HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

# TRANSPARENCY COMMITTEE

## Opinion
## 19 November 2014

## LATUDA 18.5 mg, film-coated tablet
**B/28 (CIP: 3400927887130)**
## LATUDA 37 mg, film-coated tablet
**B/28 (CIP: 3400927887369)**
## LATUDA 74 mg, film-coated tablet
**B/28 (CIP: 3400927887420)**

Applicant: TAKEDA

| | |
|---|---|
| INN | lurasidone |
| ATC code | N05AE05 (antipsychotics) |
| Reason for the request | **Inclusion** |
| Lists concerned | **National Health Insurance (French Social Security Code L.162-17)**<br>**Hospital use (French Public Health Code L.5123 2)** |
| Indication concerned | **“LATUDA is indicated for the treatment of schizophrenia in adults aged 18 years and over. "** |

| | |
|---|---|
| **Actual Benefit** | **The actual benefit of LATUDA is substantial in the treatment of schizophrenia in adults aged 18 years and over.** |
| **Improvement in Actual Benefit** | **LATUDA does not provide an improvement in actual benefit (level V, non-existent) in the treatment of schizophrenia in adults.** |

# 01 ADMINISTRATIVE AND REGULATORY INFORMATION

| | |
|---|---|
| Marketing Authorisation (centralised procedure) | 21/03/2014 |
| Prescribing and dispensing conditions/ special status | List I |

| | |
|---|---|
| ATC Classification | N Nervous system<br>N05 Psycholeptics<br>N05A Antipsychotics<br>N05AE05 lurasidone |

# 02 BACKGROUND

This is an application for inclusion for reimbursement for LATUDA, a new oral antipsychotic in the treatment of schizophrenia in adults.

# 03 THERAPEUTIC INDICATION

“LATUDA is indicated for the treatment of schizophrenia in adults aged 18 years and over."

# 04 DOSAGE

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

LATUDA tablets are to be taken with meals.

Note: lurasidone is metabolised mainly by CYP3A4. Co-administration of potent CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) with potent CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort [Hypericum perforatum]) is contraindicated.

# 05 THERAPEUTIC NEED

Schizophrenia is a psychiatric disease that is characterised by the presence, to various degrees, of delirium, hallucinations, disorganised thinking and mental impoverishment.
Schizophrenia is a severe disease given the handicap it causes, the age of onset (late adolescence, young adulthood) and its personal, social, familial or professional impact. Its progression is most often chronic, due to residual or relapsing symptoms that are common in the disease. It is often associated with many psychiatric and somatic comorbidities.

The treatment of schizophrenia is comprehensive, combining pharmacological treatment and non-drug measures (psychological care, support measures and socio-professional reintegration).

Antipsychotics are the standard pharmacological treatment for schizophrenia.

# 06 CLINICALLY RELEVANT COMPARATORS

## 06.1 Medicinal products

The clinically relevant comparators for LATUDA are the other antipsychotics indicated in the treatment of schizophrenia:

- Eighteen oral antipsychotics (6 second generation and 12 first generation (see Table 1);
- Eight injectable antipsychotics in the maintenance treatment of schizophrenia (see Table 2).

**Table 1. Oral antipsychotics indicated in the treatment of schizophrenia.**

| Name (INN) | Company | Date of latest TC Opinion | AB | IAB | Reimbursed |
|---|---|---|---|---|---|
| **Second-generation antipsychotic** | | | | | |
| **XEROQUEL** (quetiapine XR) | Astra-Zeneca | 30/11/2011 and 14/03/2012 (re-assessment) | Substantial | IAB III in treatment | Yes (NHI/Hospital) |
| **ABILIFY** (aripiprazole) | Otsuka | | | | |
| **RISPERDAL, RISPERDALORO and generics** (risperidone) | Jannsen Cilag | | | | |
| **SOLIAN and generics** (amisulpiride) | Sanofi | | | | |
| **LEPONEX and generics**[$] (clozapine) | Novartis | | | | |
| **ZYPREXA, ZYPREXA VELOTAB** (olanzapine) | Lilly | 11/04/2012 (RI) | | | |
| **First-generation antipsychotic** | | | | | |
| **LOXAPAC** (loxapine) | Eisai | 07/11/2012 (RI) | Substantial | Not assessed | Yes (NHI/Hospital) |
| **HALDOL and generics** (haloperidol) | Janssen Cilag | | | | |
| **ORAP** (pimozide) | | | | | |
| **FLUANXOL** (flupentixol) | Lundbeck | | | | |
| **CLOPIXOL** (zuclopenthixol) | | | | | |
| **TERCIAN** (cyamemazine) | Sanofi | | | | |
| **LARGACTIL** (chlorpromazine) | | | | | |
| **MODITEN** (fluphenazine) | | | | | |
| **NOZINAN** (levomepromazine) | | | | | |
| **PIPORTIL** (pipotiazine) | | | | | |
| **NEULEPTIL** (propericiazine) | | | | | |
| **DOGMATIL and generics** (sulpiride) | | | | | |

[$] *indicated as second-line treatment in treatment-resistant patients or patients with severe neurological adverse events with other antipsychotics; RI: renewal of inclusion*

**Table 2. Injectable antipsychotics indicated in the maintenance treatment of schizophrenia.**

| Name (INN) | Company | Date of latest TC Opinion | AB | IAB | Reimbursed |
|---|---|---|---|---|---|
| **Second-generation antipsychotic** | | | | | |
| **ABILIFY MAINTENA** (aripiprazole) | Otsuka | 23/04/2014 (Inclusion) | Substantial | IAB V | In progress |
| **XEPLION** (paliperidone palmitate) | Janssen Cilag | 01/02/2012 (Inclusion) | | IAB V | Yes (NHI/Hospital) |
| **RISPERDALCONSTA LP** (risperidone) | | 19/02/2014 (RI) | | IAB IV | |

| | | | | | |
|---|---|---|---|---|---|
| **ZYPADHERA** (olanzapine) | Lilly | 23/09/2009 (Inclusion) | Moderate | IAB V | Yes (Hospital use) |
| **First-generation antipsychotic** | | | | | |
| **FLUANXOL LP** (flupentixol) | Lundbeck | 07/11/2012 (RI) | Substantial | Not assessed | Yes (NHI/Hospital) |
| **HALDOL DECANOAS** (haloperidol) | Janssen Cilag | | | | |
| **MODECATE** (fluphenazine) | Sanofi Aventis | 23/03/2012 (RI) | | | |
| **PIPORTIL** (pipotiazine) | Sanofi Aventis | 11/04/2012 (RI) | | | |

*RI: renewal of inclusion*

## Conclusion

**The clinically relevant comparators for LATUDA are antipsychotics indicated in the treatment of schizophrenia.**

# 07 ANALYSIS OF AVAILABLE DATA

## 07.1 Efficacy

The efficacy of LATUDA was evaluated in six controlled studies:
- three short-term (6 weeks) placebo-controlled studies in the treatment of acute episodes of schizophrenia:
    - o PEARL 1 (D1050229),
    - o PEARL 2 (D1050231),
    - o PEARL 3 (D1050233).
- three 7 to 12-month studies in the maintenance treatment of schizophrenia:
    - o one placebo-controlled study (D105238),
    - o one risperidone-controlled non-inferiority study (D105237),
    - o one quetiapine XR-controlled non-inferiority study in patients who participated in PEARL 3 (D1050234).

The following studies will not be detailed in the opinion:
- the non-comparative extension phases of PEARL 1 and 2 (D1050229 and D1050231) and D105237;
- an open-label study in patients switched from other antipsychotics for a 6-week duration followed by a 24-week extension phase.[1]

In clinical studies, the lurasidone doses are expressed in lurasidone hydrochloride (20, 40, 80, 120 and 160 mg of lurasidone hydrochloride corresponding to 18.5, 37, 74, 111 and 148 mg of lurasidone active ingredient).

### 7.1.1 Treatment of acute episodes of schizophrenia

#### 7.1.1.1 Methodology of placebo-controlled studies

PEARL 1, PEARL 2 and PEARL 3 are multicentre, randomised, double-blind, placebo-controlled superiority studies.

The objective was to evaluate the efficacy of lurasidone compared with placebo in the treatment of acute episodes of schizophrenia.

Subjects included, in particular:
- were adults with schizophrenia (DSM-IV) for at least 1 year with an acute exacerbation of psychotic symptoms associated with a pronounced worsening of their functional status or hospitalised for this exacerbation;
- had a total baseline PANSS score[2] ≥ 80 with a score ≥ 4 (moderate) in at least two of the following five items: delusions, conceptual disorganisation, hallucinations, thoughts of unusual nature and hostility;
- had a CGI-S score[3] ≥ 4.

The PEARL studies were conducted in three phases:

[1] McEvoy JP et al. Effectiveness of lurasidone in patients with schizophrenia or schizoaffective disorder switched from other antipsychotics: a randomized, 6-week, open-label study. J Clin Psychiatry. 2013 Feb; 74(2): 170-9.
[2] The PANSS (Positive and Negative Syndrome Scale) contains 30 items, scored from 1 (no symptoms) to 7 (extremely severe symptoms), divided into 3 groups: 7 items are part of a positive scale, 7 other items of a negative scale and the remaining 16 are a general psychopathology scale.
[3] The CGI-S (Clinical Global Impression–Severity) scale is scored from 1 (not sick) to 7 (among the sickest patients). This scale permits a global assessment of the patient at a given moment.

- a 14-day screening phase,
- a 3 to 7-day washout phase during which patients no longer received antipsychotics,
- a 6-week double-blind treatment phase in which the patients must be hospitalised for at least the first 3 weeks.

The subjects were randomised into four treatment arms. Several fixed doses of lurasidone between 40 mg/day (PEARL 1 AND 2) and 160 mg/day (PEARL 3) were evaluated (see Table 3). PEARL 2 and 3 included an active-controlled arm treated with olanzapine (PEARL 2) or quetiapine XR (PEARL 3).

**Table 3. PEARL treatment arms**

| Study | Treatments studied |
|---|---|
| PEARL 1 | - lurasidone 40 mg/day (fixed dose)<br>- lurasidone 80 mg/day (fixed dose)<br>- lurasidone 120 mg/day (fixed dose) after 3 days of treatment with lurasidone 80 mg/day<br>- placebo |
| PEARL 2 | - lurasidone 40 mg/day (fixed dose)<br>- lurasidone 120 mg/day (fixed dose)<br>- placebo<br>- control arm treated with olanzapine at the dose of 15 mg/day (fixed dose) after 7 days of treatment with the 10 mg/day dose. |
| PEARL 3 | - lurasidone 80 mg/day (fixed dose)<br>- lurasidone 160 mg/day (fixed dose) after 2 days of treatment with lurasidone 120 mg/day<br>- placebo<br>- control arm treated with quetiapine XR 600 mg/day (fixed dose) after 2 days of treatment with quetiapine XR 300 mg/day |

The primary efficacy endpoint in these three studies was the change in PANSS score between baseline and after 6 weeks of treatment.

It was planned to include 120 patients per group to detect a difference between lurasidone 40, 80, 120/160 mg/day and placebo of, respectively, 6.8, 8.0 and 10.0 points in the PANSS score at 6 weeks with a power > 80% (these differences were based on the results of the phase II studies D1050006 and D1050196).

#### 7.1.1.2 Results

**a) PEARL 1**[4]

A total of 500 patients were randomised. There were 30% to 33% early withdrawals in the lurasidone arm and 43% in the placebo arm. The main reason for withdrawal was insufficient clinical response (16, 6 and 15% in the lurasidone 40 mg, 80 mg and 120 mg groups versus 25% in the placebo group).
Lurasidone was superior to placebo in reducing the PANSS score at the dose of 80 mg but not at the dose of 40 mg or 120 mg (see Table 4).

[4] Nasrallah HA et al. Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomized, placebo-controlled study. J Psychiatr Res. 2013; 47: 670-7.

**Table 4. Change in total PANSS score in PEARL 1 (ITT population)**

| | Lurasidone 40 mg (N=121) | Lurasidone 80 mg (N=118) | Lurasidone 120 mg (N=123) | Placebo (N=124) |
|---|---|---|---|---|
| **Total PANSS score mean ± SD** | 96.6 ± 11.5 | 95.6 ± 10.2 | 95.8 ± 9.5 | 96.8 ± 11.1 |
| **Change in total PANSS score between baseline and after 6 weeks of treatment** | | | | |
| Mean (SD) | -19.2 (1.7) | -23.4 (1.8) | -20.5 (1.8) | -17.0 (1.8) |
| 95% CI | (-22.6; -15.7) | (-26.9; -19.9) | (-24.0; -17.1) | (-20.5; -13.6) |
| **Difference versus placebo after 6 weeks** | | | | |
| Mean (SD) | -2.1 (2.5) | -6.4 (2.5) | -3.5 (2.5) | |
| 95% CI | (-7.0; 2.8) | (-11.3; -1.5) | (-8.4; 1.4) | |
| p | 0.394 | 0.011 | 0.163 | |

*Means, SDs, CIs and p values obtained using a mixed model repeated measures (MMRM) approach with an unstructured covariance matrix with a fixed effect for all sites, time, total PANSS score at baseline, treatment and treatment-time interaction*

### b) PEARL 2

A total of 478 patients were randomised. Early withdrawals were 36% in the lurasidone 40 mg arm, 45% in the lurasidone 120 mg arm, 32% in the olanzapine arm and 39% in the placebo arm. The main reason for withdrawing was an insufficient clinical response and the occurrence of adverse events.

Lurasidone was superior to placebo in reducing the PANSS score at the dose of 40 mg or 120 mg (see Table 5).

Olanzapine was also superior to placebo in reducing the PANSS score at 6 weeks. No comparison was done between lurasidone and olanzapine.

**Table 5. Change in total PANSS score in PEARL 2 (ITT population)**

| | Lurasidone 40 mg (N=119) | Lurasidone 120 mg (N=118) | Olanzapine 15 mg (N=122) | Placebo (N=114) |
|---|---|---|---|---|
| **Total PANSS score mean ± SD** | 96.6 ± 10.7 | 97.9 ± 11.3 | 96.3 ± 12.2 | 95.8 ± 10.8 |
| **Change in total PANSS score between baseline and after 6 weeks of treatment** | | | | |
| N | 118 | 118 | 121 | 114 |
| Mean (SD) | -25.7 (2.0) | -23.6 (2.1) | -28.7 (1.9) | -16.0 (2.1) |
| 95% CI | (-29.6; -21.8) | (-27.8; -19.4) | (-32.4; -24.9) | (-20.1; -12.0) |
| **Difference versus placebo after 6 weeks** | | | | - |
| Mean (SD) | -9.7 (2.9) | -7.5 (3.0) | -12.6 (2.8) | |
| 95% CI | (-15.3; -4.1) < | (-13.4; -1,7) | (-18.2; -7.1) | |
| p | 0.001 | 0.011 | < 0.001 | |

*Means, SDs, CIs and p values obtained using a MMRM approach with an unstructured covariance matrix with a fixed effect for all sites, time, total PANSS score at baseline, treatment and treatment-time interactions*

### c) PEARL 3

A total of 488 patients were randomised. Early withdrawals were 29% in the lurasidone 80 mg arm, 23% in the lurasidone 160 mg arm, 19% in the quetiapine XR arm and 39% in the placebo arm. The main reason for withdrawing was an insufficient clinical response and the occurrence of adverse events.

Lurasidone was superior to placebo in reducing the PANSS score at the dose of 80 mg or 160 mg (see Table 6).

Quetiapine XR was also superior to placebo in reducing the PANSS score at 6 weeks. No comparison was done between lurasidone and quetiapine.

**Table 6. Change in total PANSS score in PEARL 3 (ITT population)**

| | Lurasidone 80 mg (N=125) | Lurasidone 160 mg (N=121) | Quetiapine XR 600 mg (N=116) | Placebo (N=120) |
|---|---|---|---|---|
| **Total PANSS score mean ± SD** | 97.7 ± 9.7 | 97.5 ± 11.8 | 97.7 ± 10.2 | 96.6 ± 10.2 |
| **Change in total PANSS score between baseline and after 6 weeks of treatment** | | | | |
| N | 125 | 121 | 116 | 120 |
| Mean (SD) | -22.2 (1.8) | -26.5 (1.8) | -27.8 (1.8) | -10.3 (1.8) |
| 95% CI | (-25.7; -18.7) | (-30.0; -23.0) | (-31.3; -24.2) | (-13.9; -6.7) |
| **Difference versus placebo after 6 weeks** | | | | - |
| Mean (SD) | -11.9 (2.6) | -16.2 (2.5) | -17.5 (2.6) | |
| 95% CI | (-16.9; -6.9) | (-21.2; -11.2) | (-22.5; -12,4) | |
| p | < 0.001 | < 0.001 | 0.001 | |

*Means, SDs, CIs and p values obtained using a MMRM approach with an unstructured covariance matrix with a fixed effect for all sites, time, total PANSS score at baseline, treatment and treatment-time interactions*

### 7.1.2 Maintenance treatment of schizophrenia

#### 7.1.2.1 Treatment discontinuation study

#### a) Study design

Study D1050238 is a multicentre, randomised, double-blind, placebo-controlled "treatment discontinuation" superiority study lasting 28 weeks.

The objective was to evaluate the efficacy of lurasidone in maintenance treatment compared with placebo in patients with schizophrenia.

Subjects included, in particular:
- were adults with schizophrenia (DSM-IV) for at least 1 year,
- had had at least one acute exacerbation of psychotic symptoms during the previous 2 years,
- had a total baseline PANSS score2 ≥ 80 with a score ≥ 4 (moderate) in at least two of the following five items: delusions, conceptual disorganisation, hallucinations, thoughts of unusual nature and hostility;
- had a CGI-S score[3] ≥ 4.

After an open-label stabilisation phase of 12 to 24 weeks during which patients were treated with lurasidone between 40 and 80 mg/day (flexible dose), clinically stable patients were included in a randomised, double-blind phase for a maximum duration of 28 weeks and then in an open-label 12-week follow-up phase.

The patients were randomised into two groups (ratio 1: 1):
- lurasidone (dose corresponding to the last dose received during the stabilisation phase),
- placebo.

The primary efficacy endpoint was the time until the first recurrence of psychotic symptoms.
The recurrence of psychotic symptoms was defined as presenting at least one of the following signs during the double-blind phase:
- worsening ≥ 25% of the total PANSS score compared with the baseline value and ≥ 1 point of the CGI-S score,
- a PANSS score ≥ 5 on the following items: hostility or non-cooperation or a PANSS score ≥ 5 in at least 2 of the following 4 items: thoughts of unusual nature, delusions, conceptual disorganization, hallucinatory activity,
- initiation of a new antipsychotic treatment, initiation or increase of the dose of an antidepressant or mood stabilizer, increase in lorazepam (or equivalent) doses ≥ 2 mg/day for at least 3 days, transfer into a higher level psychiatric unit, initiation of electroshock therapy,

- insufficient clinical response reported as an adverse event,
- deliberate self harm or repeated aggressive behavior,
- suicidal or homicidal ideation or active attempt,
- psychiatric hospitalisation (voluntary or involuntary) related to worsening of schizophrenia.

A total of 610 patients had to be included in the open-label phase in order to randomise 244 patients in the double-blind phase (2.5 times less than the number of patients included in the open-label phase), according to the following assumptions:

- a recurrence rate of 30% in the lurasidone group and 50% in the placebo group.
- 98 recurrences had to be observed to detect a difference of 20% between the treatment groups with a statistical power of 90% during the double-blind phase.

### b) Results

A total of 676 patients were included in the open-label stabilisation phase. Among them, 285 (42%) met the clinical stability criteria and were randomised into the double-blind phase.

According to the Kaplan-Meier method, patients treated with lurasidone showed significantly lower probability of recurrence during the 7-month double-blind phase (42.2%) compared with patients who received placebo (51.2%) (hazard ratio [HR]: 0.66; 95% CI [0.45 to 0.98]; p = 0.041; see Fig. 1 and Table 7).

**Figure 1: Time until recurrence of psychotic symptoms during the double-blind phase (Kaplan-Meier method; ITT population)**

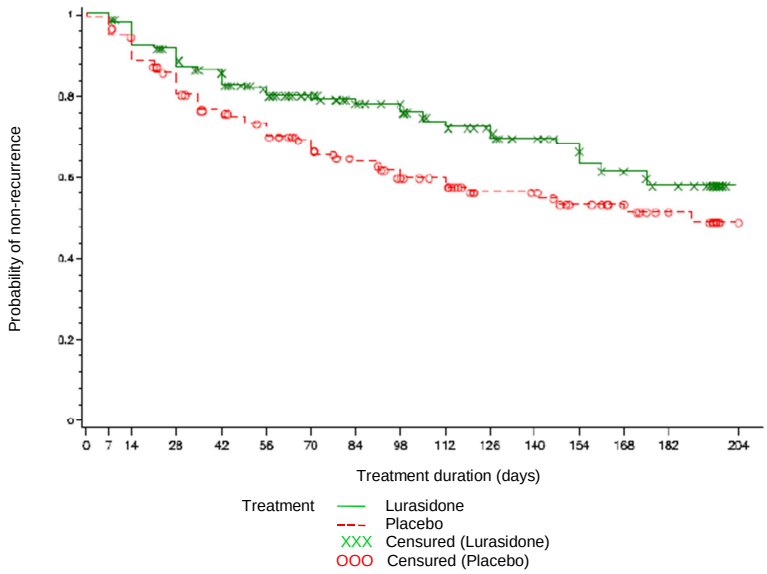

**Table 7. Time until recurrence of psychotic symptoms during the double-blind phase (ITT population)**

| | Lurasidone (N=144) | Placebo (N=141) |
|---|---|---|
| **Patients with recurrence, n (%)** | 43 (29.9) | 58 (41.1) |
| **Median time until recurrence (Kaplan-Meier)** | | |
| Time (days) | NE | 192 |
| 95% CI | (174; NE) | (113; NE) |
| **Probability of recurrence (Kaplan-Meier)** | | |
| At 1 month | 0.092 | 0.152 |
| At 2 months | 0.183 | 0.284 |
| At 3 months | 0.219 | 0.355 |
| At 4 months | 0.265 | 0.404 |
| At 5 months | 0.305 | 0.439 |
| At 6 months | 0.387 | 0.468 |
| At 7 months | 0.422 | 0.512 |
| **Log-rank test** | | |
| p | 0.039 | |
| **Cox model** | | |
| HR | 0.66 | |
| 95% CI | (0.45; 0.98) | |
| p | 0.041 | |

#### 7.1.2.2 Risperidone-controlled study

### a) Study design

Study D1050237[5] is a 12-month, multicentre, randomised, double-blind, risperidone-controlled non-inferiority study.

The primary objective was safety.
Evaluating the efficacy of lurasidone compared with risperidone in maintenance treatment of schizophrenia was a secondary objective.

The subjects included were adults with schizophrenia, clinically stable for at least 8 weeks.

The efficacy endpoint was the time until the first recurrence of psychotic symptoms.
Recurrence was defined as presenting at least one of the following signs:
- worsening ≥ 30% of the total PANSS score since baseline and
- CGI-S score ≥ 3,
- re-hospitalisation for worsening of psychosis,
- appearance of suicidal and/or homicidal ideation, appearance of risks of self-harm or harm to others.

The subjects included were randomised into two groups (ratio 2: 1):
- lurasidone 80 mg/day for 7 days and then possible adjustment between 40 and 120 mg/day;
- risperidone 2 mg/day for 2 days and then 4 mg/day for 5 days and then possible adjustment between 2 and 6 mg/day.

The number of subjects required was 600 patients (400 in the lurasidone group and 200 in the risperidone group) to demonstrate that lurasidone was as effective as risperidone on preventing recurrence at 1 year with a power of 85% using a non-inferiority margin of 1.6 for the 95% CI upper bound of the HR.

[5] Citrome L et al. Long-term safety and tolerability of lurasidone in schizophrenia: a 12-month, double-blind, active-controlled study. Int Clin Psychopharmacol. 2012; 27: 165-76.

### b) Results

A total of 629 patients were randomised. There were 65% early withdrawals in the lurasidone arm and 52% in the risperidone arm. The main reasons for withdrawal were withdrawal of consent and occurrence of adverse events.
According to Kaplan-Meier analysis, the probability of recurrence at 12 months was 26.5% in the lurasidone group and 21.0% in the risperidone group (HR: 1.31; 95% CI [0.87 to 1.97]).

It was not possible to conclude on the non-inferiority of lurasidone compared with risperidone. According to the study authors, the study is inconclusive given the small percentage of recurrence observed.

#### 7.1.2.3 PEARL 3 quetiapine-controlled extension study

### a) Study design

Patients who finished PEARL 3 were invited to participate in a 12-month double-blind extension study (D1050234[6]).

The main objective was to evaluate the efficacy of lurasidone compared with quetiapine XR in the maintenance treatment of schizophrenia.

The primary efficacy endpoint was the time to recurrence of psychotic symptoms defined as the first presentation of the following signs:
- worsening ≥ 30% of the total PANSS score compared with the value collected on day 42 of PEARL 3 and CGI-S score ≥ 3,
- re-hospitalisation for worsening of psychosis,
- appearance of suicidal and/or homicidal ideation, appearance of risks of self-harm or harm to others.

Lurasidone was declared as effective as quetiapine XR in preventing recurrence if the 95% CI upper bound of the HR for lurasidone versus quetiapine XR was not higher than the margin of non-inferiority of 1.93.

### b) Results

In all, 292 out of the 353 patients who finished PEARL 3 were included in the extension study (PEARL 3-extension). These were:
- 151 patients initially treated with lurasidone (80 mg or 160 mg) in PEARL 3 and continuing lurasidone in the extension study,
- 85 patients from the quetiapine XR 600 mg arm and continuing treatment with quetiapine XR,
- 56 patients from the placebo arm who were then treated with lurasidone.

An adjustment of the lurasidone and quetiapine doses was allowed (40 to 160 mg/day for lurasidone and 200 to 800 mg/day for quetiapine).
Among the 292 patients included in the PEARL 3-extension study, 140 finished the study: 107 patients treated with lurasidone and 33 treated with quetiapine XR.

According to Kaplan-Meier analysis, the probability of recurrence at 12 months was 23.7% in the lurasidone group and 33.6% in the quetiapine XR group (HR: 0.728; 95% CI [0.410 to 1.295]).

As the upper CI bound was below the predefined non-inferiority margin, the non-inferiority of lurasidone was demonstrated versus quetiapine XR in the prevention of psychotic recurrences.

[6] Loebel A et al. Effectiveness of lurasidone versus quetiapine XR for relapse prevention in schizophrenia: a 12-month, double-blind, noninferiority study. Schizophr Res. 2013 Jun; 147(1): 95-102.

# 07.2 Adverse events

## 7.2.1 Data from placebo-controlled studies at 6 weeks

The data from 7 phase 2 and 3 placebo-controlled clinical studies were grouped for a total of 2594 patients, of whom 1508 were treated with lurasidone.[7]
The percentage of patients with a treatment-related adverse events treatment was 44.8% in the lurasidone group and 32.2 % in the placebo group.
The most commonly observed adverse events with lurasidone were akathisia, drowsiness and sedation (see Table 8).

**Table 8. Incidence of treatment-related adverse events reported in ≥ 2% of patients treated with lurasidone in placebo-controlled clinical studies at 6 weeks***

| | Placebo (N=708) | Lurasidone (N=1508) | Olanzapine (N=122) | Quetiapine XR 600 mg (N=119) |
|---|---|---|---|---|
| **At least one adverse event** | 228 (32.2) | 675 (44.8) | 67 (54.9) | 45 (37.8) |
| Akathisia | 19 (2.7) | 184 (12.2) | 9 (7.4) | 2 (1.7) |
| Drowsiness | 19 (2.7) | 119 (7.9) | 11 (9.0) | 15 (12.6) |
| Sedation | 24 (3.4) | 113 (7.5) | 19 (15.6) | 5 (4.2) |
| Nausea | 26 (3.7) | 109 (7.2) | 5 (4.1) | 4 (3.4) |
| Insomnia | 29 (4.1) | 79 (5.2) | 6 (4.9) | 3 (2.5) |
| Vomiting | 26 (3.7) | 75 (5.0) | 2 (1.6) | 4 (3.4) |
| Parkinsonism | 3 (0.4) | 63 (4.2) | 7 (5.7) | 4 (3.4) |
| Vertigo | 8 (1.1) | 53 (3.5) | 3 (2.5) | 14 (11.8) |
| Dystonia | 3 (0.4) | 43 (2.9) | 1 (0.8) | 1 (0.8) |
| Tremor | 14 (2.0) | 42 (2.8) | 6 (4.9) | 1 (0.8) |
| Dyspepsia | 18 (2.5) | 40 (2.7) | 6 (4.9) | 2 (1.7) |
| Agitation | 14 (2.0) | 37 (2.5) | 1 (0.8) | 3 (2.5) |
| Anxiety | 14 (2.0) | 38 (2.5) | 4 (3.3) | 0 |
| Fatigue | 11 (1.6) | 33 (2.2) | 2 (1.6) | 0 |
| Salivary hypersecretion | 5 (0.7) | 31 (2.1) | 0 | 0 |
| Musculoskeletal stiffness | 10 (1.4) | 30 (2.0) | 3 (2.5) | 0 |

*Among these 7 clinical studies, there were arms with risperidone and haloperidol as active comparators. The adverse events of these groups are not detailed in the table above.

## 7.2.2 Safety data from long-term studies

### a) Active-controlled studies (D1050237 and D1050234)

The data from the risperidone-controlled (D1050237) and quetiapine XR-controlled (D1050234) comparative studies were grouped (624 patients treated with lurasidone).
The adverse events reported most frequently with lurasidone were:
- akathisia (13.6% of patients treated with lurasidone, 2.4% and 8% for quetiapine XR and risperidone),
- nausea (13.3% for lurasidone, 2.4% and 11.1% for quetiapine XR and risperidone),
- insomnia (12.8% for lurasidone, 9.4% and 13.6% for quetiapine XR and risperidone).

Drowsiness was reported in 10.1% of patients treated with lurasidone, 4.7% of those treated with quetiapine XR and 18.1% of those treated with risperidone. Sedation was reported in 9.9% of patients treated with lurasidone, 1.2% of those treated with quetiapine XR and 14.1% of those treated with risperidone.

[7] The 7 clinical studies included phase 2 studies D1050006, D1050196 and D1060049 and phase 3 studies PEARL 1 (D1050229), PEARL 2 (D1050231), PEARL 3 (D1050233) and D1001002. All the patients included form the P23STC population (Short Term Controlled studies).

### b) Placebo-controlled study (D1050238)

In placebo-controlled study D1050238 (double-blind phase), the incidence of treatment-related adverse events was 32.6% in the lurasidone group versus 25.5% in the placebo group. The most common adverse events were similar to those reported in short-term studies.

### c) Open-label extension phase of PEARL 1 and 2.

No unexpected adverse effect was demonstrated during the extension phases of PEARL 1 and 2.

## 7.2.3 Adverse effects of interest

### a) Extrapyramidal adverse events

During clinical studies[8], 820 (25.6%) patients who received lurasidone had at least one extrapyramidal adverse event.
In short-term clinical studies*7*, the percentage of patients with an extrapyramidal adverse effect was 9.2% for placebo, 24.4% for lurasidone, 23.0% for olanzapine, 7.6% for quetiapine XR and 27.7 % for risperidone.
Two patients (< 0.1%) treated with lurasidone and included in this same population reported neuroleptic malignant syndrome.

### b) Weight gain and metabolic effects

During clinical studies*8*, weight gain was reported in 134 patients (4.2%) who received lurasidone.
In short-term clinical studies*7*, weight gain was reported in 12 patients (1.7%) on placebo, 33 patients (2.2%) treated with lurasidone, 25 patients (20.5%) for olanzapine and 12 patients (10.1%) for quetiapine XR.
In D1050237, weight gain ≥ 7% from baseline to 12 months was observed in 30 patients (7%) treated with lurasidone versus 27 patients (14%) treated with risperidone.
In PEARL 3 and its extension phase (D1050234), weight gain ≥ 7% of baseline body weight was observed in 16 patients treated with lurasidone (12.2%) versus 16 patients treated with quetiapine XR (21.9%).
Rare cases of dyslipidaemia and hyperglycaemia (< 1% of subjects treated) have been reported.

[8] Grouped safety data from 22 controlled or uncontrolled clinical studies including a total of 3202 patients treated with lurasidone. D1050238 was not included in this analysis.

## 07.3 Summary & discussion

The efficacy of lurasidone in treatment of exacerbations of schizophrenia was evaluated at 6 weeks in three placebo controlled superiority clinical studies (PEARL 1, 2 and 3):

- lurasidone at fixed doses comprised between 40 mg and 160 mg/day was more effective than placebo on reducing psychotic symptoms on the PANSS scale in PEARL 2 and 3;
- in PEARL 1, the efficacy of lurasidone compared with placebo was demonstrated for the dose of 80 mg/day but not for the two other doses studied, 40 mg/day and 120 mg/day.

The efficacy of lurasidone in the prevention of relapses in maintenance treatment of schizophrenia was evaluated in three clinical studies:

- in a 28-week placebo-controlled treatment discontinuation study, patients treated with lurasidone had a significantly lower probability of relapse (42.2%) compared with patients who received placebo (51.2%) (HR: 0.66; 95% CI [0.45 to 0.98]).
- in a 12-month risperidone-controlled non-inferiority study, the probability of relapse was 26.5% in the lurasidone group and 21.0% in the risperidone group (HR: 1.31; 95% CI [0.87 to 1.97]). It was not possible to draw a conclusion on the non-inferiority of lurasidone compared with risperidone;
- during the 12-month extension phase of PEARL 3, the probability of relapse was 23.6% in the lurasidone group and 33.6% in the quetiapine XR group (HR: 0.728; 95% CI [0.410 to 1.295]).

The most commonly reported adverse events in patients treated with lurasidone were akathisia, drowsiness and sedation.

# 08 THERAPEUTIC USE[9,10,11]

Antipsychotics are the standard pharmacological treatment for schizophrenia. They are used in acute phase treatment and in maintenance treatment in the prevention of relapses.
Antipsychotic monotherapy should be preferred.
The choice of antipsychotic takes into account the response to prior treatments, the safety profile of the antipsychotic and the susceptibility of the individual patient to adverse events.
A multidimensional approach is needed in patients with schizophrenia. Drug treatments should be combined with individual or group psychotherapy, institutional or familial management, and social interventions.

**LATUDA is a new alternative to other oral antipsychotics indicated in the treatment of schizophrenia.**

[9] Hasan A. et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. The World Journal of Biological Psychiatry, 2013; 14: 2 44.
[10] National Institute for Health and Clinical Excellence. Schizophrenia. Core interventions in the treatment and management of schizophrenia in primary and secondary care. London: NICE; 2009.
http://www.nice.org.uk/nicemedia/pdf/CG82FullGuideline.pdf.
[11] Buchanan RW et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull 2010; 36(1): 71-93.

# 09 TRANSPARENCY COMMITTEE CONCLUSIONS

**In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:**

## 09.1 Actual benefit

- Schizophrenia is a severe disease given the handicap it causes, the age of onset (late adolescence, young adulthood) and its personal, social, familial or professional impact. Its progression is most often chronic, due to residual or relapsing symptoms that are common in the disease. It is often associated with many psychiatric and somatic comorbidities.

- LATUDA is a symptomatic treatment for acute exacerbations of schizophrenia and a maintenance treatment for preventing relapses.

- The efficacy/adverse events ratio for LATUDA is high.

- There are treatment alternatives: the other antipsychotics indicated in the treatment of schizophrenia.

    - Given the other treatments available, it is not expected that the LATUDA proprietary medicinal products will have a public health impact.

**Taking account of these points, the Committee considers that the actual benefit of LATUDA is substantial.**

## 09.2 Improvement in actual benefit (IAB)

**LATUDA does not provide an improvement in actual benefit (level V, non-existent) in the treatment of schizophrenia in adults.**

## 09.3 Target population

According to data from the general scheme on 31/12/2012,[12] the prevalence of chronic conditions for schizophrenia or other psychotic disorders (CIM-10 code: F20 to F29) was 462 per 100,000 affiliates.
Extrapolated to the French population, the number of patients treated for schizophrenia as a chronic condition is estimated at approximately 300,000 people.

# 010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

### ◗ Proposed reimbursement rate: 65%

### ◗ Packaging

Packaging in a box of 28 tablets is not suitable.
The Committee wishes to reiterate that, in accordance with its deliberations of 20 July 2005, it recommends standardisation of pack sizes for treatments lasting one month to the equivalent of 30 days of treatment.

[12] Prevalence of chronic conditions on 31/12/2012 Available online: http://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/affection-de-longue-duree-ald/