antipsychotics (eg, chlorpromazine) are associated with sedative effects (induced via histamine blockade), while other typical drugs (such as haloperidol with higher potency at D2 receptors and lower potency at H1 receptors) are associated with less sedative side effects.
2) Atypical antipsychotics are newer and are both effective and less likely to cause EPS (associated with typical antipsychotics) or agranulocytosis (associated with clozapine). These medications include olanzapine, quetiapine, risperidone, aripiprazole, and paliperidone. While these medications may be

less likely to cause EPS, they are associated with weight gain, which increases the risk of diabetes and metabolic abnormalities including increased cholesterol, triglyceride and glucose levels.

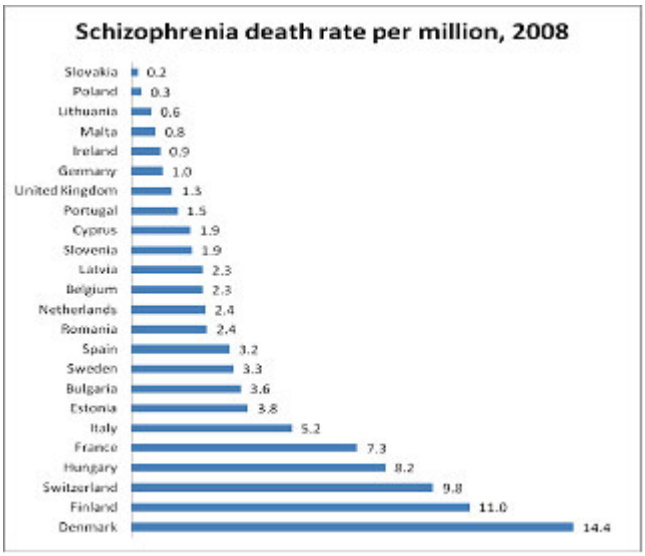
The current management of schizophrenia includes first-line atypical antipsychotics, which may be associated with a high potential of failure due to lack of efficacy, side effects, and as a result noncompliance [Miller 2008]. After failure of first line treatment, patients are switched to another antipsychotic and efforts are made to optimize the treatment by ensuring compliance with treatment and providing additional supportive treatment. When failure with at least 2 different antipsychotic medications given at adequate doses and prescribed for adequate duration occurs (treatment resistance), patients are switched to clozapine and/or combination of therapies, which will depend on the medical history, severity of illness, and past therapeutic treatment of the patient. To date, clozapine is the only evidence-based treatment for treatment-resistant schizophrenia subjects, and the role of antipsychotic polypharmacy and other augmentation strategies remains unclear.

To date, approved second-generation antipsychotic agents in children and adolescents are limited. In the US, lurasidone, aripiprazole, risperidone, quetiapine, olanzapine, and paliperidone have been approved for use in adolescents with schizophrenia (13 to 17 years of age). In the European Union, aripiprazole is approved for the treatment of schizophrenia in adolescents aged ≥ 15 years.

## NATURAL HISTORY OF THE INDICATED CONDITION

Mortality

The graphic [WHO 2011] shows data for mortality from schizophrenia, where schizophrenia is recorded as the underlying cause of death in the general population.




This demonstrates the extreme variation within Europe from a rate of 0.2 per million in Slovakia to 14.4 per million in Denmark. These data underestimate the number of deaths within the subpopulation of patients with schizophrenia. However, Tiihonen et al. in a population-based cohort study in Finland for schizophrenia patients with a mean age of 51 at follow up, showed all causes death rates of 31.3 per 1,000 and 37.1 per 1000 for males and females respectively [Tiihonen 2009].

In relation to cause of death, in a UK cohort, compared with the General population, a study showed standardized mortality ratios (SMRs) of 298, 232, and 1,273 for all cause, natural causes, and unnatural causes, respectively [Brown 2000].

Data from Saha et al. showed the all cause median SMR from 37 studies (22 of which were European) to be 258, with median SMR values of 429, 422, and 1286 for infectious diseases, nervous diseases, and suicides, respectively [Saha 2007].

Morbidity

Schizophrenia is a severe mental illness characterized by psychotic symptoms affecting the patient's thoughts, feelings and behavior. It is primarily characterized by 2 classes of symptoms; "positive" and "negative." "Positive" symptoms suffered during an acute episode include hallucinations (e.g., hearing voices or seeing things that are not really there), delusions (inaccurate beliefs or paranoia), and disturbed behavior. "Negative" symptoms include poor concentration, impaired communication, social withdrawal, and a loss of interest in daily activities. The course of the condition and relative experience of positive and negative symptoms varies widely across individual sufferers.

Schizophrenia most commonly manifests in adulthood, however longitudinal studies using birth cohorts

have helped identify typical early premorbid phases of the illness [Lewis 2000]. These studies have shown that development of schizophrenia is often preceded by developmental delay in childhood and adolescence including motor, speech and language, cognitive, attention, and social deficits [Boydell 2001, Lewis 2000]. Neurodevelopmental anomalies are also evident among patients with schizophrenia, including larger lateral ventricular volume and reduced cerebral volume compared with nonschizophrenia [Wright 2000]. This early premorbid phase is typically followed by a prodromal phase (a precursor to the fully developed condition), which can be characterized by behaviors that hint at positive-type symptoms such as illusions, magical thoughts and heightened superstitiousness, symptoms of negative mood such as anxiety and irritability, and cognitive and social deficits [Lewis 2000].

With appropriate treatment positive symptoms in particular, schizophrenia can be successfully managed and may lead to remission of psychotic symptoms. Hence, provided treatment is maintained a relatively stable or “residual” phase can be observed during in the latter stages of the illness in middle age and senescence [Lewis 2000].

**IMPORTANT CO-MORBIDITIES**

Expected co-morbidities

Leucht et al. [Leucht 2009] reviewed the literature and highlighted that people with schizophrenia were different to the general population in relation to the prevalence of comorbid conditions. They have higher prevalence for HIV infection, hepatitis, osteoporosis, altered pain sensitivity, sexual dysfunction, obstetric complications, cardiovascular diseases, overweight, diabetes, dental problems, and polydipsia.

It is difficult to provide a unified summary of incidence and prevalence across the literature because of a mix of patient populations, study designs and time varying influences of such factors as smoking, inactivity, poor diet and substance abuse.

For example, data from Dickey et al. [Dickey 2000], extracted from a paid claims database, examining claims in a 12-month follow-up period, show the heavy influence of substance abuse on the level of comorbidity.

| Comorbidity % | With Substance Abuse | Without Substance Abuse |
|---|---|---|
| Diabetes | 3.82 | 4.58 |
| Hypertension | 7.13 | 8.10 |
| Heart disease | 8.99 | 6.44 |
| Asthma | 5.27 | 3.13 |
| GI diseases | 10.85 | 6.95 |
| Infections of skin | 10.54 | 6.07 |
| Cancer | 2.17 | 1.64 |
| Acute respiratory disease | 28.00 | 19.74 |

| Comorbidity % | With Substance Abuse | Without Substance Abuse |
|---|---|---|
| Ill-defined conditions | 51.34 | 32.56 |
| Injury and poisoning | 37.29 | 16.06 |

More recently the concurrent psychiatric comorbidities that schizophrenics suffer from have been examined. Buckley et al. [Buckley 2009] produced crude weighted average estimates of prevalence across studies, which are listed in the table below:

| Psychiatric Comorbidity | Weighted Average Estimate |
|---|---|
| Panic attacks | 25% |
| Panic disorders | 15% |
| Post-traumatic stress disorder | 29% |
| Obsessive compulsive disorder | 23% |

In a small study by McGurk et al. [McGurk 2009], an interesting insight into the multiplicity of comorbidities is provided by their summary data, which shows that 20.6%, 23.5%, 17.6%, and 11.7% suffer from 1, 2, 3, 3+ concurrent comorbidities, respectively.

The life expectancy of schizophrenia patients in 2005 was in the region of 15 years shorter than the general population [Hennekens 2005]. Although there is an acceptance that the absolute risk of suicide is greater (10% vs 1% in the general population), the main cause of premature death was coronary heart disease (50%-75% vs 33% in the general population). Risk factors, in particular, smoking, obesity, insulin resistance, diabetes, and hypertension, being responsible for this excess.

Expected co-medications

Antipsychotics are the main pharmacological treatment for schizophrenia, but other concomitant medications are frequently used with antipsychotics to improve schizophrenia symptoms or minimize side effects.

A variety of different concomitant medications are prescribed in schizophrenia, including: anticholinergics to treat extrapyramidal syndrome and other side effects of antipsychotics; anxiolytics including benzodiazepines to treat antipsychotic-induced akathisia as well as reducing anxiety, insomnia, agitation, global impairment and psychotic symptoms; antidepressants to improve the negative flattening aspect of schizophrenia; and antiepileptics to reduce anxiety and hostility.

In an observational study of the use of concomitant medication with antipsychotic treatment in European outpatients with schizophrenia (Schizophrenia Outpatient Health Outcome [SOHO]) [Novick 2005] the proportion of patients using concomitant medications at baseline ranged from 53.2% to 66.3% across all the cohorts. The most frequently administered groups of medications were as follows:

[redacted]

- Anxiolytics/hypnotics 28.5% to 46.7% patients.
- Anticholinergics 18.4% to 29.4% patients.
- Antidepressants 9.5% to 25.1% patients.
- Mood stabilizers 4.9% to 14.5% patients.

In the clinical trials with lurasidone, the most common concomitant medications at Baseline were anxiolytics, and hypnotics/sedatives, which is consistent with the findings of the SOHO trial.

Substantially greater prevalence in schizophrenia patients than in the general population has been reported for: cardiovascular disease and hypertension; insulin resistance, hyperglycaemia and diabetes mellitus; infections (including human immunodeficiency virus [HIV]); pulmonary disease including chronic obstructive pulmonary disease; obesity; dyslipidaemia; and smoking and substance abuse [23]. Other studies have also reported higher rates of hypothyroidism, dermatitis, eczema, epilepsy, viral hepatitis, and fluid/electrolyte disorders [Carney 200, Weber 2009].

Consequently, persons with schizophrenia may be prescribed medication in addition to their ongoing antipsychotic therapy to treat these comorbid conditions. These concomitant medications may include aspirin and other anticoagulants such as clopidogrel and ticlopidine, β-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, insulin and other antidiabetic agents, and lipid lowering therapies such as statins [Newcomer 2009, Mitchell 2012]. There are insufficient data in literature regarding the prescription of antiretroviral agents in persons with schizophrenia [Mitchell 2012].

# PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

## TOXICITY

The nonclinical toxicity studies achieved adequate exposure margins relative to the clinical dose and demonstrated a favourable safety profile.

In a fertility study, oestrus cycle irregularities were seen at 1.5 mg/kg and above and fertility was reduced only at 150 mg/kg/day in female rats but this effect on fertility was reversible after a 14-day drug-free period. Fertility was not affected in male rats treated orally with lurasidone for 64 consecutive days prior to mating and during the mating period at doses up to 150 mg/kg.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 1.5- and 6-fold, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 160 mg/day based on body surface area (BSA).

No adverse developmental effects were seen in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day (0.6-fold the MRHD based on BSA).

The toxicokinetics parameters ($C_{max}$, $t_{max}$, and $AUC_{24}$) of lurasidone and 2 metabolites (ID-20219 and ID-20220) were retrospectively determined in pregnant and lactating rats and pregnant rabbits in order to support completed reproductive and developmental toxicity studies of lurasidone. Dose-related increases in exposure to lurasidone, ID-20219, and ID-20220 were observed. The results of these studies indicate no new, major nonclinical findings that would affect the overall risk assessment for lurasidone.

Dose range-finding and definitive juvenile toxicity studies have been completed in rats. Data from these juvenile animal studies did not suggest an increase in sensitivity to lurasidone in the juvenile rats compared to the adult rats. The dosing period of PND 21 to 91 in the definitive juvenile rat toxicity study corresponds to the age range of 2 to 16 years in the paediatric population.

## SAFETY PHARMACOLOGY

Cardiovascular system

Lurasidone inhibited the human ether-à-go-go–related gene current with a 50% inhibitory concentration (IC50) at approximately 121-fold multiples of the maximum steady-state plasma free-drug concentration at the MRHD of 160 mg/day, and there were no effects on action potential duration in guinea pig papillary muscle or on inotropic/chronotropic action in guinea pig atrium. In conscious telemetered dogs, lurasidone (a single oral dose of 100 mg/kg) increased heart rate but did not affect blood pressure, corrected QT (QTc), and QRS intervals. After a single oral dose of 300 mg/kg, QTc interval became prolonged but QT and QRS intervals were not affected. In a 39-week toxicology study in dogs, lurasidone (repeated oral dose of 100 and 200 mg/kg) produced QT prolongation. Prolongation of the QT or QTc interval in dogs occurred at maximum observed serum concentration ($C_{max}$) of lurasidone at 4769 to 9913 ng/mL, which is at least

approximately 20-fold higher than the average $C_{max}$ associated with the maximum recommended human dose of 160 mg.

There was no evidence of adverse effects associated with QTc prolongation in the short and long-term phase 2/3 clinical program or from post-marketing experience in the United States. A thorough QTc study (D1050249) showed that lurasidone is devoid of any clinically relevant effect on QTc interval.

Nervous system

Lurasidone slowed spontaneous electroencephalogram (EEG) (but not the arousal response EEG) in rabbits when intravenously administered at 1 mg/kg and inhibited emetic response in apomorphine-treated dogs following oral administration, but exerted no other potent effects on the central nervous system (anti-acetylcholine action, anti-hypoxic action, effects on cerebral blood flow, convulsion facilitating action or antiadrenergic action).

Prolactin levels

Similar to other antipsychotic drugs that bind to the dopamine D2 receptor, lurasidone has been shown to elevate serum prolactin levels in mice, rats, dogs, and monkeys. Elevated serum prolactin levels in long-term repeated-dose studies in female rats were associated with effects on bones, adrenal glands and reproductive tissues. Mammary gland and/or pituitary gland tumors were observed in mouse and rat carcinogenicity studies. These findings are common in rodents treated with antipsychotic drugs possessing dopamine D2 blocking activity. Tumor development is most likely related to increased blood prolactin.

Effects on eye

Lurasidone has also been shown to bind to melanin. Consequently, effects on the eye were assessed. In a nonclinical study using [$^{14}$C] lurasidone, there was a 20-fold higher level of radioactivity detected in the eyes of pigmented rats than that of albino rats, and relatively high concentration of radioactivity was detected in monkey retina indicating that lurasidone has a tendency for a specific distribution and retention in melanin-containing tissues.

Ophthalmologic examinations were performed in the 1-year study in cynomolgus monkeys and 9-month study in dogs, which showed no abnormalities attributable to lurasidone administration.

Effects on the eye were assessed in clinical studies D1050237 and D1050237E. Of the shifts from normal to abnormal in ophthalmologic parameters that were reported, the shifts were assessed to be clinically significant in only 2 of 248 lurasidone-treated subjects (0.8%): Subject [redacted] had a post-Baseline clinically significant intraocular pressure (both left and right eyes) at Month 12 due to glaucoma (present at Screening) and Subject [redacted] had a post-Baseline clinically significant corneal dystrophy (both left and right eyes) at Month 12/Early Discontinuation visit (6 weeks after Screening). The subject had Baseline clinically significant abnormal optic nerve (head), cup to disc ratio (0.7) and lens (nuclear sclerosis).

[redacted]

There were no other clinically meaningful shifts in ophthalmologic assessments from Baseline to last observation carried forward (LOCF) endpoint with lurasidone.

Lactation

Lurasidone was excreted in the milk of rats during lactation. It is not known whether lurasidone or its metabolites are excreted in human milk.

Breastfeeding in women receiving lurasidone should only be considered if the potential benefit justifies the potential risk to the child.

# PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Lurasidone is a novel atypical antipsychotic synthesized by Sumitomo Dainippon Pharma Co., Ltd., (Sumitomo).
LATUDA was first approved on 28OCT2010 in the US for the treatment of schizophrenia, and then in Australia, Canada, EU, Russian Federation, Singapore, Switzerland, Taiwan and Thailand. In the US and Canada, it is also approved for the treatment of bipolar depression.
Sunovion Pharmaceuticals Europe Ltd (SPE) acquired the European rights in February 2016 from Takeda Pharma A/S. Previously, Takeda had held the European rights from March 2011 and had been responsible for developing lurasidone for the treatment of schizophrenia in Europe. Prior to that global development had been initiated by Sumitomo and subsequently undertaken by Merck, Sharp & Dohme before rights were returned to Sumitomo.
On 14MAR2018, the MA holderships of LATUDA in EU have been transferred to Angelini S.p.A..

## CLINICAL TRIAL EXPOSURE

Overall

As of 27OCT2017, 10,682 adult subjects and 927 paediatric subjects have participated in the lurasidone clinical development program in various types of clinical studies to date, and approximately 8,360 adults and 870 paediatric subjects have been exposed to lurasidone. Approximately, 80 clinical studies have been initiated or completed with lurasidone. Studies were conducted in the US, Canada, EU, Asia, Australia, Central and South America.

The estimated cumulative subject exposure in clinical trials is provided in the following Table (data extracted from the Periodic Benefit-Risk Evaluation Report of 08DEC2017, by SPE).

| **Treatment †** | **Total number of cumulative subjects including ongoing studies *** | |
|---|---|---|
| | **Adults** | **Pediatrics** |
| **Lurasidone** | 8,360 | 870 |
| **Comparator** | 1,033 | 0 |
| **Placebo** | 1,289 | 57 |
| **Total** | 10,682 | 927 |

* If a subject was exposed to both lurasidone and placebo, then this subject will only be counted in the lurasidone category. If a subject was exposed to both comparator and placebo, then this subject will only be counted in the comparator category. If a subject was only exposed to placebo, then this subject will only be counted in the placebo category.

[redacted]

† In case of double blind studies, the numbers of subjects were assigned to respective treatment groups based on the ratio of planned number of subjects for respective groups.

The lurasidone clinical development program satisfied International Conference on Harmonization requirements for minimum number of subjects exposed for 6 months duration (1,238 and 971 unique individuals had at least 24 weeks exposure in the schizophrenia and bipolar populations, respectively) and for 12 months duration (591 and 268 unique individuals had at least 52 weeks exposure in the schizophrenia population and bipolar populations, respectively).

Schizophrenia - Adults

The Integrated Clinical Database (IDB) for adults with schizophrenia includes 54 completed studies (30 clinical pharmacology studies and 24 Phase 2 or 3 clinical safety and efficacy studies) in the schizophrenia clinical development program. As of the last integration, which had a data cut point of 27 October 2015, the IDB for adults with schizophrenia comprises 5,151 subjects exposed to lurasidone (671 subjects in Phase 1 studies and 4480 subjects in Phase 2/3 studies, of which 2,111 subjects were enrolled in short-term, double-blind, placebo-controlled studies, and 2370 subjects were enrolled in other studies). The Phase 2 and 3 clinical studies in adult subjects with schizophrenia were 3 weeks through 28 months in duration and evaluated doses of lurasidone from 20 to 160 mg/day.

Safety data from the 24 controlled and uncontrolled clinical studies were pooled for safety analyses to generate the primary study groupings. These study groupings are:

**P23STC:** Phase 2/3 short-term, double-blind, placebo-controlled studies, which are the pooled data from the nine short-term, 6-week, double-blind, placebo-controlled studies (Study numbers D1001002, D1001056, D1050006, D1050049, D1050196, D1050229, D1050231, D1050233, 1050303).

**P23ALL:** **All 24*** Phase 2/3 controlled and uncontrolled studies comprise the study grouping P23ALL (Study numbers D1001001, D1001002, D1001016, D1001017, D1001036, D1001048, D1001056, D1050006, D1050049, D1050174, D1050196, D1050199, D1050229, D1050229E, D1050231, D1050231E, D1050233, D1050234, D1050237, D1050237E, D1050238, D1050254, D1050289, D1050290, D1050298 (Schizophrenia subjects), D1050303, and D1050307).

An overview of the number of subjects and groupings is presented in the following Table. This listing contains 27 study codes as three studies (D1050229, D1050231 and D1050237) were comprised of a study and an extension phase (D1050229E, D1050231E and D1050237E).

[redacted]

| | Placebo | Lurasidone | Other |
|---|---|---|---|
| **Clinical Pharmacology Studies (Phase 1)** | | | |
| Total Number of Subjects Exposed to Lurasidone in Phase 1 Studies | NA | 671 | NA |
| **Clinical Studies for Schizophrenia (Phase 2/3)** | | | |
| Short-Term Double-blind Placebo-Controlled (P23STC) | 971 | 2,111 | 378 |
| Total Number of Subjects Exposed to Lurasidone in Phase 2/3 Studies (P23ALL) | NA | 4,480 | NA |
| Total Number of Subjects Exposed to Lurasidone | NA | 5,151 | NA |

NA = not applicable.

The Safety Population for the P23STC studies comprised 3,460 subjects. This total included 2,111 subjects who received lurasidone (doses of 20, 40, 80, 120, and 160 mg once daily), 971 subjects who received placebo, 72 who received haloperidol, 122 who received olanzapine, 119 who received quetiapine XR, and 65 who received risperidone.
The median age of the subjects who received lurasidone was 40.0 years; 87% of subjects were aged < 55 years, and 3% were 65 years of age or older. Of the 2,111 lurasidone-treated subjects, 1,412 (67%) were male, 789 (37%) were White, and 517 (25%) were Black or African American. With respect to geographic region, 913 (43%) of the 2111 lurasidone-treated subjects were from North America, 722 (34%) were from Asia, and 427 (20%) were from Europe.

The demographic profile of the P23ALL grouping was similar to the P23STC grouping. A total of 4,480 subjects were treated with lurasidone during P23ALL. Subject age ranged from 18 to 74 years, with a mean age of 41.2 years. Of the 4,480 subjects, 66% of subjects were male, 29% were Asian, 33% were White, and 33% were Black or African American. Fifty-two percent of subjects were from the North American geographical region.

The phase 2/3 clinical development population for adults with schizophrenia is summarized by numbers of subjects and person-years exposure to lurasidone and stratified by subject age, gender, race and ethnicity, and lurasidone dose. The P23STC grouping is presented first in the following Table, the P23ALL grouping is presented in the subsequent Table.

| ***P23STC study grouping (adults with schizophrenia)*** | | |
|---|---|---|
| **Duration of Exposure (Days)** | **n** | 2,111 |
| | **Mean (SD)** | 32.6 (13.88) |

[redacted]

| | | |
|---|---|---|
| | **Median** | 41.0 |
| | **Min, Max** | 1, 48 |
| | **Q1, Q3** | 21.0, 42.0 |

| **Exposure by Dose Group** | **Persons** | **Person time (years)** |
|---|---|---|
| 20 mg | 172 | 15.11 |
| 40 mg | 637 | 56.68 |
| 80 mg | 847 | 76.04 |
| 120 mg | 291 | 24.19 |
| 160 mg | 164 | 16.64 |

| **Exposure by Age Groups and Gender** | **Persons** | | **Person time (years)** | |
|---|---|---|---|---|
| | **Male** | **Female** | **Male** | **Female** |
| < 55 years | 1,268 | 575 | 111.67 | 52.02 |
| ≥ 55 years | 144 | 124 | 13.27 | 11.70 |
| < 65 years | 1,386 | 670 | 122.31 | 60.88 |
| ≥ 65 years | 26 | 29 | 2.63 | 2.84 |

| **Race** | **Persons** | **Person time (years)** |
|---|---|---|
| White | 789 | 70.75 |
| Black or African American | 517 | 42.71 |
| Asian | 735 | 68.88 |
| American Indian or Alaska Native | 2 | 0.18 |
| Native Hawaiian or Other Pacific Islander | 2 | 0.17 |
| Other | 66 | 5.97 |
| **Ethnicity*** | | |
| Hispanic or Latino | 101 | 8.97 |
| Not Hispanic or Latino | 1,050 | 98.89 |

| **Total Clinical Trial Exposure** | **Persons** | **Person Years** |
|---|---|---|
| Total exposure | 2,111 | 188.66 |

SD = standard deviation; Q1 = first quartile (25th percentile); Q3 = third quartile (75th percentile).
Note: In Study D1050303, subjects who were early lurasidone 80 mg non-responders and randomized to lurasidone 160 mg at Week 2 were included in the lurasidone 160 mg.
*Studies D1001002, D1050006, D1050049, D1050196 and D1001056 did not collect ethnicity.

| ***P23ALL study grouping (adults with schizophrenia)*** | | |
|---|---|---|
| **Duration of Exposure (Days)** | **n** | 4,480 |

[redacted]

| | | |
|---|---|---|
| | **Mean (SD)** | 123.2 (154.74) |
| | **Median** | 42.0 |
| | **Min, Max** | 1, 729 |
| | **Q1, Q3** | 24.0, 186.0 |
| **Duration of Exposure** | **Persons** | **Person time (years)** |
| ≥ 1 days | 4,480 | NA |
| ≥ 7 days | 4,190 | NA |
| ≥ 21 days | 3,552 | NA |
| ≥ 42 days | 2,799 | NA |
| ≥ 63 days | 1,833 | NA |
| ≥ 84 days | 1,659 | NA |
| ≥ 112 days | 1,470 | NA |
| ≥ 168 days | 1,238 | NA |
| ≥ 182 days | 1,161 | NA |
| ≥ 224 days | 856 | NA |
| ≥ 280 days | 649 | NA |
| ≥ 336 days | 579 | NA |
| ≥ 350 days | 562 | NA |
| ≥ 364 days | 519 | NA |
| **Dose Summary** | **N=4,480** | **1511.44** |
| > 0 to < 40 mg | 260 | 37.96 |
| 40 to < 60 mg | 1,111 | 307.83 |
| 60 to < 80 mg | 73 | 36.55 |
| 80 to < 120 mg | 2,052 | 723.71 |
| 120 to < 160 mg | 831 | 341.30 |
| 160 mg | 139 | 59.48 |
| Flexible (80 or 120 mg) | 14 | NA |

| **Exposure by Age Groups and Gender** | **Persons** | | **Person time (years)** | |
|---|---|---|---|---|
| | **Male** | **Female** | **Male** | **Female** |
| **Overall** | 2,975 | 1,505 | NA | NA |
| < 55 -years | 3,868 | | NA | |
| ≥ 55 years | 613 | | NA | |

| | | |
|---|---|---|
| < 65 years | 4,415 | NA |
| ≥ 65 years | 66 | NA |
| **Exposure by Race** | **Persons** | **Person time (years)** |
| White | 1,537 | NA |
| Black or African American | 1,460 | NA |
| Asian | 1,300 | NA |
| American Indian or Alaska Native | 10 | NA |
| Native Hawaiian or Other Pacific Islander | 9 | NA |
| Other | 164 | NA |
| Ethnicity | | |
| Hispanic or Latino | 302 | NA |
| Not Hispanic or Latino | 2,518 | NA |
| Unknown | 1,660 | NA |
| **Total Clinical Trial Exposure** | **Persons** | **Person Years** |
| Total Exposure | 4,480 | 1,511.44 |

SD = standard deviation; Q1 = first quartile (25th percentile); Q3 = third quartile (75th percentile); NA = not available.

Clinical trial exposure in special populations (subjects with renal or hepatic impairment) is presented in the following Table.

| | **Persons** | **Person Years** |
|---|---|---|
| **Renal impairment** | **36** | **0.10** |
| Healthy matched controls | 9 | n/a |
| Mild (CrCl 50 to 80 mL/min, inclusive) | 9 | n/a |
| Moderate (CrCl ≥30 and <50 mL/min) | 9 | n/a |
| Severe (CrCl <30 mL/min) | 9 | n/a |
| **Hepatic impairment** | **21** | **0.06** |
| Healthy matched controls | 6 | n/a |
| Mild (Child-Pugh Class A) | 6 | n/a |
| Moderate (Child-Pugh Class B) | 6 | n/a |
| Severe (Child-Pugh Class C) | 3 | n/a |

CrCl=creatinine clearance, n/a=Not available.
Includes Studies D1050264 and D1050265

***Schizophrenia - Adolescents***

The safety of lurasidone in the treatment of adolescent subjects with schizophrenia (aged 13 to 17 years) was evaluated in one 6-week, placebo-controlled study of patients (D1050301; N = 326), while the long-term use of lurasidone in the paediatric population was evaluated in an open-label, 104-week, multicentre study (Study D1050302).

The clinical trial D1050302 was an extension study designed to evaluate the long-term safety, tolerability, and effectiveness of flexibly dosed lurasidone (20, 40, 60, or 80 mg/day) in paediatric subjects who completed a 6-week treatment period in one of three preceding studies of various indications: Study D1050301 (schizophrenia), Study D1050325 (irritability associated with autistic disorder), or Study D1050326 (bipolar depression). Subjects who met entry criteria were transitioned to this extension study directly after their last assessment in the preceding study.

As the current application is being submitted to support an indication for adolescent subjects with schizophrenia, only results for subjects with schizophrenia who enrolled from Study D1050301 are discussed.

Lurasidone was demonstrated to be generally safe and well-tolerated across the lurasidone daily dose range studied (20 to 80 mg) in adolescent subjects with schizophrenia, including exposures of 28 weeks or longer. Lurasidone has been shown to have no clinically relevant effects on vital signs or ECG assessments. In addition, no consistent adverse effects on measures of body weight or laboratory parameters including prolactin, lipids, and measures of glycemic control have been observed. Based on evidence derived from the lurasidone pediatric development program, lurasidone exhibits a favorable benefit versus risk profile in the treatment of adolescent patients with schizophrenia within the proposed dose range of 40 to 80 mg/day.
The safety profile of lurasidone in adolescent subjects with schizophrenia is consistent with that seen in the adult population.
The lurasidone pediatric development program for adolescents with schizophrenia is summarized by numbers of subjects and person-years exposure to lurasidone and stratified by subject age, gender, race and ethnicity, and lurasidone dose. The short-term study is presented in the following Table, and the long-term study is presented in subsequent Table.

| ***Short-term study (adolescent with schizophrenia)*** | | |
|---|---|---|
| **Duration of Exposure (Days)** | n | 214 |

[redacted]

| | | |
|---|---|---|
| | Mean (SD) | 39.8 (7.96) |
| | Median | 42.0 |
| | Min, Max | 2, 47 |
| **Duration of Exposure** | **Persons** | **Person time (years)** |
| ≥ 4 days | 213 | NA |
| ≥ 7 days | 210 | NA |
| ≥ 14 days | 207 | NA |
| ≥ 21 days | 203 | NA |
| ≥ 28 days | 197 | NA |
| ≥ 35 days | 195 | NA |
| ≥ 41 days | 179 | NA |
| Total Exposure | 214 | 23.3 |
| **Exposure by Dose Group** | | |
| 40 mg | 110 | NA |
| 80 mg | 104 | NA |

| **Exposure by Age Groups and Gender** | **Persons** | | **Person time (years)** | |
|---|---|---|---|---|
| | **M** | **F** | **M** | **F** |
| Overall | 137 | 77 | 15.11 | 8.19 |
| 13-15 years | 105 | | 11.30 | |
| 16-17 years | 109 | | 11.99 | |

| **Exposure by Race** | **Persons** | **Person time (years)** |
|---|---|---|
| American Indian or Alaska Native | 0 | 0 |
| Asian | 10 | 1.15 |
| Black or African American | 38 | 3.77 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 |
| White | 146 | 16.14 |
| Other | 20 | 2.23 |

NA = not available.

***Long-term study (adolescent with schizophrenia)***

[redacted]

| | | | | |
|---|---|---|---|---|
| **Duration of Exposure (Days)** | n | | 271 | |
| | Mean (SD) | | 526.8 (271.09) | |
| | Median | | 727.0 | |
| | Min, Max | | 3, 744 | |
| **Duration of Exposure** | **Persons** | | **Person time (years)** | |
| ≥ 14 days | 269 | | NA | |
| ≥ 28 days | 264 | | NA | |
| ≥ 56 days | 245 | | NA | |
| ≥ 84 days | 238 | | NA | |
| ≥ 112 days | 230 | | NA | |
| ≥ 140 days | 226 | | NA | |
| ≥ 168 days | 220 | | NA | |
| ≥ 196 days | 214 | | NA | |
| ≥ 252 days | 208 | | NA | |
| ≥ 308 days | 196 | | NA | |
| ≥ 364 days | 190 | | NA | |
| ≥ 547 days (18 months) | 170 | | NA | |
| ≥ 638 days (21 months) | 162 | | NA | |
| ≥ 720 days | 158 | | NA | |
| ≥ 728 days (24 months) | 124 | | NA | |
| **Total Exposure** | **271** | | **390.9** | |
| **Exposure by Age Groups and Gender** | **Persons** | | **Person time (years)** | |
| | **M** | **F** | **M** | **F** |
| Overall | 170 | 101 | NA | NA |
| 13-17 years | 257 | | NA | |
| 18-20 years | 14 | | NA | |
| **Exposure by Race** | **Persons** | | **Person time (years)** | |
| American Indian or Alaska Native | 0 | | NA | |
| Asian | 11 | | NA | |
| Black or African American | 38 | | NA | |
| Native Hawaiian or Other Pacific Islander | 0 | | NA | |

| | | |
|---|---|---|
| White | 197 | NA |
| Other | 25 | NA |

NA = not available.

# PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

## *SIV.1 Exclusion criteria in pivotal clinical studies within the development program*

The clinical studies for lurasidone recruited patients with very similar demographics to the target population. In particular, the severity of disease was representative of those seen in the target populations.

The main exclusion criteria for the clinical trials were designed to either ensure that the safety profile of lurasidone could be accurately ascertained or to protect subjects, such as unborn children.

The exclusion criteria "*Hypersensitivity to a medicine or history of an allergic reaction*" and "*Treatment with any potent cytochrome P-450 (CYP)3A4 inhibitors or inducers during the study*", used within the development program, were confirmed as specific contraindications to lurasidone and included in section 4.3 (Contraindications) of the SmPC.

The following criteria were also assessed in adults.

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 1. Subject was or was planning to become pregnant or lactating | To ensure no risk to the foetus or newborn child.<br>Atypical antipsychotics have been associated with effects on the unborn foetus in the last trimester of pregnancy; therefore, due to the unknown effect of lurasidone in pregnancy, these patients were excluded. | Yes | NA |
| 2. Imminent suicidal ideation or injury to self, others or property | Included as an exclusion criterion to ensure that patients with these risk factors were not put at further risk by being randomized to placebo. | No | This patient group is covered by a class warning across all atypical antipsychotic medications: the occurrence of suicidal behavior 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. |
| 3. Parkinson's disease or evidence of any chronic organic disease of the central nervous system (CNS) (other than schizophrenia) | Chronic organic disease of the CNS had to be excluded from clinical trials because of potential risk of worsening their condition with a centrally acting compound such as lurasidone. | No | For scientific and ethical reasons, diagnosis of functional psychiatric disorders is based on exclusion of organic disorders. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 4. Infection with HIV or hepatitis viruses (C or B) | Chronic and severe physical illnesses such as HIV and hepatitis viruses C or B are excluded from clinical trials to avoid any potential harmful effects of a compound that is still under evaluation.<br>To ensure that the results of the safety and efficacy results were not confounded.<br>To ensure the safety of the study staff at sites and laboratory testing facilities by not exposing them to high risk blood samples. | No | There is no contraindication for patients with HIV or hepatitis per se; however, patients receiving medications for HIV infection (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) should not receive lurasidone as per contraindication with cytochrome P-450 (CYP)3A4 inhibitors or inducers.<br>Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 5. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2× upper limit of normal (ULN) | Prior to the evaluation of lurasidone in patients with hepatic impairment, patients with AST/ALT > 2×ULN were excluded to ensure patients with impaired hepatic function were not put at risk while hepatic safety with lurasidone was still being evaluated. | No | Hepatic impairment has been evaluated in clinical pharmacology studies and dose adjustments included in the SmPC to enable patients with hepatic impairment to be managed appropriately. |
| 6. Clinically significant renal disorder creatinine clearance (CrCl) | Prior to the evaluation of lurasidone in patients with renal impairment, to ensure patients with impaired renal function were not put at risk while renal safety with lurasidone was still being evaluated. | No | Renal impairment has been evaluated in clinical pharmacology studies and dose adjustments included in the SmPC to enable patients with renal impairment to be managed appropriately. |
| 7. Hepatitis or clinically significant impaired hepatic dysfunction ALT ≥ 3ULN | Prior to the evaluation of lurasidone inpatients with hepatic impairment, to ensure patients with impaired hepatic function were not put at risk while hepatic safety with lurasidone was still being evaluated. | No | Hepatic impairment has been evaluated in the clinical pharmacology studies and dose adjustments included in the SmPC to enable patients with hepatic impairment to be managed appropriately. |
| 8. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed – Text revision diagnosis of schizophreniform disorder, schizoaffective disorder or schizophrenia, residual type or catatonic type | To ensure the population of patients being treated was limited to patients with schizophrenia only.<br>Other conditions were excluded in the clinical trials to avoid potential confounding effects of differential treatment response. | No | Patients with these diagnoses are routinely treated with antipsychotic medication and their physician will adjust the treatment based on their clinical response. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 9. History of gastrointestinal, liver or kidney disease, or other condition that would interfere with the absorption, distribution, metabolism, and excretion (ADME) of medications | To ensure that the patients received the anticipated systemic exposure of lurasidone. Patients with abnormal ADME could experience higher or lower exposure than expected. This could put patients at risk and confound the interpretation of the safety and efficacy data. | No | Hepatic and renal impairment have been evaluated in clinical pharmacology studies and dose adjustments included in the SmPC to enable patients with hepatic or renal impairment to be managed appropriately.<br>For all conditions potentially affecting the ADME of lurasidone, in the clinic, the physician can monitor the treatment response and adjust the dosage or change the medication as required. |
| 10. Treatment with depot neuroleptics within 1 standard cycle | Depot neuroleptics take approximately 4 to 6 months to wash out of the system completely. Administration of lurasidone on top of a depot neuroleptic could have put patients at risk and confounded the efficacy and safety results | No | In the clinic, oral antipsychotics are combined with depot injection under clinical supervision. Combination treatment is not expected to cause serious adverse reactions to warrant inclusion as a contraindication. |
| 11. Resistance to neuroleptic treatment | Exposing treatment resistant patients to compounds under evaluation in clinical trials would be deemed unacceptable by ethics committees, family, and treating physicians. Furthermore, it could have confounded the efficacy signal. | No | Only clozapine is currently licensed for the treatment of treatment-resistant schizophrenia; however, patients do not always respond to clozapine. Under these circumstances, patients are treated with combinations of multiple antipsychotics and other medications under supervision. Use of lurasidone in such circumstances should be based on overall benefit risk assessment. |
| 12. History of treatment with clozapine for refractory psychosis and/or subject had been treated with clozapine within 4 months of randomization | Clozapine is usually used to treat treatment-resistant psychosis. Exposing treatment-resistant patients to compounds under evaluation in clinical trials would be deemed unacceptable by ethics committees, family, and treating physicians. Furthermore, it could have confounded the efficacy signal. | No | Only clozapine is currently licensed for the treatment of treatment-resistant schizophrenia; however, patients do not always respond to clozapine. Under these circumstances, patients are treated with combinations of multiple antipsychotics and other medications under supervision. Use of lurasidone in such circumstances should be based on overall benefit risk assessment. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 13. Risperidone at doses of 6 mg/day or more and for whom the investigator judged that the psychotic symptoms did not improve at doses up to 6 mg/day | Risperidone was a comparator drug in study D1001002; therefore, patients who had previously failed treatment on risperidone were excluded. | No | Only study D1001002 excluded risperidone, and this was specifically because risperidone was a comparator in that study. Risperidone use was not excluded in any other study in the clinical program and there is no reason to contraindicate its use with lurasidone. |
| 14. Exposure to antidepressants or reversible monoamine oxidase (MAO) inhibitors within 1 week of entry into the washout period (within 1 months for fluoxetine or irreversible MAO inhibitors, e.g., deprenyl) | This was an exclusion criterion to ensure that the interpretation of the efficacy and safety was not confounded. | No | There is suspicion of an increased risk in patients taking concomitant antidepressants or reversible MAO inhibitors. Any use in such patients should be based on the benefit risk evaluation by the treating physician and in accordance with the Product Information recommendations. |
| 15. History of drug abuse or drug dependency, or a history of alcohol abuse or alcohol dependency within 6 months prior to screening | The coadministration of lurasidone with alcohol or illegal drugs could have put patients at risk and confounded efficacy and safety results.<br>Administering a compound under evaluation to patients who have both schizophrenia and an alcohol or substance dependency with may be unacceptable ethically. | No | There is suspicion of a potential risk in patients taking alcohol or drugs. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 16. Electroconvulsive shock therapy (ECT) within 3 months of entry into the washout period of the study | ECT can cause increases in creatine kinase (CK) levels. Increased CK levels are also seen in patients with heart disease and rhabdomyolysis, therefore patients who had undergone ECT were excluded in order to ensure the elevated CK levels were not masking these important ADRs. In addition, patients receiving ECT could have other underlying psychiatric conditions which might have confound efficacy and safety.<br>Furthermore, the duration of effect of ECT can last for several months and therefore could confound the effects of lurasidone if not excluded within 3 months of entry into the washout period of the study. | No | There is no suspicion of an increased risk in patients receiving concomitant ECT. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 17. Narrow angle glaucoma, cataracts or retinal disease | In 1 non-clinical study, lurasidone was shown to bind melanin and be retained in melanin-containing (e.g., retinal) tissues. Lens opacities may cause obstruction and therefore not allow proper retinal examination as part of physical examination to be performed. Therefore, patients with eye conditions were excluded from the studies to ensure they were not put at additional risk, and to avoid confounding the interpretation of the safety data. | No | There is no suspicion of an increased risk in patients with narrow angle glaucoma, cataracts or retinal disease. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 18. Prolactin levels of >100/200 ng/mL at Screening or Baseline | All drugs acting at the D2 receptors can cause an increase in prolactin levels. Patients with high prolactin levels were excluded to ensure they were not put at further risk, and so the effect of lurasidone on prolactin levels could be evaluated. | No | There is no suspicion of an increased risk in patients with increased prolactin levels. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 19. History of neuroleptic malignant syndrome (NMS), water intoxication, or paralytic ileus | NMS is a life-threatening condition has been reported to occur with antipsychotics; therefore, patients with a history of NMS were not included to ensure they were not put at risk.<br>Water intoxication causes an electrolyte imbalance and increases the risk of convulsions. Patients with a history of water intoxication were not included for safety reasons.<br>Paralytic ileus is a condition which could potentially affect absorption of lurasidone. Patients with abnormal ADME could experience higher or lower exposure than expected. This could put patients at risk and confound the interpretation of the safety and efficacy data. | No | NMS is a known class effect of antipsychotics.<br>There is suspicion of a potential risk in patients with a history of NMS, water intoxication or paralytic ileus. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 20. History or complication of malignancy | Patients with a history or complication of malignancy were excluded for safety reasons, and to ensure that the interpretation of the efficacy and safety was not confounded by pre-existing conditions. | No | No evidence at the moment that there is a risk for patients with malignancies. |
| 21. Evidence of severe tardive dyskinesia, severe chronic tardive dystonia, or any other severe chronic movement disorder | Medications acting at the D2 receptors can cause dyskinesia and movement disorders. This was an exclusion criterion to ensure patients who already had signs of movement disorders were not put at further risk, to ensure the safety data was not confounded by pre-existing movement conditions, and so the effect of lurasidone on movement disorders could be evaluated. | No | Severe tardive dyskinesia, severe chronic tardive dystonia, and any other severe chronic movement disorder are known class effects of antipsychotics.<br>Medical assessment of the risk/benefit will determine whether patients should receive lurasidone. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 22. Clinically significant medical complications such as serious cardiovascular, hepatic, renal, organic brain, hematologic, endocrine, or convulsive disease; or subject had a history of these conditions | Patients with clinically significant medical complications were excluded for safety reasons, and to ensure that the interpretation of the efficacy and safety was not confounded by pre-existing conditions. | No | There is a potential risk to patients generally. Medical assessment of the risk/benefit for each patient will determine whether they should receive lurasidone. |
| 23. Body mass index greater than 40 kg/$m^2$ or less than 18.5 kg/$m^2$ | Weight gain has been observed with atypical antipsychotics. This exclusion criterion was included to evaluate the metabolic effects of lurasidone. | No | Patients with schizophrenia are more prone to obesity than the general population. There is no evidence to suggest that patients who are underweight or overweight should not receive lurasidone. |
| 24. Treatment with a drug that prolongs QT interval | To ensure that patients were not put at risk, and that the interpretation of any effects of lurasidone on QT interval were not confounded by other medications that prolong QT. | No | The thorough QT study showed that lurasidone at the supratherapeutic dose of 600 mg per day was not associated with an increase in QT interval, therefore patients with long QT syndrome and patients taking medications that prolong QT interval are not contraindicated. |
| 25. Long QT syndrome and subject who is treated with Class Ia (quinidine, procainamide etc) or III (amiodarone, sotalol etc) antiarrhythmic drugs) | To ensure that patients with long QT syndrome were not put at risk, and that the interpretation of any effects of lurasidone on QT interval were not confounded by other medications that prolong QT. | No | Per the SmPC, 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. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 26. Under the potent influence of CNS depressants such as barbiturates or chloral hydrate | To ensure patients taking CNS depressants were not put at risk, and to ensure interpretation of the safety and efficacy data were not confounded. | No | There is suspicion of a potential risk in patients receiving concomitant CNS depressants (such as barbiturates or chloral hydrate). Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 27. Treatment with epinephrine | Study-specific requirement to ensure interpretation of the safety and efficacy data were not confounded. | No | There is no suspicion of an increased risk in patients receiving concomitant epinephrine. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |

The following criteria were assessed in the double-blind placebo-controlled study (D1050301) performed in adolescents. In the open-label extension study (D1050302), only criteria reported at points 7 and 25 of the following table were used.

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 1 Axis I or Axis II diagnosis other than schizophrenia | To ensure the population of patients being treated was limited to patients with schizophrenia only.<br>Other conditions were excluded in the clinical trials to avoid potential confounding effects of differential treatment response. | No | Patients with these diagnoses are routinely treated with antipsychotic medication and their physician will adjust the treatment based on their clinical response. |
| 2. Mental retardation, neuroleptic malignant syndrome, or any neurologic disorder, or severe head trauma | Neuroleptic malignant syndrome is a life-threatening condition has been reported to occur with antipsychotics; therefore, patients with a history of NMS were not included to ensure they were not put at risk. | No | Neuroleptic malignant syndrome is a known class effect of antipsychotics.<br>There is suspicion of a potential risk in patients with a history of mental retardation, neuroleptic malignant syndrome, or any neurologic disorder, or severe head trauma. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 3. HIV positive or AIDS, or history of Hepatitis B or C | Chronic and severe physical illnesses such as HIV and hepatitis viruses C or B are excluded from clinical trials to avoid any potential harmful effects of a compound that is still under evaluation.<br>To ensure that the results of the safety and efficacy results were not confounded.<br>To ensure the safety of the study staff at sites and laboratory testing facilities by not exposing them to high risk blood samples. | No | There is no contraindication for patients with HIV or hepatitis per se; however, patients receiving medications for HIV infection (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) should not receive lurasidone as per contraindication with cytochrome P-450 (CYP)3A4 inhibitors or inducers.<br>Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 4. Chromosomal disorder with developmental impairment | To ensure the population of patients being treated was limited to patients with schizophrenia only.<br>Other conditions were excluded in the clinical trials to avoid potential confounding effects of differential treatment response. | No | There is no suspicion of an increased risk in patients suffering from chromosomal disorder with developmental impairment. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 5. Chronic organic disease of the CNS | Chronic organic disease of the CNS had to be excluded from clinical trials because of potential risk of worsening their condition with a centrally acting compound such as lurasidone. | No | For scientific and ethical reasons, diagnosis of functional psychiatric disorders is based on exclusion of organic disorders. |
| 6. PANSS total scores ≥ 120 at screening or baseline | In general, higher values of PANSS scores represent greater severity of illness. | No | There is no suspicion of an increased risk in patients PANSS total scores ≥ 120. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 7. Extrapyramidal symptoms, dystonia, tardive dyskinesia, or other movement disorder | Medications acting at the D2 receptors can cause dyskinesia and movement disorders. This was an exclusion criterion to ensure patients who already had signs of movement disorders were not put at further risk, to ensure the safety data was not confounded by pre-existing movement conditions, and so the effect of lurasidone on movement disorders could be evaluated. | No | Severe tardive dyskinesia, severe chronic tardive dystonia, and any other severe chronic movement disorder are known class effects of antipsychotics.<br>Medical assessment of the risk/benefit will determine whether patients should receive lurasidone. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 8. History of electroconvulsive therapy | ECT can cause increases in creatine kinase (CK) levels. Increased CK levels are also seen in patients with heart disease and rhabdomyolysis, therefore patients who had undergone ECT were excluded in order to ensure the elevated CK levels were not masking these important ADRs. In addition, patients receiving ECT could have other underlying psychiatric conditions which might have confound efficacy and safety.<br>Furthermore, the duration of effect of ECT can last for several months and therefore could confound the effects of lurasidone if not excluded within 3 months of entry into the washout period of the study | No | There is no suspicion of an increased risk in patients receiving concomitant ECT. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 9. Resistance to antipsychotic treatment | Exposing treatment resistant patients to compounds under evaluation in clinical trials would be deemed unacceptable by ethics committees, family, and treating physicians. Furthermore, it could have confounded the efficacy signal. | No | In these patients there is suspicion of potential lack of efficacy. Use of lurasidone in such circumstances should be based on overall benefit risk assessment. |
| 10. Neurological, metabolic (including type 1 diabetes), hepatic, renal, haematological, pulmonary, cardiovascular, gastrointestinal, carcinoma, and/or urological disorder | These disorders may represent a risk to the subjects if they were to participate in the study or that might confound the results of the study. | No | There is suspicion of a potential risk in these patients. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 11. History of malignancy < 5 years | Patients with a history or complication of malignancy were excluded for safety reasons, and to ensure that the interpretation of the efficacy and safety was not confounded by pre-existing conditions. | No | No evidence at the moment that there is a risk for patients with malignancies. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 12. Clinically significant finding(s) on physical examination | These findings may represent a health concern to the subject while on study. | No | Medical assessment of the risk/benefit for each patient will determine whether they should receive lurasidone. |
| 13. Clinically relevant abnormal laboratory values or abnormal vital sign values/findings | Patients with clinically significant laboratory/vital signs alterations were excluded for safety reasons, and to ensure that the interpretation of the efficacy and safety was not confounded by pre-existing conditions. | No | There is no considered increased risk to patients generally. Medical assessment of the risk/benefit for each patient will determine whether they should receive lurasidone. |
| 14. Clinically significant abnormal ECG | To ensure that patients were not put at risk, and that the interpretation of any effects of lurasidone on ECG (including QT interval). | No | Per the SmPC, 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. |
| 15. History of a medical or surgical condition interfering with the absorption, metabolism, or excretion of orally administered lurasidone | To ensure that the patients received the expected systemic exposure of lurasidone. Patients with abnormal ADME could experience higher or lower exposure than expected. This could put patients at risk and confound the interpretation of the safety and efficacy data. | No | For all conditions potentially affecting the ADME of lurasidone, in the clinic, the physician can monitor the treatment response and adjust the dosage or change the medication as required. |
| 16. Alcohol abuse/dependence or drug abuse/dependence, or positive urine test at screening or baseline for drug abuse | The coadministration of lurasidone with alcohol or illegal drugs could have put patients at risk and confounded efficacy and safety results.<br>Administering a compound under evaluation to patients who have both schizophrenia and an alcohol or substance dependency with may be unacceptable ethically. | No | There is suspicion of a potential risk in patients taking alcohol or drugs. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 17. Females who were pregnant, lactating, or likely to become pregnant during the study | To ensure no risk to the foetus or newborn child.<br>Atypical antipsychotics have been associated with effects on the unborn foetus in the last trimester of pregnancy; therefore, due to the unknown effect of lurasidone in pregnancy, these patients were excluded. | Yes | NA |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 18. Recent participation to a clinical trial | These patients were excluded to avoid the presence of confounding factors in the analysis of the study results. | No | There is no considered increased risk for these patients generally. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 19. Recently donated whole blood | These finding may represent a health concern to the subject while on study. | No | There is no suspicion of an increased risk in these patients. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 20. Concomitant medications that consistently prolong the QT/QTc interval | To ensure that patients were not put at risk, and that the interpretation of any effects of lurasidone on QT interval were not confounded by other medications that prolong QT. | No | Per the SmPC, 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. |
| 21. Depot neuroleptics in the last month | Depot neuroleptics take approximately 4 to 6 months to wash out of the system completely. Administration of lurasidone on top of a depot neuroleptic could have put patients at risk and confounded the efficacy and safety results | No | In the clinic, oral antipsychotics are combined with depot injection under clinical supervision. Combination treatment is not expected to cause serious adverse reactions to warrant inclusion as a contraindication. |
| 22. Treatment with antidepressants, stimulants, or atomoxetine within 3 days prior to randomization, fluoxetine hydrochloride within 21 days of randomization, monoamine oxidase (MAO) inhibitor within 28 days of randomization, or clozapine within 120 days of randomization | Potential drug-drug interactions. Therefore, interpretation of the efficacy and safety may result confounded. | No | There is suspicion of a potential risk in patients taking concomitant antidepressants or reversible MAO inhibitors. Any use in such patients should be based on the benefit risk evaluation by the treating physician and in accordance with the Product Information recommendations. |

| Criterion | Reason for Exclusion | Missing information (Yes/No) | Rationale (if not missing) |
|---|---|---|---|
| 23. Carbamazepine, oxcarbazepine, eslicarbazepine acetate, or fluvoxamine, within 3 days prior to randomization (7 days for aripiprazole) and until follow-up | Potential drug-drug interactions. Therefore, interpretation of the efficacy and safety may result confounded. | No | There is suspicion of a potential risk in patients taking concomitant carbamazepine, oxcarbazepine, eslicarbazepine acetate, fluvoxamine or aripiprazole. Any use in such patients should be based on the benefit risk evaluation by the treating physician and in accordance with the Product Information recommendations. |
| 24. Prolactin concentration ≥ 100 ng/mL at screening | All drugs acting at the D2 receptors can cause an increase in prolactin levels. Patients with high prolactin levels were excluded to ensure they were not put at further risk, and so the effect of lurasidone on prolactin levels could be evaluated. | No | There is no suspicion of an increased risk in patients with increased prolactin levels. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 25. Current suicidal ideation or at imminent risk of suicide or injury | Included as an exclusion criterion to ensure that patients with these risk factors were not put at further risk by being randomized to placebo. | No | This patient group is covered by a class warning across all atypical antipsychotic medications: the occurrence of suicidal behavior 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. |
| 26. Special diet for the 28 days prior to drug administration | This exclusion criterion was included to evaluate the metabolic effects of lurasidone without potential confounding factors. | No | There is no suspicion of an increased risk in patients under special diet. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 27. Newly diagnosed Type 2 diabetes during screening or past hospitalization for diabetes | This exclusion criterion was included to evaluate the effects of lurasidone on blood glucose in non-diabetic patients. | No | There is no suspicion of an increased risk in patients any Type 2 diabetes. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |
| 28. Clinically significant orthostatic hypotension | Lurasidone may cause orthostatic hypotension. Patients with pre-existing significant orthostatic hypotension were excluded to avoid additional risks. | No | This patient group is covered by a specific warning in the Product Information. Any use in such patients should be based on the benefit risk evaluation by the treating physician. |

[redacted]

## *SIV.2 Limitations to detect adverse reactions in clinical trial development programmes*

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

## *SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes*

| Type of special population | Exposure |
|---|---|
| **Pregnant women** | Not included in the clinical development program. However, there were a number of subjects who became pregnant during a lurasidone clinical trials. This information is reflected in the lurasidone SmPC section 4.6.<br><br>Use in pregnant women is considered missing information for lurasidone. |
| **Breastfeeding women** | Not included in the clinical development program. Cumulatively, there have been a few reports of lurasidone exposure of infants through breastfeeding. This information is reflected in the lurasidone SmPC section 4.6.<br><br>Use in breastfeeding women is considered missing information for lurasidone. |
| **Patients with relevant comorbidities:** | |
| • Patients with hepatic impairment | Subjects with hepatic impairment were excluded from the lurasidone phase 2/3 clinical studies.<br><br>A phase 1 study was conducted to examine the effects of hepatic impairment on lurasidone PK. Accordingly, dose adjustment is recommended in subjects with moderate hepatic impairment (Child-Pugh Class B), and severe hepatic impairment (Child-Pugh Class C). This information is reflected in the lurasidone SmPC section 4.2. |
| • Patients with renal impairment | Subjects with renal impairment were excluded from the lurasidone phase 2/3 clinical studies.<br><br>A phase 1 study was conducted to examine the effects of renal impairment on lurasidone PK. Accordingly, specific dose limitations are recommended in patients with moderate and severe renal impairment and in patients with end stage renal disease. This information is reflected in the lurasidone SmPC section 4.2. |
| • Patients with cardiovascular impairment | Not included in the clinical development program. Due to lack of information, lurasidone should be used with caution in patients with known cardiovascular |

| Type of special population | Exposure |
|---|---|
| | disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.<br>The cumulative clinical (SAE data only) and post-marketing experience to date shows that there is a number of cases in which a cardiac disorder was noted in the past and/or present medical history. This information is reflected in the lurasidone SmPC section 4.4.<br>Use in patients with cardiac impairment is considered missing information for lurasidone. |
| • Immunocompromised patients | NA |
| • Patients with a disease severity different from inclusion criteria in clinical trials | NA |
| **Population with relevant different ethnic origin** | NA |
| **Subpopulations carrying relevant genetic polymorphisms** | NA |
| **Children** | NA |
| **Elderly** | Across most phase 2/3 clinical trials, individuals age 65 years and older were excluded; limited data therefore are available for this patient subgroup.<br>Two PK studies (D1001049 and D1050253) were conducted to evaluate the safety and the effects of age on lurasidone serum PK in healthy subjects. No differences in tolerability and exposure were noted between the elderly or young adult subjects.<br>This information is reflected in the lurasidone SmPC section 4.2. |

# PART II: MODULE SV – POST-AUTHORIZATION EXPERIENCE

## *SV.1 Post-authorization exposure*

The paediatric indication for lurasidone is not yet approved in the EU, and no changes requiring an update of the risk evaluation have been implemented (e.g. population exposed in a new indication). Therefore, this section does not need to be updated [EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V rev.2).

## *SV.1.1 Method used to calculate exposure*

Unless otherwise specified, patients' exposure in post-marketing is calculated assuming average lurasidone dose of 61.5 mg/day and average therapy duration of 103 days (Encuity Data Source).
Patient Years of treatment is calculated according to the formula:
Patient Years = number of patients exposed * 103 days / 365 days

## *SV.1.2 Exposure*

Cumulative overall (excluding EU countries) patient exposure to commercial lurasidone from the time of first product launch through 27OCT2016 is estimated at approximately 3,246,164 patients and 916,043 Patient Years as per the following Table.

| ***Cumulative exposure from marketing experience (non-EU countries)*** | | |
|---|---|---|
| **Asia** | | |
| Hong Kong | 29 | 8 |
| Russian Federation | 0 | 0 |
| Singapore | 9 | 3 |
| Taiwan | 1,074 | 303 |
| Thailand | 120 | 34 |
| **Oceania** | | |
| Australia | 12,044 | 3,399 |
| **Non-EU** | | |
| Switzerland | 8,491 | 2,396 |
| **North America** | | |
| Canada | 366,057 | 103,300 |

[redacted]

| *Cumulative exposure from marketing experience (non-EU countries)* | | |
|---|---|---|
| US | 2,858,340 | 806,600 |
| Brazil | 0 | 0 |
| **Total** | **3,246,164** | **916,043** |

Cumulative overall patient exposure in EU countries to commercial lurasidone from the time of first product launch through 31MAR2018 is estimated at approximately 20,750 patients and 5,649 Patient Years as per the following Table.

| *Cumulative exposure from marketing experience (EU countries)* | | | |
|---|---|---|---|
| **Country** | **Reference Period** | **Number of Patients Exposed** | **Patient Years of Treatment** |
| | | **Cumulative** | **Cumulative** |
| United Kingdom | OCT2014-MAR2018 | 12,485 | 3,524 |
| Denmark | JUL2014- MAR2018 | 2,550 | 301 |
| Sweden | OCT2014-MAR2018 | 1,029 | 289 |
| Finland | OCT2014-MAR2018 | 713 | 201 |
| Norway | OCT2014-MAR2018 | 2,051 | 577 |
| Netherlands | NOV2014-MAR2018 | 1,803 | 723 |
| Italy | OCT2017-MAR2018 | 92 | 26 |
| Germany | Up to MAR2018* | 27 | 8 |
| | **TOTAL** | **20,750** | **5,649** |

* Based on shipping data

No stratification of post-marketing non-study data by population was possible, as the data parameters were not captured to allow stratification.

[redacted]

# PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

## POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSE

Lurasidone has not been systematically studied in humans for its potential for abuse or physical dependence or its ability to induce tolerance. While clinical studies with lurasidone did not reveal any tendency for drug-seeking behavior, these observations were not systematic, and it is not possible to predict the extent to which a central nervous system–active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs of lurasidone misuse or abuse (e.g., development of tolerance, drug-seeking behavior, increases in dose).

# PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

## *SVII.1 Identification of safety concerns in the initial RMP submission*

### *SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP*

**KNOWN RISKS THAT REQUIRE NO FURTHER CHARACTERISATION**

These risks are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU member state where the product is authorised).

**Somnolence**

In P23STC, somnolence occurred in 130 lurasidone-treated subjects (8.6%), 24 (3.4%) placebo, 9 (12.5%) haloperidol, 11 (9.0%) olanzapine, 16 (13.4%) quetiapine XR, and 0 risperidone. Somnolence increased with increasing lurasidone dose up to the 120 mg dose group but decreased in subjects in the 160 mg dose group (3 [4.2%] 20 mg group, 37 [7.6%] 40 mg group, 40 [7.4%] 80 mg group, 42 [14.4%] 120 mg group, and 8 [6.6%] 160 mg group).

In P23LTC, somnolence occurred in 63 (8.2%) in lurasidone flex, 4 (4.7%) quetiapine XR, and 36 (18.1%) risperidone subjects; no somnolence was reported in the placebo group (n=141).

In P23ALL, somnolence occurred in 378 all–lurasidone-treated subjects (9.7%).

No severe somnolence was seen in P23STC or P23LTC with lurasidone, compared with 3 risperidone subjects (1.5%) (P23LTC).

Moderate somnolence was seen in P23STC in 34 (2.3%) lurasidone, 4 (0.6%) placebo, 6 (5.0%) quetiapine, 3 (4.2%) haloperidol and 0 olanzapine and risperidone subjects. In P23LTC moderate somnolence was reported in 16 (2.1%) lurasidone flex, 11 (5.5%) risperidone flex and 3 (3.5%) quetiapine flex subjects.

Mild somnolence was seen in P23STC in 96 (6.4%) lurasidone, 20 (2.8%) placebo, 10 (8.4%) quetiapine, 11 (9.0%) olanzapine, 6 (8.3%) haloperidol, and 0 risperidone subjects. In P23LTC, mild somnolence was reported by 47 (6.1%) lurasidone flex, 22 (11.1%) risperidone flex, and 1 (1.2%) quetiapine flex subjects.

In P23STC, somnolence was reported in 63 (4.2%), 46 (3.3%), and 21 (1.9%) of lurasidone-treated subjects at (<7 days exposure), 7 to 20 days and ⩾21 days exposure, respectively.

Thus, it would appear that the frequency of first occurrence of somnolence decreased over the period of exposure in the short-term studies.

In the paediatric population, somnolence occurred in 43 out of 304 lurasidone-exposed patients (14.1%), sedation in 12/304 (3.9%) and hypersomnia in 5/304 (1.6%). On the whole, drug-related somnolence

(including hypersomnia, sedation, and somnolence) was observed in 60 out of 304 lurasidone-exposed patients (19.7%). It was mainly mild in intensity.

Male sex, cataplexy, restless legs, anxiety and depression, insomnia, somatic disease, age, and being overweight are risk factors for somnolence [Pallesen 2001, Theorell-Haglow 2006].

Antagonistic action at the α1 adrenergic and histamine H1 receptors are thought to contribute to sedation [Reynolds 2010].

Somnolence is included as a very common ADR (in both adults and adolescents) in section 4.8 of the lurasidone SmPC with a caution in section 4.7 around driving and operating machinery.

**Temperature dysregulation**

In P23STC, TEAEs suggestive of dysregulation of body temperature, (e.g., pyrexia, hyperthermia, feeling hot, body temperature increase) occurred in from <0.1% to 13 lurasidone subjects (0.9%) and in from 0 to 12 placebo subjects (1.7%).

In P23LTC, pyrexia was experienced by 4 (0.5%) flexible-lurasidone treated subjects and 2 (1.0%) risperidone treated patients but there were no reports of body temperature increased, hyperthermia or feeling hot.

In P23ALL, in the all-lurasidone group, pyrexia was reported in 57 patients (1.5%), flushing in 1 subject (<0.01%) and hot flush by 11 subjects (0.3%).

In P23STC, there were no temperature dysregulation TEAEs of severe intensity. Moderate pyrexia was seen in 4 placebo subjects (0.6%) and 4 lurasidone subjects (0.3%), and moderate hyperthermia in 2 lurasidone subjects (0.1%); all other events were mild in intensity.

Of the 4 events of pyrexia in the P23LTC studies, 1 was mild and 3 were moderate intensity.

In the paediatric population, drug-related pyrexia occurred in 2 out of 304 lurasidone-exposed patients (0.6%), while no events of hyperthermia, feeling hot and body temperature increase were reported. No cases of drug-related severe pyrexia were observed.

Many AEs associated with temperature dysregulation reactions manifest in the period after initiating antipsychotic therapy or an antipsychotic dose increase. Comorbid infection, pre-existing brain damage (affecting the anterior hypothalamic region) and a diagnosis of schizophrenia are risk factors for temperature dysregulation [van Marum 2007].

Antipsychotics that have a stronger affinity with the 5-HT2a receptor compared with the D2-receptor can cause serotonin-induced hypothermia [van Marum 2007]. Antipsychotics that block the alpha2-adrenergic receptors can also induce hypothermia by inhibition of responses to cooling such as vasoconstriction and shivering [van Marum 2007].

Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotics. There were few reports in the lurasidone clinical program and rates were similar to those with placebo.

**AEs related to hyperprolactinemia**

In P23STC, amenorrhea was reported in 2 lurasidone-treated subjects (0.1%), and erectile dysfunction was reported in 3 lurasidone-treated subjects (0.2%).

In P23LTC, amenorrhea was reported in 3 flexible dose lurasidone subjects (0.4%) and erectile dysfunction was reported in 5 flexible dose lurasidone subjects (0.7%).

In P23ALL, AEs of blood prolactin increased and blood prolactin abnormal occurred in 101 (2.6%) and 1 (0.1%), subjects treated with lurasidone, respectively. AEs of galactorrhea, amenorrhea, and erectile dysfunction occurred in 3 (0.1%), 13 (0.3%), and 14 (0.4%) all-lurasidone subjects, respectively. There were no occurrences of TEAE of gynecomastia in P23ALL.

In P23STC, there were no AEs related to hyperprolactinemia of severe intensity.

Mild and moderate amenorrhea were seen in <0.1% lurasidone patients in P23STC and P23LTC.

Mild and moderate blood prolactin increased (2 [0.1%] and 1 [< 0.1%]) were seen in P23STC with lurasidone compared to 5 (7.7%) with risperidone and 0 for all other groups.

Mild and moderate erectile dysfunction (2 [0.1%] and 1 [< 0.1%]) were seen in P23STC with lurasidone and 0 and 1 (0.1%) with placebo. Mild and moderate erectile dysfunction (2 [0.3%] and 3 [0.5%]) were seen in P23LTC with lurasidone flex, 0 and 4 (2.0%) with risperidone flex and 0 with quetiapine flex.

In the paediatric population, drug-related hyperprolactinaemia occurred in 1 out of 304 lurasidone-exposed patients (0.3%), drug-related blood prolactin increased in 3/304 (1%), drug-related erectile dysfunction in 5/304 (1.6%) and drug-related amenorrhea in 2/304 (0.6%).No severe cases were reported.

Male sex, menopause in women, substance abuse, smoking, low physical activity/immobility, nutritional deficiency and low exposure to sunshine are risk factors for low bone density [Hummer 2005, Ross 1996].

Certain antipsychotics can induce elevated prolactin levels by blockade of the hypothalamic-pituitary axis D2 receptors. Elevation of prolactin is associated with inhibition of luteinizing hormone production and a decline in sex hormone production which can lead to a decline in bone density.

Hyperprolactinemia, or elevations above normal in serum prolactin values are a well-recognized consequence of drugs that block the D2 receptor.

Clinically relevant increases in prolactin were not observed with lurasidone treatment in the short and long-term phase 2/3 studies.

Information has been added to the warning and precautions section 4.4 of the lurasidone SmPC in line with other antipsychotic medications.

**Orthostatic hypotension**

In P23STC, treatment-emergent orthostatic hypotension occurred in 5 lurasidone-treated subjects (0.3%), 1 (0.1%) placebo, 2 (1.6%) olanzapine, 3 (2.5%) quetiapine XR, and no risperidone or haloperidol subjects.

In P23LTC, there was 1 (0.1%) report in the lurasidone flex group, compared with 3 (1.5%) in the risperidone flex group and none in the quetiapine flex group.

In P23ALL, orthostatic hypertension was reported in 11 (0.3%) all-lurasidone treated subjects.

[redacted]

No severe orthostatic hypotension was reported in P23STC and P23LTC.
Moderate orthostatic hypotension was reported in P23STC by 2 (0.1%) lurasidone, 1 (0.8%) olanzapine subjects and none from the other groups. Moderate orthostatic hypotension was not reported in P23LTC.
Mild orthostatic hypotension was reported in P23STC by 3 (0.2%) lurasidone, 1 (0.1%) placebo, 1 (0.8%) olanzapine, 3 (2.5%) quetiapine and 0 haloperidol and risperidone. In P23LTC, mild orthostatic hypotension was reported by 1 (0.1%) lurasidone flex, 3 (1.5%) risperidone flex patients and 1 (0.7%) placebo patients.
In the paediatric population, a drug-related orthostatic hypotension occurred in 1 out of 304 lurasidone-exposed patients (0.3%). It was mild in intensity.
Older age, cardiovascular disease, and certain medications including: antihypertensives, some cardiac medications (e.g., organic nitrates), antipsychotics, tricyclic antidepressants, acetylcholinesterase inhibitors and Gardasil are risk factors for orthostatic hypotension [Mosnaim 2010].
Orthostatic hypotension is related to the α1 adrenergic antagonistic properties of antipsychotic drugs [Stahl 2002].
Orthostatic hypotension is included as an uncommon ADR (in both adults and adolescents) in section 4.8 of the lurasidone SmPC and information has been included in the warning and precautions section 4.4 in line with other antipsychotic medications.

**Venous thromboembolism (VTE)**
No occurrences of deep vein thrombosis were reported across the lurasidone clinical program, in both adults and adolescents.
Patients with a predisposition to VTE, that is, with underlying bleeding or coagulation disorders, may be at greater risk of developing an event. Prolonged immobilization and during a peri-operative period with certain surgeries also represent risk factors.
Lack of physical activity/ sedentary life-style, immobilization due to sedation or mechanical restraint in severely psychotic patients, obesity and smoking have been implicated in VTE associated with antipsychotic treatment in persons with schizophrenia [Jonsson 2009]. Enhanced platelet aggregation and activation have also been associated with VTE [Jonsson 2009]. In addition, a number of other factors such as raised levels of antiphospholipid antibodies associated with antipsychotic treatment and raised homocysteine levels have also been implicated [Hagg 2002].
Cases of VTE have been reported with antipsychotic drugs. A statement is already included to the warning and precautions section 4.4 of the lurasidone SmPC in line with other antipsychotic medications.

### *SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP*

The scientific evidence that initially has led to the inclusion are hereinafter briefly discussed.

**IMPORTANT IDENTIFIED RISKS**

**Extrapyramidal Symptoms**
Results from pivotal clinical studies showed that EPS, namely akathisia, dystonia, parkinsonism, may occur in patients under treatment with lurasidone. Post-marketing data confirmed this finding.
All lurasidone treated subjects experiencing EPS SAEs recovered without sequelae, but some patients discontinued from the study as a result of EPS TEAEs.
Potentially, any EPS adverse effects may cause distress to the individual patient and may affect patient's continuation with therapy. This important identified risk is considered in the global risk-benefit balance of the product.

**Drug interactions with strong cytochrome P-450 3A4 inhibitors or inducers**
Lurasidone is predominantly metabolised by CYP3A4 and therefore inhibition/induction of this enzyme would reduce/increase the metabolism of the compound. With a reduction/increase in the metabolism of lurasidone an increase/decrease in exposure to lurasidone would be expected.
Results from pivotal clinical studies showed that adverse reactions related to drug interactions with strong cytochrome P-450 3A4 inhibitors or inducers may occur in patients under treatment with lurasidone.
CYP3A4 interaction may produce increased occurrence of the identified and potential risks of lurasidone as a result of increased exposure, or subtherapeutic efficacy. This important identified risk is considered in the global risk-benefit balance of the product.

**Hypersensitivity**
Results from pivotal clinical studies showed that adverse reactions related to hypersensitivity may occur in patients under treatment with lurasidone. Post-marketing data confirmed this finding.
Hypersensitivity reactions could be life-threatening (e.g. anaphylaxis) and should be taken seriously. Advice from a health care professional should be sought; discontinuation following reaction onset is recommended.
Hypersensitivity to the product may affect the ability of a patient to remain on lurasidone treatment. This important identified risk is considered in the global risk-benefit balance of the product.

**Neuroleptic Malignant Syndrome**
Results from pivotal clinical studies showed that adverse reactions related to NMS may occur in patients under treatment with lurasidone. Post-marketing data confirmed this finding.

[redacted]

The most widely accepted mechanism by which antipsychotics produce NMS is that of dopamine $D_2$ receptor antagonism. In this widely accepted model, central $D_2$ receptor blockade in the hypothalamus, nigrostriatal pathways, and spinal cord leads to increased muscle rigidity and tremor via extrapyramidal pathways. Hypothalamic $D_2$ receptor blockade results in an elevated temperature set point and impairment of heat-dissipating mechanisms. Peripherally, antipsychotics lead to increased calcium release from the sarcoplasmic reticulum, resulting in increased contractility, which can contribute to hyperthermia, rigidity, and muscle cell breakdown.
NMS is potentially life-threatening and distressing for patients. This important identified risk is considered in the global risk-benefit balance of the product.

**IMPORTANT POTENTIAL RISKS**

**Metabolic profile**
Results from pivotal clinical studies showed that some adverse reactions related to metabolic profile, namely hyperglycaemia, weight increased, dyslipidaemia, may occur in patients under treatment with lurasidone. Post-marketing data partially confirmed this finding.
The exact mechanism for changes in metabolic profile is unknown. Lifestyle factors such as increased food intake, high calorific content of meals, lack of exercise and contributory effects from drug and alcohol use have been implicated [Reynolds 2001].
Uncontrolled hyperglycemia in the longer term is associated with a higher risk of diabetes, metabolic syndrome, and cardiovascular disease. In the short-term elevated serum lipids may be associated with significant weight gain, and in the longer term may lead to development of cardiovascular disease. Weight gain is also associated with decreased compliance with antipsychotic treatment, which can cause relapse of symptoms of schizophrenia.
These important potential risks are considered in the global risk-benefit balance of the product.

**Rhabdomyolysis**
Rhabdomyolysis occurred in 2 (<0.1%) lurasidone-treated subjects, both occurred in the short-term placebo-controlled studies. Few cases were retrieved from post-marketing data.
Rhabdomyolysis may have significant impact on the quality of life of an individual patient, including potential for residual physical effects. This important potential risk is considered in the global risk-benefit balance of the product.

**Suicidality**
Schizophrenia is strongly associated with an increased risk of suicidality, and suicide is the leading cause of death among patients with schizophrenia.

Results from pivotal clinical studies showed that suicidality (suicidal ideation, suicidal behaviour, suicide attempt, self-harm and completed suicide) may occur also in patients under treatment with lurasidone, even if no suicide attempts or completed suicides were observed in studies, except for one completed suicide reported in the lurasidone flex group.
The highest risk of suicide among patients with schizophrenia occurs in the first 3 to 4 years after illness onset [Alaraisanen 2009, Kuo 2005]. A systematic review identified the following list of factors which were strongly associated with an increased risk of suicide among patients with schizophrenia: previous depressive disorders, previous suicide attempts, drug misuse, agitation or motor restlessness, fear of mental disintegration, poor adherence to treatment and recent loss [Hawton 2005].
Suicidality has a substantial impact not only on the patient's quality of life but also have a detrimental impact on family and society. This important potential risk is considered in the global risk-benefit balance of the product.

**Agranulocytosis**
There were no TEAEs of agranulocytosis in lurasidone clinical trials, and few cases were retrieved from the global safety database. However, several other drugs are associated with agranulocytosis/leukopenia/neutropenia, including: thyroid inhibitors, aminosalicylates, antibacterial drugs, non-opioid analgesics, NSAIDs, antidepressants, ulcer healing drugs, antiepileptics, and disease modifying antirheumatic drugs [van Staa 2003].
Potentially, patients with agranulocytosis may suffer from a severely suppressed immune system and are therefore at serious risk of infection. This important potential risk is considered in the global risk-benefit balance of the product.

**Seizure**
In pivotal clinical studies, seizure was rarely reported in lurasidone treated patients.
Patients with schizophrenia are more prone to seizure than the general population. In large investigations, seizure incidences have been reported to range from ~0.1 to ~1.5% in patients treated with therapeutic doses of most commonly used antipsychotics. The incidence of the first unprovoked seizure in the general population is reported to be from 0.07 to 0.09% [Pisani, 2002].
It is unclear whether this excess risk is inherent in schizophrenia, is secondary to exposure to antipsychotic medications that may lower the seizure threshold or is the result of some combination of the two.
In any case, depending on the nature and the severity of seizure, there could be significant impact to an individual patient's quality of life including social and physical effects. This important potential risk is considered in the global risk-benefit balance of the product.

**Increased serum creatinine**

[redacted]

In pivotal clinical studies, few patients experienced TEAEs suggestive of impaired renal function. Only one case of renal failure occurred. It was assessed as not related to lurasidone.
The mild and transient outcomes of the reported occurrences of increase in serum creatinine are considered to be of low significance to a patient. This important potential risk is considered in the global risk-benefit balance of the product.

**Use in patients with moderate or severe renal impairment**
The exposure to lurasidone of patients with moderate or severe renal impairment is limited to 9 subjects with moderate creatinine clearance (CrCl) (≥30 and <50 mL/min) and 9 subjects with severe CrCl (<30 mL/min) in study D1050265. There were no safety or tolerability issues in these patients.
The cumulative clinical trial (SAE data only) and post-marketing experience to date shows that there are some cases in which moderate to severe renal impairment was noted in the past and/or present medical history.
Any impact on a patient can be minimised with sensible dosaging and monitoring in properly managed patients. This important potential risk is considered in the global risk-benefit balance of the product.

**Use in patients with moderate or severe hepatic impairment**
The exposure to lurasidone of patients with moderate or severe hepatic impairment is limited to 6 subjects with moderate hepatic impairment (Child Pugh Class B) and 3 subjects with severe hepatic impairment (Child Pugh Class C) in study D1050264. There were no safety or tolerability issues in these patients.
The cumulative clinical (SAE data only) and post-marketing experience to date shows that there are some cases in which moderate to severe hepatic impairment was noted in the past and/or present medical history.
Any impact on a patient can be minimised with sensible dosing and monitoring in properly managed patients.
This important potential risk is considered in the global risk-benefit balance of the product.

**Off-label use**
There is some evidence that older age is associated with a higher risk of off-label use of second generation antipsychotics. According to the 2004 National Nursing Home Survey, of the 308,990 elderly nursing home residents receiving at least 1 second-generation antipsychotic (SGA), 86.3% received them for off-label indications.
A review of off-label use of antipsychotics [Haw 2007] reported that in the United Kingdom, between 0.4% and 1% of patients were prescribed antipsychotics above the recommended dosage range.
Off-label use may impact on the clinical benefit of lurasidone. This important potential risk is considered in the global risk-benefit balance of the product.

**Third trimester exposure during pregnancy and risk to neonates**
Of the 392 total cases of exposure during pregnancy, there were 61 maternal cases and two neonate cases

involving apparent exposure to lurasidone during the third trimester of pregnancy.
Information on delivery or outcome were reported for 36 cases. Sixteen cases reported the delivery of a healthy baby or delivery with no complications, 10 pregnancies were still ongoing at the time of the assessment. Complication were reported for ten cases.
Foetal exposure to antipsychotics in the third trimester of pregnancy is associated with neonatal withdrawal syndrome characterised by EPSs such as tremor, jitteriness, irritability, feeding problems, and somnolence [Coppola 2007]. This important potential risk is considered in the global risk-benefit balance of the product.

## MISSING INFORMATION

### Elderly patients

Across most phase 2/3 clinical trials, individuals age 65 years and older were excluded.
Limited data therefore are available for this patient subgroup. Nevertheless, in 2 PK studies (D1001049 and D1050253) no differences in tolerability and exposure were noted between the elderly or young adult subjects.

### Patients with cardiac impairment

Patients with cardiovascular impairment were not included in the clinical development program.
Due to lack of information, lurasidone should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications).

### Pregnant or lactating women

Pregnant or lactating women were not included in the clinical development program, even if there were a number of subjects who became pregnant during a lurasidone clinical trials. Lurasidone should not be used during pregnancy unless clearly necessary. Breast feeding in women receiving Latuda should be considered only if the potential benefit of treatment justifies the potential risk to the child.

### Children less than 18 years of age

There are limited data regarding children less than 18 years of age in the clinical development program.
A paediatric pharmacokinetic study and 1 six-week paediatric efficacy and safety study have completed since the time of the last version of the RMP. The completion of a second long-term efficacy and safety study is expected for April 2018.

The lurasidone SmPC reports in section 4.2 that “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”.

**Long-term safety**

Clinical trials with long-term data are available and results are reported in section 5.1 of the SmPC. However, further safety data are needed as reflected in the PASS program.

## *SVII.2 New safety concerns and reclassification with a submission of an updated RMP*

Following the unlimited renewal granted to Latuda in 2018 (EMA/CHMP/375267/2018), the CHMP recommended to remove the safety concerns *hypersensitivity*, *increased serum creatinine* and *children less than 18 years of age* from safety specifications of the RMP. It was suggested to do this in the next regulatory procedure affecting the RMP or in the next PSUR.

According to the CHMP, the risks *hypersensitivity* and *increased serum creatinine* were considered as well-characterised and appropriately managed, while *children less than 18 years of age* should be removed since populations should be included as missing information only when they are relevant for the approved indications.

Therefore, the following changes to the list of safety concerns were implemented.

The important identified risk *hypersensitivity* was removed from the list of safety concerns.

The important potential risk *increased serum creatinine* was removed from the list of safety concerns.

The missing information *children less than 18 years of age* was removed from the list of safety concerns.

**PASS outcome**

On 04DEC2020, the Category 3 PASS “Evaluation of the safety profile of lurasidone: a post-authorisation safety study using United States administrative claims databases” (EU PAS 34004) was finalized with the issue of the Clinical Study Report. This was submitted to EMA as a Type II (C.I.13) variation on 21DEC2020 and approved by the Agency on 02MAR2021.

The PASS was part of the lurasidone pharmacovigilance plan initially agreed with EMA jointly with the medicinal product marketing authorization.

The aim of this study was to evaluate the safety profile of lurasidone for treatment of schizophrenia in a real-world setting. The primary objective was to compare the incidence of important identified risks and important potential risks in patients treated with lurasidone to patients treated with other second-generation

oral atypical antipsychotics (OAAs), namely aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone.

This was a comparative, retrospective cohort study in commercially-insured and Medicaid-insured patient populations in the US. Patients newly prescribed lurasidone for the treatment of schizophrenia (lurasidone cohort) were compared to patients newly prescribed other OAAs for the treatment of schizophrenia (OAA cohort). The main analysis population (schizophrenia only) consisted of 1,447 patients in the lurasidone cohort and 34,512 patients in the OOA cohort.

The following risks were assessed.

Important identified risks

- Extrapyramidal symptoms: dystonia, akathisia, parkinsonism, and tardive dyskinesia.
- Drug interactions with strong cytochrome P-450 3A4 inhibitors: boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole; or P-450 3A4 inducers: carbamazepine, phenobarbital, phenytoin, rifampicin, and St John's wort.
- Neuroleptic malignant syndrome.

Important potential risks

- Metabolic profile: hyperglycaemia, weight increase, dyslipidaemia.
- Rhabdomyolysis.
- Suicidality: suicidal ideation, suicidal behaviour, suicide attempt or self-harm, or completed suicide
- Agranulocytosis.
- Seizures: any epileptic seizures with indication of an adverse effect of other antipsychotics and neuroleptics.
- Use with severe or moderate renal impairment: chronic kidney disease (stage 3, 4, or 5), end-stage renal disease (ESRD), or dialysis procedure.
- Use with severe or moderate hepatic impairment: any diagnosis for chronic liver diseases and cirrhosis, alcoholic liver disease, hepatic failure, chronic hepatitis, fibrosis and cirrhosis of the liver, or other inflammatory liver disease in combination with one or more of the following: medications (e.g., diuretics, beta-blockers, medications to treat encephalopathy), or procedures (e.g., paracentesis, esophageal banding), or indication of upper gastrointestinal bleeding.
- Third trimester exposure during pregnancy.

[redacted]

Although some study limitations typical of retrospective observational studies using medical and pharmacy administrative claims were identified, the lurasidone safety profile observed in this study resulted comparable to that of the other second-generation OAAs.

Indeed, the adjusted incidence rates of important identified and potential risks were not significantly different between the two cohorts except for drug interactions, which was lower in the lurasidone cohort by approximately 36%. A significant difference in the adjusted incidence rates was found for the risk of third trimester pregnancy exposure, which was approximately 6 times greater in the lurasidone cohort. The risk of seizures was not observed in either cohort. The risk of neuroleptic malignant syndrome was observed in 1 patient in the lurasidone cohort and in no patients in the OAA cohort. These findings were substantially confirmed in the sensitivity analysis.

The analysis on subgroups was possible when important identified and potential risks were observed frequently enough to compare between the two cohorts. However, the adjusted incidence rates were not statistically significant between the two cohorts in the subgroups of elderly patients, cardiac impaired patients, severe or moderate renal impaired patients, severe or moderate hepatic impaired patients, and patients with post-index period greater than 6 months. These findings were substantially confirmed in the overall sensitivity analysis; however, some significant differences were detected in the sensitivity analysis in subgroups.

In the subgroup of pregnant women, only third trimester exposure was observed frequently enough to calculate and compare incidence rates between the two cohorts, which was significantly greater in the lurasidone cohort. This result, jointly with the outcome of the main analysis, seemingly indicates a moderate attitude of physicians in prescribing lurasidone instead of other OAAs to pregnant women in the US. The interpretation of this finding is not simple.

The European SmPC of LATUDA® states that lurasidone should not be used during pregnancy unless clearly necessary. Management of schizophrenia during pregnancy and postpartum is very challenging since the treating physicians have to take into account various factors. When considered as necessary, the choice of drug for the treatment of schizophrenia during pregnancy should depend on the careful balance between the safety and efficacy profiles.

According to the results observed in the PASS, the list of lurasidone safety concerns can be reclassified based on the definitions of the GVP guideline Module V – Risk management systems (Rev 2) dated March 28th, 2017 [EMA/838713/2011 Rev 2*, Section V.A.1 Terminology].

Indeed, the RMP should focus on the **important identified risks** that are likely to have an impact on the risk-benefit balance of the product. An important identified risk to be included in the RMP would usually warrant further evaluation as part of the pharmacovigilance plan or risk minimization activities (i.e., specific clinical actions reported in the product information, such as measures which are not routinely established in daily clinical practice, or additional risk minimisation activities).

[redacted]

The **important potential risks** to be included in the RMP are those important potential risks that, when further characterised and if confirmed, would have an impact on the risk-benefit balance of the medicinal product. Important potential risks included in the RMP would usually require further evaluation as part of the pharmacovigilance plan.

**Missing information** relevant to the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterised so far.

Currently, no identified or important risks are part of the lurasidone pharmacovigilance plan or risk minimization activities (i.e., specific clinical actions reported in the product information, such as measures which are not routinely established in daily clinical practice, or additional risk minimisation activities) . The routine pharmacovigilance activities, i.e. the specific adverse reaction follow-up questionnaires (see Section III.1) do not regards identified or important risks initially presented in the RMP.

Therefore, the MAH proposes to reclassify the lurasidone safety concerns as following.

The important identified risk *Extrapyramidal symptoms* should be removed from the list of safety concerns.

The important identified risk *Drug interactions with strong cytochrome P-450 3A4 inhibitors or inducers* should be removed from the list of safety concerns.

The important potential risk *Metabolic profile (hyperglycaemia, weight increased, dyslipidaemia)* should be removed from the list of safety concerns.

The important potential risk *Rhabdomyolysis* should be removed from the list of safety concerns.

The important potential risk *Suicidality (suicidal ideation, suicidal behaviour, suicide attempt, self-harm and completed suicide)* should be removed from the list of safety concerns.

The important potential risk *Agranulocytosis* should be removed from the list of safety concerns.

The important potential risk *Seizure* should be removed from the list of safety concerns.

The important potential risk *Use in patients with moderate or severe renal impairment* should be removed from the list of safety concerns.

The important potential risk *Use in patients with moderate or severe hepatic impairment* should be removed from the list of safety concerns.

The important potential risk *Off-label use: Bipolar disorder, Elderly with dementia, Doses higher than 148 mg/day Latuda (160 mg/day lurasidone hydrochloride)* should be removed from the list of safety concerns.

The missing information *Elderly patients* should be removed from the list of safety concerns.

[redacted]

The missing information *Patients with cardiac impairment* should be removed from the list of safety concerns.

The missing information *Long-term safety* should be removed from the list of safety concerns.

As recommended in the PRAC Assessment Report (EMA/122166/2022), the missing information *Third trimester exposure during pregnancy and risk to neonates* (initially considered as an important potential risk, and subsequently reclassified as missing information in version 9.0 of the RMP – not approved) is removed from the list of safety concerns.

## *SVII.3 Details of important identified risks, important potential risks, and missing information*

Based on the definitions of the GVP guideline Module V – Risk management systems (Rev 2) dated March 28th, 2017 [EMA/838713/2011 Rev 2*, Section V.A.1 Terminology], and following the results of the lurasidone PASS, currently no important identified risks or important potential risks are reported.

### *SVII.3.1. Presentation of important identified risks*

Not applicable.

### *SVII.3.2. Presentation of important potential risks*

Not applicable.

### *SVII.3.3. Presentation of the missing information*

**PREGNANT OR LACTATING WOMEN**

EVIDENCE SOURCE
Lurasidone clinical trials.

ANTICIPATED RISK/CONSEQUENCE OF THE MISSING INFORMATION
Pregnant or lactating women were not included in the clinical development program.
However, there were a number of subjects who became pregnant during a lurasidone clinical trials. Lurasidone should not be used during pregnancy unless clearly necessary. Breast feeding in women receiving Latuda should be considered only if the potential benefit of treatment justifies the potential risk to the child.
This information is reflected in the lurasidone SmPC section 4.6.

[redacted]

[redacted]

## PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1 - Summary of Safety Concerns

| **Summary of Safety Concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | Pregnant or lactating women |

# PART III: PHARMACOVIGILANCE PLAN (including post-authorization safety studies)

## *III.1 Routine pharmacovigilance activities*

This RMP section describes the routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

### SPECIFIC ADVERSE REACTION FOLLOW-UP QUESTIONNAIRES

SEVERE CUTANEOUS ADVERSE REACTIONS (SCAR)

A specific adverse event follow-up form was designed to collect structured information on SCAR, including Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Acute Generalised Exanthematous Pustulosis (AGEP).

For these adverse events, follow-up information should be collected by using a dedicated questionnaire, as reported in Annex 4. Attempts to medically confirm the information are also requested.

ANGIOEDEMA

A specific adverse event follow-up form was designed to collect structured information about angioedema. For this adverse event, follow-up information should be collected by using a dedicated questionnaire.

Potential reports of angioedema were expedited to the US FDA as 15-Day Alert reports based on the Special Reporting Requirement that was outlined in the US Approval of LATUDA in October 2010. As a result, Sunovion (the MAH in the US) established a targeted questionnaire to fully characterize angioedema and to gather as much additional information as possible. In addition, angioedema/hypersensitivity was captured as an identified risk in the lurasidone US RMP and subject to ongoing monitoring and reviews. Since the International Birth Date, Sunovion has received over 650 reports suggestive of angioedema which have not changed the current understanding of this risk.

Considering the duration that LATUDA has been commercially approved and based on the post-marketing data received, in June 2020, Sunovion requested that the FDA suspend the requirement to expedite reports of angioedema associated with the use of LATUDA. The FDA granted the waiver to suspend expedited submission of these reports in June 2021.

Accordingly, the EU MAH of LATUDA proposes to discontinue the use of the targeted questionnaire for angioedema (previously reported in Annex 4).

[redacted]

HOMICIDAL IDEATION

During the period covered by the last PBRER (28OCT2016-27OCT2017), the former MAH of Latuda identified the signal “Homicidal ideation”. It was assessed, refused, and closed. However, a targeted questionnaire was developed as a follow-up measure. The updated version 3.0 (30SEP2019) is reported in Annex 4.

**OTHER FORMS OF ROUTINE PHARMACOVIGILANCE ACTIVITIES**

Not applicable.

## *III.2 Additional pharmacovigilance activities*

On 04DEC2020, the Category 3 PASS “Evaluation of the safety profile of lurasidone: a post-authorisation safety study using United States administrative claims databases” (EU PAS 34004) was finalized with the issue of the Clinical Study Report.

The Clinical Study Report was submitted to EMA on 21DEC2020 through a Type II (C.I.13) variation and approved on 11MAR2021.

### *III.3 Summary Table of additional Pharmacovigilance activities*

Not applicable.

# PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Excluding the Paediatric Investigational Plan (PIP) described in Part II Module SIV, no planned and/or ongoing post-authorisation efficacy studies imposed by the competent authority are in place.

# PART V: RISK MINIMIZATION MEASURES

## RISK MINIMIZATION PLAN

Since important risks and one missing information have been removed from the list of safety concerns (see Part II, Module SVII.2), this part is applicable only to the current missing information.

### *V.1. Routine risk minimization measures*

| | |
|---|---|
| Pregnant or lactating women | Routine risk communication:<br>• SmPC section 4.6.<br>• PL section 2.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None<br>Other routine risk minimisation measures beyond the Product Information:<br>None |

### *V.2. Additional Risk Minimization Measures*

Not applicable.

### *V.3. Summary of risk minimization measures*

Since important risks and one missing information have been removed from the list of safety concerns (see Part II, Module SVII.2), this part is applicable only to the current missing information.

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | | |
| Pregnant or lactating women | Routine risk minimization measures:<br>• SmPC section 4.6.<br>• PL section 2.<br>Additional risk minimization measures:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | | Additional pharmacovigilance activities:<br>None |

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## Summary of risk management plan for Latuda (lurasidone)

This is a summary of the risk management plan (RMP) for Latuda. The RMP details important risks of Latuda, how these risks can be minimised, and how more information will be obtained about Latuda's risks and uncertainties (missing information).
Latuda's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Latuda should be used.
This summary of the RMP for Latuda should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Latuda's RMP.

### *I. The medicine and what it is used for*

Latuda is authorised for the treatment of schizophrenia in adults aged 18 years and adolescent aged 13 years and over (see SmPC for the full indication). It contains lurasidone as the active substance and it is given by oral route of administration.
Further information about the evaluation of Latuda's benefits can be found in Latuda's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002713/WC500164685.pdf

### *II. Risk associated with the medicine and activities to minimize or further characterize the risks*

Important risks of Latuda, together with measures to minimise such risks and the proposed studies for learning more about Latuda's risks, are outlined below.
Measures to minimise the risks identified for medicinal products are:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

[redacted]

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Latuda is not yet available, it is listed under "missing information" below.

### *II.A List of important risks and missing information*

Important risks of Latuda are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Latuda. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | Pregnant or lactating women |

### *II.B Summary of important risks*

| | |
|---|---|
| | |

| **Missing information: Pregnant or lactating women** | |
|---|---|
| Risk minimisation | Routine risk minimization measures: |

[redacted]

| **Missing information: Pregnant or lactating women** | |
|---|---|
| measures | • SmPC section 4.6.<br>• PL section 2.<br>Additional risk minimization measures:<br>None |

### *II.C Post-authorization development plan*

*II.C.1 Studies which are conditions of the marketing authorisation*

There are no studies which are conditions of the marketing authorisation or specific obligation of Latuda.

*II.C.2 Other studies in post-authorization development plan*

There are no studies required for Latuda.

## *Annex 4 – Specific adverse drug reaction follow-up forms*

**List of contents**

## Case Definition and Targeted Questionnaire:
## Stevens Johnson Syndrome (SJS)
## Toxic Epidermal Necrolysis (TEN)
### Acute Generalised Exanthematous Pustulosis (AGEP)

**General:**
A serious, severe adverse cutaneous reaction caused by a drug, is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompass all adverse events related to drug eruption, regardless of etiology.

**Stevens Johnson Syndrome (SJS)**
SJS begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters, eventually causing the top layer of the skin to die and shed.

**Toxic Epidermal Necrolysis (TEN)**
TEN also known as Lyell's syndrome, is considered a more severe form of Stevens–Johnson syndrome. The severe findings of TEN are often preceded by 1 to 2 weeks of fever. These symptoms may mimic those of a common upper respiratory tract infection. When the rash appears it may be over large and varied parts of the body.

**Acute Generalised Exanthematous Pustulosis (AGEP)**
AGEP is an acute febrile drug eruption characterized by numerous small, primarily non-follicular, sterile pustules, arising within large areas of edematous erythema. The eruption follows a self-limiting course and will end within a week once the causative agent is discontinued. It is accompanied by fever, neutrophilia, and sometimes by facial edema, hepatitis and eosinophilia. The differential diagnosis includes Stevens–Johnson syndrome (SJS), however, contrary to SJS, in AGEP, mucosa are not affected, which means that there are no blisters in the mouth or vagina.

**SJS, TEN, AGEP Cases**
Within the context of the definitions above, PTs included in the following MedDRA SMQ will help identify a potential case of SJS, TEN or AGEP *:

*Severe cutaneous adverse reactions SMQ*

*Upon medical review, if a diagnosis of SJS, TEN or AGEP is **suspected or confirmed**, cases should be **expedited to the FDA/EMA,** as applicable.

**Targeted questions:**
In addition to collecting routine information for these adverse events, please ensure the following additional information is provided and make attempts to medically confirm the information.

**Event Description:**

Time to onset of cutaneous symptoms after starting the suspected medication?

Time to onset of general systemic symptoms after starting the suspected medication?

Start and stop date(s) of skin lesion(s)

Did the patient present with any of the following signs or symptoms? **Check all that apply**

| | | |
|---|---|---|
| ☐ Rash | ☐ Joint aches | ☐ Headache |
| ☐ Blistering of rash | ☐ Visual symptoms | ☐ Body aches |
| ☐ Desquamation (skin loss)/skin peeling | ☐ Eating/Swallowing difficulties | ☐ Electrolyte imbalances |
| ☐ General ill feeling | ☐ Genital lesions | ☐ Fever |
| ☐ Involvement of mucous membrane | ☐ Chills | |
| ☐ Infiltration | ☐ Cough | ☐ **Other, specify**..... |
| ☐ Itching | ☐ Necrosis | ☐ **None of the above** |

Description of the lesion (e.g. erythematous, vesicular, pustular, target lesions)

Part(s) of the body affected and estimated percentage of body surface area involved

## Case Definition and Targeted Questionnaire:
## Stevens Johnson Syndrome (SJS)
## Toxic Epidermal Necrolysis (TEN)
### Acute Generalised Exanthematous Pustulosis (AGEP)

Was there any involvement of the mucous membranes?
☐ **Yes** *(please describe)* ☐ **No** ☐ **Unknown**

Was the rash associated with any other systemic symptoms or abnormalities?
☐ **Yes** *(please describe)* ☐ **No** ☐ **Unknown**

**Patient History:**
Does the patient have a history of previous allergies to drugs? ☐ **Yes** *(please list)* ☐ **No** ☐ **Unknown**

Does the patient have a history of any of the following prior to the start of the suspect drug?
**Check all that apply**

☐ Herpes simplex
☐ Streptococcal infection
☐ Immunization
☐ HIV
☐ Influenza
☐ Typhoid
☐ Excessive UV light exposure
☐ Carrying HLA-B12 gene
☐ Psoriasis
☐ Staphylococcal infection
☐ Mycoplasma pneumonia
☐ Bone marrow or organ transplant
☐ Non-drug allergy *(please specify)*
☐ Hepatitis
☐ Diphtheria
☐ Radiation therapy
☐ Systemic lupus erythematosus
☐ Other relevant history *(please specify)*
☐ **None of the above**

Was the patient taking any of the following drugs concomitantly?
**Check all that apply**

| Anticonvulsants | Antipsychotics | Others |
|---|---|---|
| ☐ Carbamazepine (e.g. Tegretol) | ☐ Aripirazole (e.g., Abilify) | ☐ Allopurinol |
| ☐ Barbiturates | ☐ Asenapine (e.g. Sapharis) | ☐ Corticosteroids |
| ☐ Felbamate (e.g. Felbatol) | ☐ Iloperidone (e.g. Fanapt) | ☐ NSAIDS |
| ☐ Lamotrigine (e.g. Lamictal) | ☐ Olanzapine (e.g. Zyprexa) | ☐ Paracetamol |
| ☐ Phenytoin (e.g. Dilantin) | ☐ Paliperidone (e.g. Invega) | ☐ Sulfonamides |
| ☐ Valproic acid (e.g. Depakene, Depakote, Valparin) | ☐ Quetiapine (e.g. Seroquel) | ☐ Non-sulfonamide antibiotics |
| | ☐ Ziprasidone (e.g. Geodon) | ☐ Tetracyclines |
| ☐ **None of the above** | | ☐ Oral antinfungals |
| ☐ **Any Other** | | ☐ Hydroxycholoroquine |

Any other, specify..... ..... .....

**Diagnostic Tests:**
Were any of the following diagnostic tests performed?
**Check all that apply and specify which test(s), and include all applicable and significant laboratory results**

☐ Skin biopsy
☐ Microscopic examination of skin
☐ Genetic test
►Was genotyping of HLA (Human Leukocyte Antigen) done? ☐ Yes ☐ No ☐ Unknown
HLA types identified? If so, specify: _____

**Was there a final diagnosis?** _____

☐ **Yes** *(please describe and whether it was confirmed by a dermatologist* ☐ **No** ☐ **Unknown**

## Case Definition and Targeted Questionnaire: Homicidal Ideation and Homicide

**Homicidal Ideation and Homicide in patients who are under Lurasidone treatment**

As a routine pharmacovigilance activity (additional data collection using a targeted questionnaire), any adverse events indicative of homicidal ideation/homicide which are reported to the DSP Group Companies from any source (solicited and non-solicited) will be actively followed-up with the targeted questions below in an effort to ensure that all data in the global safety database pertaining to Lurasidone and homicide/homicidal ideation is consistent, comprehensive and of a quality which will facilitate robust routine pharmacovigilance monitoring of this topic.

Adverse events coded to the following MedDRA PT terms are considered indicative of Homicidal ideation/ Homicide. If any of these terms appear please check the box on the list below and initiate case follow up for additional information using this targeted questionnaire.

- Search criteria for Homicidal ideation (based on MedDRA SMQ for Hostility/aggression)

☐ Aggression
☐ Anger
☐ Antisocial behaviour
☐ Belligerence
☐ Defiant behaviour
☐ Homicidal ideation
☐ Homicide
☐ Hostility
☐ Physical abuse
☐ Physical assault
☐ Violence-related symptom

**For consumer report, please request occurrence of homicide/homicidal ideation to be confirmed by a health care provided**

**Event Description:**

1. Was the patient receiving LATUDA (lurasidone) at the time of occurrence of the homicide/homicidal ideation?

   ☐ Yes
   ☐ No
   ☐ Unknown

2. Was the patient compliant (against prescription instructions) with administering LATUDA (lurasidone) at the time of occurrence of homicide/homicidal ideation?

   ☐ Yes
   ☐ No *(please describe non-compliance)* _____
   ☐ Unknown

3. Please provide detail on any other suspect medication(s) below (please include any other antipsychotic medications):

   - Suspect medication #1
     Name:_____ Dose:_____

     Start date: _____ (MM/DD/YYYY) Stop date:_____ (MM/DD/YYYY)

Case Definition and Targeted Questionnaire:
Homicidal Ideation and Homicide

- Suspect medication #2
  Name:_____ Dose:_____
  Start date: _____ (MM/DD/YYYY) Stop date:_____ (MM/DD/YYYY)
- Suspect medication #3
  Name:_____ Dose:_____
  Start date: _____ (MM/DD/YYYY) Stop date:_____ (MM/DD/YYYY)

4. Was the patient compliant with other prescription/concomitant medications at the time of occurrence of homicide/homicidal ideation?

   ☐ Yes
   ☐ No *(please describe non-compliance)* _____
   ☐ Unknown

5. Was LATUDA (lurasidone) discontinued due to the event?

   ☐ Yes
   ☐ No
   ☐ Unknown

6. Upon discontinuation of LATUDA (lurasidone) did the homicidal activities/homicidal ideations resolve?

   ☐ Yes
   ☐ No
   ☐ Unknown

7. Was the patient psychotic at the time of the event?

   ☐ Yes
   ☐ No
   ☐ Unknown

Patient History:

8. Does the patient have a history of homicide/homicidal ideation:

   ☐ Yes *(please describe relevant history)* _____
   ☐ No
   ☐ Unknown

**Case Definition and Targeted Questionnaire:**
**Homicidal Ideation and Homicide**

9. Does the patient have a history of drug abuse/alcohol abuse:

☐ Yes *(please describe relevant history)* _____
☐ No
☐ Unknown

10. Does the patient have a history of violent behaviour:

☐ Yes *(please describe relevant history)* _____
☐ No
☐ Unknown

11. Does the patient have a family history of violence?

☐ Yes *(please describe relevant history)* _____
☐ No
☐ Unknown

Concomitant Medications:

12. Has the patient taken antipsychotic medications prior to administration of LATUDA (lurasidone):

☐ Yes *(please describe previous antipsychotic use)* _____
☐ No
☐ Unknown



[redacted]

## *Annex 6 – Details of proposed additional risk minimisation activities*

Not applicable.