18 October 2018
EMA/841602/2018
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Latuda

International non-proprietary name: lurasidone

Procedure No. EMEA/H/C/002713/II/0021

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

An agency of the European Union

© European Medicines Agency, 2018. Reproduction is authorised provided the source is acknowledged.

# Table of contents

1. Background information on the procedure ..... 3

2. Overall conclusion and impact on the benefit/risk balance ..... 3

3. Recommendations ..... 5

4. EPAR changes ..... 6

5. Introduction ..... 8

6. Clinical Efficacy aspects ..... 8

# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Aziende Chimiche Riunite Angelini Francesco S.p.A. submitted to the European Medicines Agency on 13 July 2018 an application for a variation.

The following changes were proposed:

| Variation requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.3.b | C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH | Type II | I |

Update of section 5.1 of the SmPC to add new paediatric data available in children and adolescent patients (10-17 years of age) with bipolar I disorder, upon request by CHMP following the assessment of the paediatric study D1050326 submitted according to Art. 46 procedure (EMEA/H/C/002713/P46/008).

The requested variation proposed amendments to the Summary of Product Characteristics.

# 2. Overall conclusion and impact on the benefit/risk balance

The MAH submitted this Type II Variation to update Section 5.1 of the SmPC of Latuda, in line with new paediatric data available from the clinical Study D1050326, as requested by the CHMP recommendation included in the Final Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006 (procedure no. EMEA/H/C/002713/P46/008).

In addition to the submission of the short-term study D1050326 data, the interim analysis data of an ongoing, open-label, 104 week, multicenter study (D1050302) using a data cut-off date of October 27, 2016 has also been presented.

In the EU, Latuda is only authorised for the treatment of schizophrenia in adults, ie not in paediatric patients with any indication, nor for treatment of bipolar depression in adults.

Study D1050326 was a 6-week randomized, parallel-group, double-blind, placebo-controlled, flexibly-dosed, multicenter study in children and adolescents with bipolar depression.

The study included children and adolescent patients (10-17 years of age) who met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) criteria for a major depressive episode associated with bipolar I disorder, with or without rapid cycling, and without psychotic features. Patients were randomized to flexibly dosed lurasidone 18-74 mg (equivalent to 20 80 mg lurasidone hydrochloride) once daily or placebo.

The primary endpoint was the CDRS-R total score. The key secondary efficacy measure was the Clinical Global Impression-Bipolar Version (CGI-BP-S) depression score. The endpoints and treatment duration were in line with EMA Guidelines on depression and are acceptable.

The clinical study D1050326 was well designed and well conducted.

The exposure was comparable for lurasidone and placebo: 175 vs 172 subjects.

For the primary efficacy analysis parameter, change in the CDRS-R total score from Baseline to Week 6, there was a significant treatment difference favouring lurasidone over placebo in improving depressive symptoms with LS mean change (SE) -21.0 (1.06) and -15.3 (1.08), respectively.

For the key secondary efficacy analysis parameter, change in the CGI-BP-S depression score from Baseline to Week 6, there was a significant treatment difference favoring lurasidone over placebo in improving the severity of depressive symptoms.

Significant treatment differences from placebo were observed in the lurasidone group beginning at Week 2 and maintained at each study visit through to the end of the study for both primary and key secondary efficacy endpoints.

Sensitivity analyses for the primary and key secondary endpoints showed similar results as the primary analyses.

Thus the short-term efficacy of lurasidone in the treatment of bipolar depression in children and adolescents was demonstrated in this single clinical study, although the effect was modest/moderate in this paediatric population.

However, efficacy was mainly demonstrated in the 15 to 17 years old age stratum and not in younger patients. Placebo-adjusted LS mean change from Baseline to Week 6 LOCF in CDRS-R total score for the lurasidone group was -1.8 (-5.6, 2.0) for subjects in the 10- to 14-year-old age stratum and was -8.6 (-12.4, -4.8) for subjects in the 15- to 17-year-old age stratum.

An interim analysis with a cut-off date of October 27, 2016 on study D1050302 (an ongoing, open-label, 104 week, multicenter study) has been provided. This study will evaluate the data of long-term use of lurasidone in the treatment of bipolar depression in children and adolescents. However, only 17 subjects (7.6%) have completed the 104-week study by the time of interim analysis. The provided data included too limited information to allow any reliable conclusion to be drawn at this stage. The complete CSR for this study is expected in June 2019.

Regarding safety aspect, as of October 27, 2016, a total of 283 children and adolescent subjects with bipolar depression have been exposed to lurasidone (175 subjects in the completed double-blind study D1050326 and 108 subjects newly exposed to lurasidone in the open-label extension study D1050302).

In open-label extension Study D1050302 (subjects from Study D1050326) at the data cut-off date (October 27, 2016): there is still limited experience on long-term use of lurasidone in the open-label extension study. Less than 100 patients exposed to lurasidone at least 1 year and only 17 subjects (7.6%) have completed the 104-week study by the time of interim analysis.

Safety data was assessed in the previous procedure EMEA/H/C/002713/P46/008. It was concluded that treatment with lurasidone was generally safe and well tolerated in the dose range studied (20-80 mg/day). However, the frequency for weight increased (TEAEs and MMRM analysis) was higher in the lurasidone group than in the placebo group and there was an increase in BMI in the lurasidone group compared to the placebo group. These findings are not surprising but of special importance in children and adolescents. No clinically meaningful differences for other metabolic parameters were found. The safety was in line with the safety profile of earlier experience and studies in adults.

In the current submission, while weight increased occurred more frequently in lurasidone than in placebo group (6.9% and 1.7%, respectively), it was stated that the proportion of patients with a $\geq$ 7% increase in body weight (at endpoint) was 4.0% and 5.3% for lurasidone- and placebo-treated subjects, respectively. Thus based on these figures, the effect on body weight seems inconsistent in lurasidone- and placebo-treated subjects.

No deaths occurred during the lurasidone pediatric studies summarized in this submission.

The MAH has presented /discussed the areas of clinical laboratory evaluation (including liver and renal function tests, metabolic parameters, muscle function, hormone assessments, C-reactive protein, hematology and urinalysis); vital signs, physical findings, and other observations (including growth parameters, menstrual cyclicity and Tanner staging, other clinical assessments such as effect on suicidal ideation or behavior, cognitive performance); overdose, drug abuse, withdrawal and rebound, based on D1050326 and D1050302 studies. Lurasidone did not have clinically relevant effects on vital signs or ECG assessments in these studies.

The post-marketing data summarises the exposure and safety data as of October 27, 2016. According to the MAH, there were no potential signals of unanticipated or emerging risk with exposure to lurasidone post-marketing. The safety profile does not differ from that observed in the clinical development program.

### Conclusions

The MAH provided data from the short-term study D1050326 in children and adolescents with bipolar depression, providing evidence of efficacy at least in the older age stratum (15 to 18 years). The study, failed however to show a statistically significant efficacy in younger patients (10- to 14-year-old) despite the similar size of the age strata.

The MAH is proposing to include in SmPC 5.1 the new information in children considered relevant to prescribers, even if there is no authorised indication in any subset of the paediatric population. Although the data is not deemed sufficient to support a change of the wording of the indication, it is agreed that relevant data should be presented in section 5.1 under the heading “Paediatric population”, which is in line with paediatric legislation and guidelines, and as requested by CHMP following the assessment of the paediatric study D1050326 in the previous procedure (EMEA/H/C/002713/P46/008).

The safety in the studied paediatric patients was in line with the safety profile seen in earlier experience and studies in adults, although the number of subjects and lurasidone treatment duration in the exposed children are still limited. No changes in Section 4.8 of the SmPC are recommended before further data are available based on a more extensive exposure in number of patients and duration, which was also the conclusion in the previous procedure EMEA/H/C/002713/P46/008.

## 3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.3.b | C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH | Type II | I |

Update of sections 5.1 of the SmPC to add new paediatric data available in children and adolescent patients (10-17 years of age) with bipolar I disorder, upon request by CHMP following the assessment of the paediatric study D1050326 submitted according to Art. 46 procedure (no.

EMEA/H/C/002713/P46/008). In addition, section 4.2 of the SmPC has been updated to cross refer to section 5.1.

☒ is recommended for approval.

### *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I are recommended.

## 4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

### *Scope*

Please refer to the Recommendations section above

### *Summary*

For study D1050326 the primary efficacy endpoint was defined as the mean change from baseline to Week 6 in Children's Depression Rating Scale, Revised (CDRS-R) Total Score. The key secondary endpoint was Clinical Global Impression – Bipolar Version, Severity of Illness (CGI-BP-S) Depression Score. Statistically significant differences favouring lurasidone over placebo were shown for these endpoints for the total population studied, beginning at Week 2 and were maintained at each study visit through to the end of the study. However, the primary and key secondary efficacy endpoints were not met in younger patients (below 15 years of age).

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

Based on these paediatric data sections 4.2 and 5.1 of the SmPC have been updated accordingly.

# Annex: Rapporteur's assessment comments on the type II variation

# 5. Introduction

Lurasidone hydrochloride (lurasidone) tablets for oral administration was approved in the EU for the treatment of schizophrenia in adults aged 18 years and over.

The MAH submitted this Type II Variation to update Section 5.1 of the SmPC of Latuda, in line with new paediatric data available from the clinical Study D1050326, as requested by the CHMP recommendation included in the Final Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006 (procedure no. EMEA/H/C/002713/P46/008).

In the EU, Latuda is only authorised for the treatment of schizophrenia in adults, ie not in paediatric patients with any indication, nor for treatment of bipolar depression in adults. In the final assessment report on Study D1050326 in the above mentioned procedure , it was stated that considering the unmet medical need in children, safety risks with other treatments and potentially lower metabolic safety risks with lurasidone compared to other atypical antidepressants, it should be valuable to receive more data on efficacy and safety, including data on long term efficacy and safety and maintenance of effect, in order to assess approval of authorisation of a paediatric indication for bipolar depression. Nevertheless, the data obtained in this study constitute important information and consideration should be given to including them in the SmPC in section 5.1, which is in line with paediatric legislation and guidelines.

The MAH is proposing to include in SmPC 5.1 the new information in children considered relevant to prescribers, even if there is no authorised indication in any subset of the paediatric population.

# 6. Clinical Efficacy aspects

The efficacy of lurasidone for the treatment of bipolar depression in children and adolescents (aged 10 to 17 years) has been studied in a randomized, parallel-group, double-blind, placebo-controlled, flexibly dosed, 6-week multicenter study (Study D1050326).

Subjects who completed Study D1050326 were eligible to continue in to the open-label extension study, Study D1050302, which remains ongoing. The complete CSR for study D1050302 is expected in June 2019. An interim analysis of Study D1050302 using a data cut-off date of October 27, 2016 has been performed.

Assessor's comment:

This Type II Variation to update Latuda SmPC Section 5.1, was submitted as requested by the CHMP recommendation included in the Final Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006 (procedure no. EMEA/H/C/002713/P46/008). Since the submitted paediatric data from the clinical Study D1050326 in this Variation procedure was already assessed in the above-mentioned procedure (procedure no. EMEA/H/C/002713/P46/008), the previous assessment is referred to as appropriate, and the discussion includes also comments on sensitivity analyses as requested by the CHMP in the previous procedure.

## *6.1. Short-term Placebo-Controlled Study - D1050326*

### 6.1.1. Methods

### Study Design

The study was a 6-week randomized, parallel-group, double-blind, placebo-controlled, flexibly-dosed, multicenter study in children and adolescents with bipolar depression. The study included a screening period, a baseline assessment, a 6-week double-blind treatment period, and a follow-up visit. During the 21-day screening period, eligible subjects were tapered off all psychotropic medications except those explicitly permitted per protocol. During the double-blind treatment phase, subjects were treated with lurasidone or placebo for six weeks.

Subjects were randomly assigned to lurasidone or placebo in a 1:1 ratio. Subjects randomized to the lurasidone arm received lurasidone 20 mg/day from Day 1 to Day 7 then were flexibly dosed with lurasidone 20, 40, 60, or 80 mg/day from Day 8 to Week 6 (Day 43). Study drug was administered orally once daily, in the evening, with a meal of at least 350 calories or within 30 minutes after eating.

Assessor's comment:

The clinical study was well designed. The lurasidone doses flexibly given in the study were 18.5, 37, 55.5, and 74 mg, equivalent to 20, 40, 60 and 80 mg lurasidone hydrochloride.

### Study Population

Eligible subjects were males or non-pregnant, non-lactating females, aged 10 to 17 years, inclusive, with bipolar I disorder, most recent episode depressed, with or without rapid cycling disease course (≥ 4 episodes of mood disturbance but <8 episodes in the previous 12 months) and without psychotic features, as diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. (DSM-5) criteria. The diagnosis of bipolar I disorder was confirmed by an adequately trained clinician at the time of screening according to the Schedule for Affective Disorders and Schizophrenia for School-age Children, a semi-structured diagnostic interview that is designed to evaluate past and present episodes of psychopathology in children and adolescents. The current major depressive episode associated with bipolar I disorder, ≥ 4 weeks and <12 months in duration, was confirmed by the investigator. Eligible subjects also had a Children's Depression Rating Scale, Revised (CDRS-R) score ≥ 45, and a Young Mania Rating Scale (YMRS) score ≤ 15 (with YMRS Item 1 [elevated mood] score ≤ 2) at Screening and Baseline.

A total of 350 subjects were randomized and 343 were included in the intent-to-treat (ITT) population used for efficacy evaluations. Of the subjects in the ITT population, 173 subjects received lurasidone and 170 subjects received placebo. A total of 318 subjects (90.9% of the 350 randomized subjects) completed the study: 162 of 176 (92.0%) randomized subjects in the lurasidone group, and 156 of 174 (89.7%) randomized subjects in the placebo group.

### Efficacy Measures

The CDRS-R total score was the primary efficacy measure and the Clinical Global Impression-Bipolar Version (CGI-BP-S) depression score was the key secondary efficacy measure. Other secondary efficacy measures and endpoints included the CGI-BP-S overall bipolar illness score, the CGI-BP-S mania score, the Pediatric Anxiety Rating Scale (PARS), the Pediatric Quality of Life Enjoyment and Satisfaction

Questionnaire, the Clinician-rated Children's Global Assessment Scale, the Attention-Deficit/Hyperactivity Disorder Rating Scale, the proportion of subjects achieving remission (defined as post-baseline CDRS-R total score <28 and YMRS total score <8 and CGI-BP-S depression score <3), and the proportion of responders (defined as >50% reduction from Baseline in CDRS-R total score).

Assessor's comment:

The primary and key secondary endpoints and treatment duration were in line with EMA Guidelines on depression.

## Statistical Methodology

All statistical analyses were performed with 2-sided tests at a significance level of 0.05, and 2-sided 95% confidence intervals were calculated whenever appropriate.

The primary efficacy endpoint (the change from Baseline in the CDRS-R total score at Week 6) was analyzed using a likelihood-based mixed model for repeated measures (MMRM). The response (dependent) variable was the change from Baseline in CDRS-R total score assessed weekly (Weeks 1 to 6). The MMRM model included fixed effects terms for treatment, visit (as a categorical variable), pooled country, age stratum, CDRS-R total score at Baseline, and treatment-by-visit interaction. An unstructured covariance model was fit using restricted maximum likelihood estimation. Denominator degrees of freedom were computed with the Kenward-Rogers method. The likelihood based mixed effects model could accommodate incomplete data under the missing-at-random assumption.

The treatment difference (lurasidone group minus placebo) in least squares (LS) mean, its 2-sided 95% CI, and the associated p-value based on the MMRM model were presented.

The robustness of the MMRM results for the primary efficacy outcome in the ITT Population were explored in a sensitivity analysis using a pattern mixture model (PMM) with placebo-based multiple imputation (Attachment 4.3.1 of the SAP). The assumption that efficacy profiles of dropouts after discontinuation were similar to those of placebo subjects is very conservative because it tends to minimize the difference between lurasidone and placebo groups. To corroborate the robustness of the MMRM result, the primary efficacy outcome was analyzed with the random effects PMM to assess the impact of dropout pattern in the ITT Population.

Efficacy analyses in Study D1050326 are listed in Table 1.

## Table 1: Efficacy Assessments in Placebo-Controlled Study D1050326

| Type of Analysis | Method, Study Population, and Handling of Missing Data |
|---|---|
| **Primary Efficacy Endpoint** | |
| CDRS-R total score change from Baseline to Week 6 | MMRM, ITT, Observed<br>ANCOVA; ITT; Observed, LOCF<br>MMRM, PP, Observed<br>PMM, ITT |
| **Key Secondary Efficacy Endpoint** | |
| CGI-BP-S score (depression) change from Baseline to Week 6 | MMRM, ITT, Observed<br>ANCOVA; ITT; Observed, LOCF<br>MMRM, PP, Observed<br>PMM, ITT |
| **Secondary Efficacy Endpoints** | |
| Change from Baseline in CDRS-R total score at Weeks 1, 2, 3, 4, and 5 | MMRM, ITT, Observed<br>ANCOVA; ITT; Observed, LOCF<br>MMRM, PP, Observed |
| Change from Baseline in CGI-BP-S score (depression) at Weeks 1, 2, 3, 4, and 5 | MMRM, ITT, Observed<br>ANCOVA; ITT; Observed, LOCF<br>MMRM, PP, Observed |
| Change from Baseline in CGI-BP-S score (overall bipolar illness) at Weeks 1 ,2, 3, 4, 5, and 6 | MMRM, ITT, Observed<br>ANCOVA; ITT; Observed, LOCF |
| Change from Baseline in CGI-BP-S score (mania) at Weeks 1, 2, 3, 4, 5, and 6 | MMRM, ITT, Observed<br>ANCOVA; ITT; Observed, LOCF |
| Change from Baseline in PARS total score at Weeks 3 and 6 | MMRM, ITT, Observed<br>ANCOVA; ITT; Observed, LOCF |
| PQ-LES-Q percent maximum possible score change from Baseline at Weeks 3 and 6 | MMRM, ITT, Observed<br>ANCOVA; ITT; Observed, LOCF |
| Change from Baseline in CGAS score at Weeks 3 and 6 | MMRM, ITT, Observed<br>ANCOVA; ITT; Observed, LOCF |
| Proportion of responders at Week 6, defined as ≥ 50% reduction from Baseline in CDRS-R total score | Logistic regression; ITT; Observed, LOCF<br>Logistic regression, PP, Observed |
| Proportion of subjects achieving symptom remission at Week 6, defined as CDRS-R total Score ≤ 28, YMRS total score ≤ 8, and CGI-BP-S depression score ≤ 3 | Logistic regression; ITT; Observed, LOCF<br>Logistic regression, PP, Observed |
| Change from Baseline in ADHD-RS total score at Week 6 | ANCOVA; ITT; Observed, LOCF |

Abbreviations: ADHD-RS=Attention-Deficit/Hyperactivity Disorder Rating Scale; ANCOVA=analysis of covariance; CDRS-R=Children's Depression Rating Scale, Revised; CGAS=Children's Global Assessment Scale; CGI-BP-S=Clinical Global Impression-Bipolar Version, Severity of Illness; ITT=Intent-to-Treat; LOCF=last observation carried forward; MMRM=mixed model for repeated measures; PARS=Pediatric Anxiety Rating Scale; PMM=pattern mixture model; PP=Per Protocol; PQ-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire; YMRS=Young Mania Rating Scale

Sources: Protocol D1050326, Statistical Analysis Plan D1050326

### 6.1.2. Results

## Summary of Efficacy Results

Based on mixed model for repeated measures (MMRM) analysis for the primary efficacy endpoint (CDRS-R total score), the least squares (LS) mean change (± SE) from Baseline to Week 6 was −21.0 ± 1.06 for the lurasidone group and -15.3 ± 1.08 for the placebo group. The placebo-adjusted LS mean change (95% CI) from Baseline to Week 6 in CDRS-R total score for the lurasidone group (-5.7 (95% CI: -8.4; -3.0)) was significantly different from placebo (adjusted p<0.0001, effect size = 0.45).

Based on MMRM analysis for the key secondary efficacy endpoint (CGI-BP-S depression score), there was a statistically significant treatment difference of −0.44 (95% CI: -0.66; -0.22) (adjusted p<0.0001, effect size = 0.44) for the lurasidone group compared to the placebo group at Week 6.

These results demonstrate that lurasidone (flexibly-dosed 20 to 80 mg/day) showed statistically significant and clinically relevant efficacy in the treatment of bipolar depression in children and adolescents with bipolar depression (ages 10 to 17 years).

Assessor's comment:

Efficacy results of this study have been assessed in the previous procedure (EMEA/H/C/002713/P46/008) where it was concluded that this clinical study was well designed and well conducted. The short-term efficacy of lurasidone in the treatment of bipolar depression in children and adolescents was demonstrated in a single clinical study, although the effect was modest/ moderate in this paediatric population compared with placebo across primary (CDRS-R), key secondary (CGI-BP-S), and other secondary efficacy endpoints. However, of note, efficacy was mainly demonstrated in the older age stratum (see Subpopulations section below).

## Analysis Issues

There were no specific statistical analysis issues that would affect the interpretability of data or conclusions related to the efficacy of lurasidone. The discontinuation rate for all lurasidone-treated subjects in this study was 8.0%; the discontinuation rate for all subjects was 9.1%. Missing at random (MAR) assumptions underlying the MMRM analytic model were examined (D1050326, Section 11.1.1.1.4). A pattern mixture model (PMM) using a placebo-based multiple imputation method was performed to explore the robustness of the MMRM results for the primary efficacy variable for the ITT population. A second sensitivity analysis based on random effects PMM with two patterns (completers, dropouts) was performed to assess the impact on treatment group comparisons. The results of the PMM using a placebo-based multiple imputation method were similar, however, the estimated treatment effect was smaller.

**Sensitivity Analysis: Pattern Mixture Model with Placebo-based Multiple Imputation – CDRS-R Total Score (ITT Population)**

| Analysis | Statistic | Placebo (N = 170) | Lurasidone 20 to 80 mg (N = 173) |
|---|---|---|---|
| PMM with placebo-based multiple imputation result at Week 6 | LS Mean (SE) | -15.3 (1.08) | -20.7 (1.07) |
| | **Difference from Placebo** | | |
| | LS Mean Difference (SE) | - | -5.4 (1.39) |
| | LS Mean Difference 95% CI | - | (-8.1, -2.7) |
| | p-value | - | 0.0001** |
| MMRM result at Week 6 | LS Mean (SE) | -15.3 (1.08) | -21.0 (1.06) |
| | **Difference from Placebo** | | |
| | LS Mean Difference (SE) | - | -5.7 (1.39) |
| | LS Mean Difference 95% CI | - | (-8.4, -3.0) |
| | p-value | - | < 0.0001** |

Abbreviations: CDRS-R = Children's Depression Rating Scale, Revised; CI = confidence interval; ITT = Intent-to-Treat; LS = least squares; MMRM = mixed model for repeated measures; PMM = pattern mixture model; SE = standard error.
Note: PMM used1000 placebo-based multiple imputations using a monotone regression imputation method.
Note: MMRM was based on the fixed effects for treatment, pooled country, age stratum, visit as a categorical variable, Baseline score, and treatment by visit interaction, assuming an unstructured covariance matrix. Refer to the statistical analysis plan for details.
Note: * $p \leq 0.05$; ** $p \leq 0.01$.
Source: Table 14.2.1.1.4.

Assessor's comment:

Handling of missing data and sensitivity analyses using multiple imputation technique was provided by the MAH in the CSR in the previous procedure (EMEA/H/C/002713/P46/008). However, these analyses were not fully assessed within that procedure.

The results of the sensitivity analyses using PMM is considered as being more conservative and not over-estimating the treatment effect which can be a concern with the MMRM techniques. The results from the sensitivity analyses show a somewhat smaller treatment effect, indicating that the MMRM slightly over estimates the treatment effect.

## Efficacy Results in Subpopulations

Pre-specified efficacy analyses of subgroups, or subpopulations, were conducted for Study D1050326. The results of these analyses suggest that gender, race, ethnicity, body mass index (BMI), geographic region (non-US versus US), attention deficit/hyperactivity disorder (ADHD) stimulant usage status, and rapid versus non-rapid cycling bipolar disease course did not influence the efficacy of lurasidone, which was consistently evident.

A treatment interaction was observed for the age stratum subgroup analysis (10 to 14 years old versus 15 to 17 years old) of the change from Baseline to Week 6 in the CDRS-R total score (p=0.0134). The placebo-adjusted LS mean change from Baseline to Week 6 LOCF in CDRS-R total score for the lurasidone

group was -1.8 for subjects in the 10- to 14-year-old age stratum and was -8.6 for subjects in the 15- to 17-year-old age stratum. The efficacy of lurasidone was evident across both age stratums; the LS mean change from Baseline to Week 6 LOCF in CDRS-R total score was -18.8 and -22.9 for subjects in the 10- to 14-year-old and 15-17-year old age stratum, respectively. The larger placebo response in the 10- to 14-year-old stratum may have contributed to the placebo-adjusted treatment by subgroup interaction.

Assessor's comment:

There were approximately equal numbers of subjects in the 10- to 14-year-old age stratum and the 15- to 17-year-old age stratum (50.7% and 49.3%, respectively).

Efficacy was mainly demonstrated in the 15 to 17 years old age stratum and not in younger patients. Placebo-adjusted LS mean change from Baseline to Week 6 LOCF in CDRS-R total score for the lurasidone group was -1.8 (-5.6, 2.0) for subjects in the 10- to 14-year-old age stratum and was -8.6 (-12.4, -4.8) for subjects in the 15- to 17-year-old age stratum. The results for other secondary endpoints were in line with results for primary and key secondary endpoints, ie data was supportive.

No long-term data on effectiveness will be generated by this study.

## *6.2. Persistence of Efficacy and/or Tolerance Effects*

### 6.2.1. Short-Term Study - D1050326

In Study D1050326, MMRM analysis showed that the change from Baseline in CDRS-R total score was statistically significant compared with placebo starting at Week 2 and at each subsequent visit for the lurasidone group. ANCOVA analysis showed a similar pattern of efficacy for the lurasidone group compared with placebo group.

### 6.2.2. Long-Term Study - D1050302

The long-term use of lurasidone in the treatment of bipolar depression in children and adolescents is being evaluated in an ongoing, open-label, 104 week, multicenter study (Study D1050302) that started on November 4, 2013. This study was designed to evaluate the long-term safety, tolerability and effectiveness of flexibly-dosed lurasidone (20, 40, 60 or 80 mg/day). Subjects who met entry criteria were to be transitioned from the short-term study (Study D1050326) directly to the long-term extension study (Study D1050302). In Study D1050302, subjects were treated with lurasidone 40 mg/day for Days 1-7, then beginning with Day 8, dose adjustments to 20, 40, 60 or 80 mg/day were permitted, based on investigator judgment, to optimize tolerability and effectiveness.

An interim analysis was performed on this long-term data with a cut-off date of October 27, 2016. Data are available for 223 subjects from Study D1050326 who entered into Study D1050302. Of these 223 subjects, a total of 155 subjects (69.5%) have completed 28 weeks, 93 subjects (41.7%) have completed 52 weeks, and 17 subjects (7.6%) have completed 104 weeks. A total of 104 subjects (46.6%) have discontinued the study early, and 102 subjects (45.7%) remain ongoing in the study. Based on available data, the modal daily dose of lurasidone during the open-label treatment period was 20 mg/day in 6% of

subjects, 40 mg/day in 41% of subjects, 60 mg/day in 27% of subjects, and 80 mg/day in 26% of subjects. The mean daily dose of lurasidone during the open-label treatment period was 52.1 mg.

Long-term treatment with lurasidone was associated with maintenance of treatment effect as demonstrated by consistent improvement in both primary and key secondary efficacy measures over the study period. In the long-term, open-label extension study, improvement from open-label baseline in mean CDRS-R total score to Week 28 LOCF was −10.5 and −5.1 for subjects who were previously randomized to placebo and lurasidone, respectively (Table 2).

**Table 2: Change from DB Baseline and OL Baseline to Week 52, Week 104, and Endpoint in CDRS-R Total Score and CGI-BP-S for 326-LUR Safety Population in Study D1050302 (Interim Analysis)**

| Statistic | CDRS-R Total Score | | | CGI-BP-S | | |
|---|---|---|---|---|---|---|
| | PBO-LUR (N=108) | LUR-LUR (N=115) | 326-LUR (N=223) | PBO-LUR (N=108) | LUR-LUR (N=115) | 326-LUR (N=223) |
| **Week 52 Observed n** | **50** | **45** | **95** | **50** | **45** | **95** |
| DB Baseline mean (SD) | 55.1 (7.42) | 59.8 (8.76) | 57.3 (8.38) | 4.38 (0.490) | 4.80 (0.661) | 4.58 (0.612) |
| Mean Change from DB BL (SD) | -29.6 (8.62) | -34.7 (10.13) | -32.0 (9.66) | -2.60 (0.969) | -2.91 (0.900) | -2.75 (0.945) |
| OL Baseline mean (SD) | 38.8 (12.91) | 32.9 (10.02) | 36.0 (11.94) | 3.34 (1.062) | 3.02 (1.196) | 3.19 (1.133) |
| Mean Change from OL BL (SD) | -13.3 (13.73) | -7.8 (8.79) | -10.7 (11.92) | -1.56 (1.264) | -1.13 (1.198) | -1.36 (1.246) |
| **Week 104 Observed n** | **10** | **7** | **17** | **10** | **7** | **17** |
| DB Baseline mean (SD) | 51.5 (3.98) | 61.3 (11.25) | 55.5 (9.00) | 4.30 (0.483) | 4.86 (0.690) | 4.53 (0.624) |
| Mean Change from DB BL (SD) | -29.4 (5.04) | -42.0 (10.13) | -34.6 (9.68) | -2.90 (0.738) | -3.71 (0.756) | -3.24 (0.831) |
| OL Baseline mean (SD) | 34.2 (18.13) | 25.6 (7.68) | 30.6 (15.04) | 2.90 (1.197) | 1.86 (0.900) | 2.47 (1.179) |
| Mean Change from OL BL (SD) | -12.1 (17.59) | -6.3 (6.85) | -9.7 (14.15) | -1.50 (1.581) | -0.71 (1.113) | -1.18 (1.425) |
| **Endpoint n** | **105** | **113** | **218** | **107** | **115** | **222** |
| DB Baseline mean (SD) | 57.6 (8.06) | 58.9 (8.30) | 58.2 (8.19) | 4.40 (0.547) | 4.65 (0.636) | 4.53 (0.606) |
| Mean Change from DB BL (SD) | -28.2 (11.87) | -29.3 (13.74) | -28.8 (12.86) | -2.16 (1.311) | -2.34 (1.270) | -2.25 (1.290) |
| OL Baseline mean (SD) | 40.2 (13.35) | 35.5 (12.28) | 37.8 (13.00) | 3.29 (1.073) | 2.98 (1.108) | 3.13 (1.100) |
| Mean Change from OL BL (SD) | -10.8 (14.77) | -5.9 (11.95) | -8.3 (13.58) | -1.05 (1.668) | -0.67 (1.336) | -0.85 (1.513) |

Abbreviations: PBO-LUR: Subjects randomized to placebo in Study D1050326; LUR-LUR: Subjects randomized to lurasidone in Study D1050326; 326-LUR: All subjects who continued from Study D1050326
Source: Study D1050302 Table 14.2.61.1.1.26 and Table 14.2.64.1.1.26

Assessor's comment:

D1050302, an ongoing, open-label, 104 week, multicenter study, will evaluate the data of long-term use of lurasidone in the treatment of bipolar depression in children and adolescents in an ongoing, open-label, 104 week, multicenter study. The provided interim analysis with a cut-off date of October 27, 2016

included fewer than 100 patients exposed to lurasidone at least 1 year, and only 17 subjects (7.6%) have completed the 104-week study by the time of interim analysis, thus included limited information that does not allow reliable conclusion on efficacy to be drawn at this time.

Referring to the previous request for clarification in the Final Assesment Report (procedure EMEA/H/C/002713/P46/008) about whether long-term safety and effectiveness data in the bipolar paediatric population are forthcoming, the MAH clarifies that study D1050302 is an extension study designed to evaluate the long-term safety, tolerability and effectiveness of flexibly dosed Latuda (20, 40, 60 or 80 mg/day) in paediatric subjects who have completed the 6-week treatment period in the preceding studies, D1050301, D1050325, and D1050326 (schizophrenia, autism and bipolar depression patients respectively). Long-term safety and effectiveness data in the bipolar paediatric population are thus forthcoming. The complete CSR for study D1050302 is expected in June 2019.

## *6.3. Discussion and Conclusion on the clinical efficacy*

### Design and conduct of clinical studies

Study D1050326 was a 6-week randomized, parallel-group, double-blind, placebo-controlled, flexibly-dosed, multicenter study in children and adolescents with bipolar depression.

The study included children and adolescent patients (10-17 years of age) who met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) criteria for a major depressive episode associated with bipolar I disorder, with or without rapid cycling, and without psychotic features. Patients were randomized to flexibly dosed lurasidone 18-74 mg (equivalent to 20 80 mg lurasidone hydrochloride) once daily or placebo.

The primary endpoint was the CDRS-R total score. The key secondary efficacy measure was the Clinical Global Impression-Bipolar Version (CGI-BP-S) depression score. The endpoints and treatment duration were in line with EMA Guidelines on depression and are acceptable.

The sensitivity analyses performed using PMM shows that the primary analysis method for the primary and key secondary endpoints (MMRM) is likely to over-estimate the treatment effect.

This study has been assessed in the previous procedure (EMEA/H/C/002713/P46/008) where it was considered that the study was well designed and well conducted.

### Efficacy data and additional analyses

The main efficacy results are summarised in below table (as proposed to be included in SmPC section 5.1 by the MAH).

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

| Parameters | Study Statistic | Placebo | Lurasidone dose 18.5-74 mg (a) (b) |
|---|---|---|---|
| Primary Endpoint: | | N=157 | N=161 |

| Parameters | Study Statistic | Placebo | Lurasidone dose 18.5-74 mg (a) (b) |
|---|---|---|---|
| CDRS-R Total Score | Baseline Mean (SD) | 58.6 (8.26) | 59.2 (8.24) |
| | LS Mean Change (SE) | -15.3 (1.08) | -21.0 (1.06) |
| | Treatment Difference vs. placebo | | |
| | Estimate (SE) (95% CI) | -- | -5.7 (1.39) (-8.4; -3.0) |
| | p-value | -- | <0.0001 |
| | | | |
| Key Secondary Endpoint: CGI-BP-S Depression Score | | N=157 | N=162 |
| | Baseline Mean (SD) | 4.5 | 4.6 |
| | LS Mean Change (SE) | -1.05 (0.087) | -1.49 (0.085) |
| | Treatment Difference vs. placebo | | |
| | Estimate (SE) (95% CI) | -- | -0.44 (0.112) (-0.66; -0.22) |
| | p-value | -- | <0.0001 |

N is number of subjects per model estimate.
(a) p-values for lurasidone vs. placebo were adjusted for multiple comparisons.
(b) Lurasidone doses of 18.5, 37, 55.5, 74 mg are equivalent to 20, 40, 60 and 80 amounts of lurasidone hydrochloride.

For the primary efficacy analysis parameter, change in the CDRS-R total score from Baseline to Week 6, there was a significant treatment difference favouring lurasidone over placebo in improving depressive symptoms.

For the key secondary efficacy analysis parameter, change in the CGI-BP-S depression score from Baseline to Week 6, there was a significant treatment difference favoring lurasidone over placebo in improving the severity of depressive symptoms.

Significant treatment differences from placebo were observed in the lurasidone group beginning at Week 2 and maintained at each study visit through to the end of the study for both primary and key secondary efficacy endpoints.

A treatment interaction was observed for the age stratum subgroup analysis. Placebo-adjusted LS mean change from Baseline to Week 6 LOCF in CDRS-R total score for the lurasidone group was -1.8 (-5.6, 2.0) for subjects in the 10- to 14-year-old age stratum and was -8.6 (-12.4, -4.8) for subjects in the 15- to 17-year-old age stratum. Thus efficacy was mainly demonstrated in the 15 to 17 years old age stratum and not in younger patients.

An interim analysis with a cut-off date of October 27, 2016 on study D1050302 (an ongoing, open-label, 104 week, multicenter study) has been provided. This study will evaluate the data of long-term use of lurasidone in the treatment of bipolar depression in children and adolescents. However, only 17 subjects (7.6%) have completed the 104-week study by the time of interim analysis. The provided data included too limited information to allow any reliable conclusion on efficacy to be drawn at this stage. The complete CSR for this study is expected in June 2019.

## Conclusions on the clinical efficacy

The data from the short-term Study - D1050326 provided evidence of efficacy of lurasidone in in children and adolescents with bipolar depression, at least in the older age stratum (15 to 18 years). The study, however, failed to show a statistically significant efficacy in younger patients (10- to 14-year-old).

Although the data is not deemed sufficient to support a change of the wording of the indication, the data should be presented in section 5.1 under the heading “Paediatric population”, as requested by CHMP following the assessment of the paediatric study D1050326 submitted according to Art. 46 procedure (no. EMEA/H/C/002713/P46/008).

# 7. Clinical Safety aspects

## *7.1. Methods – analysis of data submitted*

### Patient exposure

As of October 27, 2016, a total of 283 children and adolescent subjects with bipolar depression have been exposed to lurasidone (175 subjects in the completed double-blind study and 108 subjects newly exposed to lurasidone in the open-label extension study). The short- and long-term studies involving subjects with bipolar depression treated with flexibly-dosed lurasidone (20 to 80 mg/day) were 6 weeks and 24 months in duration.

In Study D1050326, a total of 347 children and adolescent subjects aged 10-17 years received at least one dose of study medication; of these, 175 subjects received lurasidone once daily (flexibly dosed at 20 to 80 mg/day) and 172 subjects received placebo once daily. For the 175 lurasidone-treated subjects, 84.0% had at least 6 weeks (≥ 41 days) of exposure; the mean number of days of exposure was 40.3 days. The overall exposure to lurasidone in Study D1050326 was 19.3 subject-years.

In the interim analysis conducted in support of this submission, a total of 223 subjects from Study D1050326 entered the open-label extension study (D1050302) and received at least one dose of lurasidone. Of these 223 subjects, 161 (72.2%) had at least 24 weeks (≥ 168 days) of exposure and 94 (42.2%) had at least 1 year (≥ 364 days) of exposure. The mean number of days of exposure was 335.9 days, and overall exposure to lurasidone at the interim cut point was 205.1 subject-years.

Assessor’s comment:

Exposure was comparable for lurasidone and placebo in the short-term study.

Based on interim analysis of the open label long-term study, fewer than 100 patients were exposed to lurasidone for at least 1 year, and only 17 subjects (7.6%) had completed the 104-week study by the time of interim analysis.

### Clinical Studies

### Adverse Events

In the double-blind, placebo-controlled Study D1050326 (children and adolescent subjects with bipolar depression):

- A slightly higher percentage of subjects treated with lurasidone completed the study (92.0%) than placebo (89.7%). There was no difference in the proportion of subjects who discontinued due to an AE while on lurasidone or placebo (1.7% in each group).
- Of the 175 lurasidone-treated subjects, 112 (64.0%) reported one or more treatment-emergent adverse events (TEAEs). Of the 172 placebo-treated subjects, 89 (51.7%) reported one or more TEAEs.
- The number of subjects reporting one or more study drug-related TEAEs (related, probably related, and possibly related) included 79 subjects (45.1%) in the lurasidone group and 44 subjects (25.6%) randomized to placebo.
- The most frequently-reported TEAEs in the lurasidone group included Gastrointestinal Disorders and Nervous System Disorders (both 29.1%), and Psychiatric Disorders (16.0%). For subjects receiving placebo, the most common TEAEs were in the System Organ Class categories of Nervous System Disorders (25.6%) and Gastrointestinal Disorders (13.4%).
- TEAEs reported by at least 2% of subjects in the lurasidone group and which occurred at a higher incidence in the lurasidone than placebo group were nausea, somnolence, weight increased, vomiting, insomnia, decreased appetite, and abdominal pain.
- The incidence of extrapyramidal symptoms (EPS)-related TEAEs was comparable between the lurasidone (4.6%) and placebo (4.1%) groups. Akathisia was the most common EPS-related TEAE, also reported at a similar frequency for lurasidone and placebo subjects (2.9% and 3.5%, respectively).
- The incidence of metabolic TEAEs was higher in the lurasidone group (9.1%) than in the placebo group (2.9%), with the most common metabolic event being weight increased (6.9% and 1.7%, respectively).
- There were no reports of TEAEs related to suicidality and self-injury for any subject in the lurasidone group, and 1 TEAE related to suicidality and self-injury was reported in the placebo group.
- The majority of TEAEs were mild-to-moderate in severity, with 2 subjects (1.1%) in the lurasidone group and 6 subjects (3.5%) in the placebo group reported to have severe TEAEs.
- No deaths were reported during this study. Rates of serious TEAEs were comparable for subjects receiving placebo (2.3%) and lurasidone (1.1%).

Assessor's comment:

Safety data was assessed in the previous procedure EMEA/H/C/002713/P46/008. It was noted that treatment with lurasidone was generally safe and well tolerated in the dose range studied (20-80 mg/day) according to the CSR of Study D1050326. However, the frequency for weight increased (TEAEs and MMRM analysis) was higher in the lurasidone group than in the placebo group and there was an increase in BMI in the lurasidone group compared to the placebo group. These findings are not surprising but of special importance in children and adolescents. No clinically meaningful differences for other metabolic parameters were found.

In open-label extension Study D1050302 (subjects from Study D1050326) at the data cut-off date (October 27, 2016):

- A total of 17 subjects (7.6%) have completed the 104-week study and 104 subjects (46.6%) have prematurely discontinued from the study. The most common reasons for discontinuation were withdrawal of consent (16.1%) and adverse event (10.3%).
- Of the 223 lurasidone-treated subjects in the open-label extension study, a total of 176 (78.9%) subjects reported one or more TEAEs.
- The number of subjects reporting one or more study drug-related TEAEs (definite, possibly, or probably related) was 113 (50.7%) subjects.
- The percentage of lurasidone-treated subjects with EPS-related TEAEs by preferred term was 13.0%.
- The percentage of lurasidone-treated subjects with metabolic TEAEs by preferred term was 11.2%.
- The proportion of subjects experiencing TEAEs related to suicidality and self-injury was 6.3%.
- The percentage of subjects who had at least one severe TEAE was 14.8%.
- No deaths occurred during Study D1050302. A total of 29 subjects (13.0%) reported serious TEAEs, of which X were considered definite, possibly, or probably related to lurasidone by the Investigator.
- A total of 23 subjects (10.3%) discontinued the open-label extension due to a TEAE.

Assessor's comment:

There is limited experience on long-term use of lurasidone in the open-label extension study. Only 17 subjects (7.6%) have completed the 104-week study by the time of interim analysis. The final study report is expected in June 2019.

It is noted that the figures on reported serious TEAEs considered definite, possibly, or probably related to lurasidone by the Investigator in open-label extension Study D1050302, were missing. The MAH should submit a line listing for the serious TEAEs including e.g. time to onset and to recovery, severity, causality, and actions taken. **LoQ**

## Deaths

No deaths occurred during any of the lurasidone pediatric studies summarized in this submission.

## Clinical Laboratory Evaluation

## Liver Function Tests

Overall, there were no clinically meaningful changes seen in liver function parameters.

In the double-blind, placebo-controlled study:

- The mean total protein at Endpoint increased by 0.05 g/dL from Baseline in the lurasidone group compared to a decrease (-0.02 g/dL) in the placebo group.
- Shifts in alanine aminotransferase (ALT), albumin, and protein from normal at Baseline to high at Endpoint occurred in a higher percentage of lurasidone-treated subjects (5.5%, 3.1%, and 6.2%, respectively) than those in the placebo group (1.9%, 0.6%, and 3.2%, respectively).
- TEAEs of ALT increased and blood alkaline phosphatase increased each occurred in one (0.6%) subject in the lurasidone group and no subjects in the placebo group.

In the open-label extension study:

- Mean gamma-glutamyltransferase (GGT) increased at Endpoint by 1.0 U/L and 1.5 U/L relative to double-blind (DB) Baseline and open-label (OL) Baseline, respectively.
- Potentially markedly abnormal laboratory values (PMALVs) of high ALT occurred in 6 (2.8%) subjects at any open-label visit.
- A TEAE of ALT increased occurred in one (0.4%) subject.

Assessor's comment:

Alanine aminotransferase increased is labelled as an uncommon ADR in adults.

## Renal Function Tests

There were no clinically meaningful changes seen in renal function parameters.

In the double-blind, placebo-controlled study:

- An increase in mean creatinine of 0.021 mg/dL from Baseline to Endpoint was seen in the lurasidone group compared to 0.009 mg/dL in the placebo group.
- Shifts in creatinine and sodium from normal at Baseline to high at Endpoint occurred in a higher percentage of lurasidone-treated subjects (6.7% and 6.7%, respectively) than those in the placebo group (4.5% and 3.9%, respectively).
- PMALVs of high sodium and high chloride were reported in the lurasidone group (5 subjects and 1 subject, respectively); none were reported in the placebo group.

In the open-label extension study:

- Shifts from normal at DB Baseline to low at Endpoint were reported for bicarbonate (11.3%) and from normal to high for creatinine (8.5%) and phosphate (16.5%).
- PMALVs of high sodium occurred in 12 (5.5%) subjects at any open-label visit. PMALVs of high potassium occurred in 15 (6.9%) subjects, and PMALVs of low bicarbonate occurred in 44 (20.3%) subjects.
- TEAEs of blood bicarbonate decreased, blood potassium increased, hypocalcaemia, and hyponatraemia each occurred in one (0.4%) subject.

Assessor's comment:

Serum creatinine increased is labelled as a common ADR in adults.

## Metabolic Parameters

Clinical laboratory data related to the metabolic parameters that were of particular clinical interest included glucose, cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides, glycosylated hemoglobin (HbA1c), insulin, and homeostatic model assessment for insulin resistance (HOMA-IR).

In the double-blind, placebo-controlled study:

- There were no clinically meaningful differences in the change from Baseline to Endpoint in cholesterol, LDL and HDL cholesterol, triglycerides, glucose, HbA1c, insulin, and HOMA-IR for the lurasidone group.
- Shifts in cholesterol/HDL-cholesterol, LDL cholesterol, overall glucose, and overall insulin from normal at Baseline to high at Endpoint occurred more frequently in the lurasidone group than the placebo group.
- TEAEs of dyslipidemia, hyperglycemia, hyperinsulinemia, and hypertriglyceridemia each occurred in one (1.6%) subject in the lurasidone group and no subjects in the placebo group.

In the open-label extension study:

- Increases in overall and fasting glucose were noted relative to both DB and OL Baseline.
- Shifts from normal at DB Baseline to high at Endpoint were reported in overall triglycerides (14.2%), cholesterol (7.6%), and glucose (10.8%) along with shifts from normal to low at Endpoint in overall HDL-cholesterol (13.7%).
- PMALVs of high fasting triglycerides occurred in 25 (12.2%) subjects at any open-label visit. PMALVs of low fasting HDL-cholesterol occurred in 64 (31.4%) subjects.
- TEAEs of blood insulin increased, blood triglycerides increased, hyperglycemia, and hypertriglyceridemia each occurred in 2 (0.9%) subjects; TEAEs of blood glucose decreased, lipids increased, and hyperinsulinemia occurred in one (0.4%) subject each.

Assessor's comment:

Weight increased is labelled as a common ADR in adults. Decreased appetite, blood glucose increased, and hyponatraemia are labelled as uncommon ADRs in adults.

## Muscle Function

In the double-blind, placebo-controlled study:

- PMALVs of high creatine kinase (CK) occurred in 7 (4.3%) subjects in the lurasidone group and 4 (2.6%) subjects in the placebo group.
- TEAEs of blood creatinine phosphokinase increased occurred in 2 subjects (1.1%) in the lurasidone group and no subjects in the placebo group.

In the open-label extension study:

- PMALVs of high CK occurred in 16 (7.4%) subjects at any open-label visit.
- TEAEs of blood creatine phosphokinase increased occurred in 4 (1.8%) subjects.

Assessor's comment:

Blood creatine phosphokinase increase is labelled as a common ADR in adults.

## Hormone Assessments

In the double-blind, placebo-controlled study:

- Mean change from Baseline in thyrotropin was greater in the lurasidone group (-0.28 µIU/mL) compared with the placebo group (-0.03 µIU/mL).
- A TEAE of blood thyroid stimulating hormone increased was reported in one subject in the lurasidone group; none were reported in the placebo group.
- The median change from Baseline to Endpoint in overall serum prolactin levels was greater for the lurasidone group compared with the placebo group (1.10 and 0.50 ng/mL, respectively).
- For male subjects, the median change from Baseline to Endpoint in overall serum prolactin levels was greater for the lurasidone group compared with the placebo group (0.85 and 0.50 ng/mL, respectively).
- For female subjects, the median change from Baseline to Endpoint in overall serum prolactin levels was greater for the lurasidone group compared with the placebo group (2.50 and 0.55 ng/mL, respectively)
- Among female subjects, a difference between treatment groups was noted in mean estradiol measurements; however, the magnitude was dependent on the test agent used.
- Among male subjects, mean testosterone levels decreased from Baseline to Endpoint in the lurasidone group (-8.1 ng/dL), compared to an increase in the placebo group (+18.4 ng/dL); a similar trend was seen in each of the age groups. This change was small relative to age-normed testosterone ranges and to circadian variability.
- Shifts in prolactin from normal at Baseline to high at Endpoint occurred in 11 (6.7%) subjects in the lurasidone group and 3 (1.9%) subjects in the placebo group.
- PMALVs of high prolactin occurred in 15 (9.1%) subjects in the lurasidone group and 11 (7.0%) subjects in the placebo group.

In the open-label extension study:

- TEAEs of blood thyroid stimulating hormone increased and hormone level abnormal each occurred in one (0.4%) subject.
- In female subjects, mean follicle stimulating hormone increased at Endpoint relative to DB Baseline (1.40 mIU/mL) and OL Baseline (1.68 mIU/mL).
- In male subjects, increases in testosterone (mean) at Endpoint relative to DB and OL Baseline were seen (16.2 ng/dL and 23.5 ng/dL, respectively), consistent with normal development.
- Median prolactin levels increased at Endpoint overall by 1.10 and 0.15 ng/mL relative to DB and OL Baseline, for male subjects by 0.85 and 0.30 ng/mL relative to DB and OL Baseline, and for female subjects 2.00 and 0.00 ng/mL relative to DB and OL Baseline.
- Shifts in prolactin from normal to high from DB Baseline at Endpoint were reported by 6.6% of subjects, with 5.9% for female subjects and 7.3% for male subjects.
- PMALVs of high prolactin occurred in 47 (21.8%) subjects at any open-label visit.
- TEAEs of prolactin increased occurred in 3 (1.3%) subjects.

Assessor's comment:

Blood prolactin increased is labelled as an uncommon ADR in adults.

## C-Reactive Protein

There were no clinically meaningful changes in C-reactive protein with lurasidone in the double-blind, placebo-controlled study. TEAEs of C-reactive protein increased occurred in two subjects (1.1%) in the lurasidone group and one subject (0.6%) in the placebo group in Study D1050326.

In the open-label Study D1050302, the mean change from OL Baseline in C-reactive protein at Endpoint was -0.006 ± 5.4725 mg/L. Shifts in C-reactive protein from normal to high at Endpoint occurred in 23 subjects relative to DB Baseline (11.1%) and OL Baseline (11.6%). TEAEs of C-reactive protein increased occurred in two (0.9%) subjects.

Assessor's comment:

There is no ADR with C-reactive protein change labelled in adults. The number of subjects who had C-reactive protein increased is small. It is agreed that there were no clinically meaningful changes in C-reactive protein with lurasidone in the double-blind, placebo-controlled study.

## Hematology

There were no clinically meaningful changes in hematology parameters.

In the double-blind, placebo-controlled study:

- The most notable finding was a greater number of subjects with elevated (≥ 50%) hematocrit in the lurasidone group compared with the placebo group (4.8% versus 2.0%, respectively).
- The majority of PMALVs associated with hematology parameters occurred in the 13-to 17-year-old age group.

In the open-label extension study:

- Percentage neutrophils increased by 2.43 ± 12.046% at Endpoint relative to DB Baseline and 0.60 ± 10.826% relative to OL Baseline.
- Shifts in percent were reported from DB Baseline to Endpoint from normal to high in eosinophils (7.1%), from normal to low in absolute (6.2%) and percent monocytes (11.9%), and from normal to high in erythrocyte distribution width (16.1%).
- PMALVs of high percent eosinophils occurred in 12 (5.6%) subjects at any open-label study visit.
- TEAEs of anemia, leukopenia, and neutropenia each occurred in one (0.4%) subject

Assessor's comment:

There is no ADR with elevated hematocrit labelled in adults, but eosinophilia is a rare ADR labelled in adults.

## Urinalysis

There were no clinically meaningful changes in urinalysis parameters.

In the double-blind, placebo-controlled study:

- One subject (0.6%) in the lurasidone group had a TEAE of urine output increased. TEAEs of urinary tract infection and polyuria were each reported in one (0.6%) subject in the lurasidone group and one (0.6%) subject in the placebo group.

In the open-label extension study:

- PMALVs of high urine erythrocytes and high urine leukocytes occurred in 18 (21.7%) subjects and 11 (11.1%) subjects, respectively, at any open-label visit.
- TEAEs of urinary tract infection occurred in 7 (3.1%) subjects, pollakiuria and cystitis in two (0.9%) subjects each, and a TEAE of blood urine present occurred in one (0.4%) subject

Assessor's comment:

There is no ADR with urinary tract infection and polyuria labelled in adults. The number of subjects who had these events is small. It is agreed that there were no clinically meaningful changes in urinalysis parameters.

## Vital signs, Physical Findings, and Other Observations

- There were no clinically meaningful effects of lurasidone, including no dose-related effects, on vital sign parameters (blood pressure, respiration rate, heart rate, and body temperature) in Study D1050326 or for subjects who continued into the open-label extension study (D1050302).
- The results for QTcF (rather than QTcB) are considered more sensitive in the pediatric and adolescent population. Treatment with lurasidone was not associated with clinically relevant changes in any electrocardiogram parameter during the short or long-term studies. With respect to QTc prolongation, no subject had QTcF >460 msec or a ≥ 60 msec increase in QTcF from Baseline.
    - In Study D1050326, 2 subjects in each treatment group had a ≥ 30 msec increase in QTcF from Baseline at Week 6 and at Endpoint; and in the open-label extension for those continuing from Study D1050326, 12 subjects (5.7%) had a ≥ 30 msec increase in QTcF from DB Baseline.
- Changes in movement disorder signs or symptoms, as measured by the change in Simpson-Angus Rating Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS) scores, were generally absent to mild in subjects treated with lurasidone. Relatively small changes from Baseline were observed in the SAS mean score, BARS total score, and AIMS total score over the short-term double-blind and long-term open-label studies, which were not considered statistically significant or clinically relevant.

Assessor's comment:

There were no clinically meaningful effects of lurasidone on vital sign parameters.

## Growth Parameters

To analyse the effects of lurasidone on growth parameters, changes from Baseline in mean body weight, height, BMI, and waist circumference were measured. In the 6-week double-blind study, body weight and BMI for the lurasidone and placebo treatment groups were compared by applying an MMRM with fixed effects terms for treatment, visit (as a categorical variable), pooled country, age stratum, the

corresponding Baseline, and treatment-by-visit interaction. In addition, an ANCOVA model including factors of treatment, pooled country, age group, and relevant Baseline value as covariate was applied for height, waist circumference, body weight, and BMI, as well as Z-scores for height and BMI.

Z-scores were analysed in order to standardize the comparisons of growth index across the sex and different ages of subjects in these studies. Age and gender specific Z-scores and percentiles of height and BMI were obtained by using the World Health Organization (WHO) 2007 growth charts (Study D1050326). (As weight for age reference data are not available beyond the age of 10 years in the WHO 2007 growth reference for 5 to 19 years old, no age and sex specific Z score of weight was derived in this study.) In the open-label extension study (D1050302), age- and-gender specific Z-scores and percentiles presented for summaries of height and BMI were derived using the WHO 2007 growth reference. Age-and-gender specific Z-scores and percentiles presented for summaries of height, weight, and BMI were derived for US subjects using the CDC 2000 growth reference; this growth chart was also used to derive age-and-sex specific z-scores and percentiles in weight for non-US subjects.

In the open-label extension study, to better interpret changes in observed growth parameters in the absence of a placebo-controlled group the expected value of height and BMI relative to DB baseline per WHO and the expected value of height, weight, and BMI relative to DB baseline per CDC at each open-label visit were derived; corresponding changes in expected value from DB baseline were generated as well.

In Study D1050326, change (LS mean $\pm$ SE) from Baseline to Week 6 for body weight using MMRM analysis was 0.74 $\pm$ 0.145 kg in the lurasidone group and 0.44 $\pm$ 0.147 kg in the placebo group. The proportion of patients with a $\geq$ 7% increase in body weight (at Endpoint) was 4.0% and 5.3% for lurasidone- and placebo-treated subjects, respectively.

Change (LS mean ± SE) from Baseline to Endpoint in BMI Z-score based on ANCOVA was 0.055 ± 0.0217 in the lurasidone group and 0.016 ± 0.0224 in the placebo group. Relative to placebo, the changes in body weight and BMI Z-score in the lurasidone group from Baseline to Endpoint were not statistically significant (p=0.1138 and p=0.0929, respectively).

In the long-term open-label extension study, increases in weight were observed relative to expected weights predicted based on the CDC growth charts for the overall population. When reviewed by age group, the observed changes in weight demonstrated more than expected increases in weight for the two youngest age groups (10 to 12 years of age and 13 to 15 years of age) and less than expected for the oldest group ($\geq$ 16 years of age) based on the CDC growth chart, with similar findings for BMI based on the WHO growth chart. There were minor mean changes from DB Baseline in weight and BMI Z-scores for all three groups. Average changes in height from DB Baseline to Week 52 Endpoint and Study Endpoint were less than expected for the 2 youngest age groups and slightly more than expected in the oldest group (WHO growth chart).

Assessor's comment:

While weight increased occurred more frequently in lurasidone than in placebo group (6.9% and 1.7%, respectively), it was stated that the proportion of patients with a $\geq$ 7% increase in body weight (at Endpoint) was 4.0% and 5.3% for lurasidone- and placebo-treated subjects, respectively. Thus based on these figures, the effect on body weight seems inconsistent in lurasidone- and placebo-treated subjects.

## Menstrual Cyclicity and Tanner Staging

Lurasidone treatment had no apparent effect on menstrual cyclicity, as the reported frequency of menstrual cycles did not show a significant change in lurasidone-treated females between open-label Baseline and Endpoint in the long-term open-label extension study.

Few menstrual related AEs were reported during long-term treatment with lurasidone; amenorrhea and galactorrhea were reported in 1 subject each.

Physical development and sexual maturity were assessed by analysis of the frequency distribution of Tanner stage over time. Key observations are summarized below:

- Changes in Tanner staging from Baseline to Endpoint for male and female subjects in Study D1050326 were comparable between the lurasidone and placebo groups.
    - Seven percent (7.0%) of lurasidone-treated male subjects advanced 1 Tanner stage for both pubic hair and genitalia development.
    - For female lurasidone-treated subjects, the proportion advancing 1 Tanner stage for pubic hair and breast development was 9.6% and 7.2%, respectively. Only 1 lurasidone-treated subject overall advanced by 2 Tanner stages (female, pubic hair development).
- For subjects continuing from D1050326 into the open-label extension study:
    - For pubic hair development in male subjects, 28.2% shifted upwards by 1 Tanner stage, 13.6% by 2 Tanner stages, and 1.0% by 3 Tanner stages; similar results were reported for genital development (32.0%, 9.7%, and 1.0%, respectively). As expected, fewer male subjects $\geq$ 16 years of age increased in Tanner stage for genitalia development (none had an increase of 2 or more Tanner stages), while the youngest group (aged 10 to 12 years) experienced a greater percentage of upward shifts in Tanner stages compared to the overall population (particularly in increases by 2 Tanner stages).
    - For female pubic hair and breast development, an increase in 1 Tanner stage was observed in 31.2% and 26.9% of subjects, respectively, and an increase in 2 Tanner stages was observed in 6.5% and 7.5%, respectively. A larger proportion of female subjects aged 13 to 15 years experienced upward shifts in Tanner stages as compared to the overall population for both pubic hair and breast development.

Assessor's comment:

According to the MAH, in Study D1050326 lurasidone treatment had no apparent effect on menstrual cyclicity, and changes in Tanner staging from Baseline to Endpoint for male and female subjects were comparable between the lurasidone and placebo groups. Amenorrhea and galactorrhea were reported in 1 subject each.

Blood prolactin increased, breast enlargement, breast pain, galactorrhoea, erectile dysfunction, amenorrhoea, and dysmenorrhoea are labelled ADRs in adults.

## Other Clinical Assessments

The effects of lurasidone on suicidal ideation or behavior (as measured by the Columbia-Suicide Severity Rating Scale [C-SSRS]), cognitive performance (as assessed by the modified CogState Computerized

Cognitive Test Battery), changes in psychic effects (as captured by the Udvalg for Kliniske Undesogelser [UKU] Side Effect Rating Scale), and mania symptoms (as reflected on the YMRS) are summarized below.

C-SSRS:

- In Study D1050326: post-baseline suicidal ideation at any time after the start of double-blind treatment was reported by 10 (5.8%) subjects in the lurasidone group and 14 (8.2%) subjects in the placebo group. There was no reported suicidal behavior in either treatment group.
- In Study D1050302: any suicidal ideation was reported by 35 subjects (15.7%) and the emergence of serious suicidal ideation was reported by 9 subjects (4%). Any suicidal behavior was reported by 9 subjects (4%); no completed suicides reported.

CogState Computerized Cognitive Test Battery:

- In Study D1050326, there was no worsening in cognitive function in subjects treated with lurasidone when compared with subjects treated with placebo, as measured by the CogState Computerized Cognitive Test Battery.
- In Study D1050302, the mean ± SD at OL Baseline for cognitive composite standardized score was -0.94 ± 1.285; increases from OL Baseline (mean ± SD) indicated improvement starting from Week 12 (0.17 ± 1.066) and remained stable to Week 52 Endpoint (0.24 ± 1.071).

UKU:

- In Study D1050326: The changes from Baseline to Endpoint for the 4 UKU side effect category scores (psychic, neurological, autonomic, and other) and the UKU total score were generally similar between the lurasidone and placebo groups in Study D1050326, as well as between the subjects previously randomized to lurasidone and placebo groups in Study D1050302.

YMRS:

- In Study D1050326, change (LS mean ± SE) from Baseline to Endpoint in YMRS total score (using MMRM) was greater in the lurasidone group compared with the placebo group (-1.95 ± 0.305 vs. -1.09 ± 0.311, respectively, p=0.0245).
- In study D1050302, change from OL Baseline to Endpoint in YMRS total score (mean ± SD) was -2.2 ± 4.88.

Assessor's comment:

There was no reported suicidal behavior in Study D1050326, and no worsening in cognitive function in subjects treated with lurasidone compared with placebo. Any suicidal behavior was reported by 9 subjects (4%) in Study D1050302. Suicidal behaviour is a labelled ADR in adults.

# Overdose

There has been two report of lurasidone overdose in pediatric subjects with bipolar depression.

- Subject 302076003: On 17 May 2015, a nonfatal TESAE of intentional lurasidone overdose (subject reportedly ingested six 40 mg tablets) in association with a suicide attempt was reported for a 12-year-old female subject in the US after 13 days in Study D1050302. She had previously been randomized to lurasidone in the 6-week double-blind study. Study drug was withdrawn in

response to the event. The event resolved after 1 day; no concomitant therapy was reportedly initiated. The TEAE was considered possibly related to study drug by the Investigator.

- Subject 302005013: On 12 Apr 2016, a nonfatal TESAE of suicide attempt was reported for a 12-year-old female subject in the US after 457 days in Study D1050302. The subject reportedly took an overdose of 30 pills of lurasidone, 7 tablets of Vyvanse, and 12 tablets of Tylenol. She had previously been randomized to lurasidone in the 6-week double-blind study. The event was considered ongoing at the time of this report and no concomitant therapy was reportedly initiated (per the CIOMS, treatment included intravenous Acetadote [acetylcysteine]). The TEAE was considered not related to study drug by the Investigator.

Information on the management of overdose is included in the approved product label.

Assessor's comment:

Two cases of intentional lurasidone overdose in paediatric subjects with bipolar depression have been reported in the open label Study D1050302.

## Drug Abuse

No clinical studies of abuse potential with lurasidone were conducted in the pediatric population. There were no signals seen in pediatric subjects with bipolar depression suggesting drug abuse based on compliance and lack of potentially abuse-related adverse events, both during and after study drug discontinuation.

Consistent with the approved labeling, 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 (eg, development of tolerance, drug-seeking behavior, increases in dose).

## Withdrawal and Rebound

Based on the data available in the lurasidone pediatric clinical program, no safety signal has been identified following abrupt discontinuation of lurasidone treatment, nor has a withdrawal syndrome associated with lurasidone treatment cessation been observed. There have been no TEAEs of "drug withdrawal syndrome" (preferred term) reported to date in the pediatric subjects with bipolar depression.

Based on the nonclinical observation of dose-dependent motor hyperactivity in the post-treatment period (Section 5.7), hyperactivity-related adverse events with an onset after the last dose of study medication were analyzed for subjects who either early terminated Study D1050326 or did not enter the D1050302 long-term extension study. None of the 41 subjects from Study D1050326 who met these criteria experienced any post-treatment hyperactivity-related AEs. For subjects from Study D1050326 who either discontinued early or completed Study D1050302, none of the 71 subjects who met these criteria experienced any post-treatment hyperactivity-related AEs.

Assessor's comment:

According to the MAH, there were no signals seen in paediatric subjects with bipolar depression suggesting drug abuse; and no safety signal following abrupt discontinuation of lurasidone treatment, or withdrawal syndrome observed.

## Postmarketing Data

In total, the cumulative worldwide patient exposure to commercial Latuda® (lurasidone hydrochloride), from product launch through October 2016 is estimated at 2,697,692 patients and 761,267 patient-years.

As of October 27, 2016, a total of 18,697 serious and non-serious adverse drug reactions (ADRs) were received and entered in the Sunovion pharmacovigilance (PV) database. The most commonly reported ADRs categorized by MedDRA System Organ Class (SOC) were Psychiatric disorders (4,742), Nervous system disorders (3,667), General disorders and administration site conditions (2,115), and Gastrointestinal disorders (1,647).

The most commonly reported ADRs were Off label use (649), Drug ineffective (597), Nausea (568), Akathisia (537), Somnolence (459), Weight increased (410), Insomnia (355), Suicidal ideation (346), Anxiety (339), and Bipolar disorder (284).

Of the 18,697 ADRs reported, 2,095 were considered serious and 16,602 were non-serious. The most commonly reported serious ADRs were identified in the following SOCs: Psychiatric disorders (666) and Nervous system disorders (389).

The most commonly reported serious ADRs were Suicidal ideation (220), Seizure (65), Death (45), Suicide attempt (39), Neuroleptic malignant syndrome (36), Psychotic disorder (34), Completed suicide (33), and Aggression (27).

The review of the available safety data from launch to October 27, 2016 did not identify any potential signals of unanticipated or emerging risk with exposure to lurasidone. The safety profile does not differ from that observed in the clinical development program.

Assessor's comment:

The post-marketing data summarises the exposure and safety data as of October 27, 2016.

According to the MAH, there were no potential signals of unanticipated or emerging risk with exposure to lurasidone post-marketing. The safety profile does not differ from that observed in the clinical development program.

### *7.2. Discussion and Conclusion on the clinical safety*

As of October 27, 2016, a total of 283 children and adolescent subjects with bipolar depression have been exposed to lurasidone (175 subjects in the completed double-blind study D1050326 and 108 subjects newly exposed to lurasidone in the open-label extension study D1050302). The short- and long-term studies involving subjects with bipolar depression treated with flexibly-dosed lurasidone (20 to 80 mg/day) were 6 weeks and 24 months in duration.

In Study D1050326, exposure was comparable for lurasidone and placebo: 175 vs 172 subjects.

In open-label extension Study D1050302 (subjects from Study D1050326) at the data cut-off date (October 27, 2016): there is still limited experience on long-term use of lurasidone in the open-label extension study. Less than 100 patients exposed to lurasidone at least 1 year and only 17 subjects (7.6%) have completed the 104-week study by the time of interim analysis.

Safety data was assessed in the previous procedure EMEA/H/C/002713/P46/008. It was concluded in that procedure that treatment with lurasidone was generally safe and well tolerated in the dose range studied (20-80 mg/day) according to the CSR of Study D1050326. However, the frequency for weight increased (TEAEs and MMRM analysis) was higher in the lurasidone group than in the placebo group and there was an increase in BMI in the lurasidone group compared to the placebo group. These findings are not surprising but of special importance in children and adolescents. No clinically meaningful differences for other metabolic parameters were found. The safety was in line with the safety profile of earlier experience and studies in adults.

In the current submission, while weight increased occurred more frequently in lurasidone than in placebo group (6.9% and 1.7%, respectively), it was stated that the proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 4.0% and 5.3% for lurasidone- and placebo-treated subjects, respectively. Thus based on these figures, the effect on body weight seems inconsistent in lurasidone- and placebo-treated subjects.

No deaths occurred during the lurasidone pediatric studies summarized in this submission.

The MAH has presented /discussed the areas of clinical laboratory evaluation (including liver and renal function tests, metabolic parameters, muscle function, hormone assessments, C-reactive protein, hematology and urinalysis); vital signs, physical findings, and other observations (including growth parameters, menstrual cyclicity and Tanner staging, other clinical assessments such as effect on suicidal ideation or behavior, cognitive performance); overdose, drug abuse, withdrawal and rebound, based on D1050326 and D1050302 studies. Lurasidone did not have clinically relevant effects on vital signs or ECG assessments in these studies.

The post-marketing data summarises the exposure and safety data as of October 27, 2016. According to the MAH, there were no potential signals of unanticipated or emerging risk with exposure to lurasidone post-marketing. The safety profile does not differ from that observed in the clinical development program.

### Conclusion

The safety in the studied paediatric patients was in line with the safety profile of earlier experience and studies in adults, although the number of children and lurasidone treatment duration in the exposed subjects are still limited. No changes in Section 4.8 of the SmPC are recommended before further data are available based on a more extensive exposure in number of patients and duration, which was also the conclusion in the previous procedure EMEA/H/C/002713/P46/008.

## 8. Changes to the Product Information

As a result of this variation, section 5.1 of the SmPC is being updated to add new paediatric data in children and adolescent patients (10-17 years of age) with bipolar I disorder, based on study D1050326.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

(The MAH submitted the present type II - C.I.3.b variation in parallel to the ongoing renewal procedure (procedure no. EMEA/H/C/002713/R/0020 submitted on 20/05/2018). The alignment of the Product Information to the current QRD version has been proposed within the renewal procedure.)

# 9. Request for supplementary information (20 Sep 2018)

## *9.1. Other concerns*

### *Clinical aspects*

1. The amendment of SmPC section 5.1 to include the data from the D1050326 study in children and adolescent patients (10-17 years of age) with bipolar I disorder, is in principle acceptable. The proposed wording, however, needs to be revised as indicated in the attached PI-document.
2. It is noted that the figures on reported serious TEAEs considered definite, possibly, or probably related to lurasidone by the Investigator in open-label extension Study D1050302, were missing. The MAH should submit a line listing for the serious TEAEs including e.g. time to onset and to recovery, severity, causality, and actions taken.

# 10. Assessment of the responses to the request for supplementary information (received on 4th Sep 2018)

## *10.1. Other concerns*

### *Clinical aspects*

**Question 1**
The amendment of SmPC section 5.1 to include the data from the D1050326 study in children and adolescent patients (10-17 years of age) with bipolar I disorder, is in principle acceptable. The proposed wording, however, needs to be revised as indicated in the attached PI-document.

**Summary of the MAH's response**

The MAH has provided updated PI-document. The MAH has accepted most of the proposed changes of the SmPC. However, the MAH believed that NNT represents highly useful data that can provide additional information about effect size and aid clinicians in having a wider overview of the efficacy profile of the medicinal product, and provided revised text to ensure brevity as requested: "In a secondary efficacy analysis, treatment response (≥ 50% reduction in CDRS-R total score at study endpoint), was significantly greater in the lurasidone group than in the placebo group (59.5% versus 36.5%; NNT = 5; last observation carried forward [LOCF] at Week 6)."

**Assessment of the MAH's response**
Endpoints presented in SmPC section 5.1 are the primary and key secondary endpoints. The responder endpoint is not considered of such importance to the prescribers that it warrants inclusion. In addition, as mentioned in the previous sentence of the proposed SmPC text, the primary and key secondary efficacy endpoint was not met in younger patients (below 15 years of age), the calculated NNT contains uncertainties. Therefore, the revised text by the MAH is not considered acceptable.

Furthermore, the MAH is requested to clarify/confirm if the numbers presented in SmPC section 5.1 were confidence intervals. (**RSI**).

**Question 2**

It is noted that the figures on reported serious TEAEs considered definite, possibly, or probably related to lurasidone by the Investigator in open-label extension Study D1050302, were missing. The MAH should submit a line listing for the serious TEAEs including e.g. time to onset and to recovery, severity, causality, and actions taken.

**Summary of the MAH's response**

The MAH has provided a line listing for the serious TEAEs including e.g. time to onset and recovery, severity, causality, and actions taken.

**Assessment of the MAH's response**

According to the provided line listing, a total of 29 subjects (13.0%) reported serious TEAEs, with 1 considered definite, and 3 possibly, related to lurasidone by the Investigator, all being psychiatric disorders (e.g. returned or worsening of bipolar disorders, suicide attempt). In the line listing there was information on the AE start and end date, but no information on time from treatment start to onset of the AE. There were no comments on how the causality was made.

In the final report of Study D1050302, the MAH should take temporal relationship into account when making causality assessment. Issue not pursuit in this procedure.

**Conclusion**

☒ No need to update overall conclusion and impact on benefit-risk balance

# 11. Member State comments

MS1 comments:

For study D1050302, an open-label, 104 week study, an interim analysis with a cut-off date of 27 October 2016 was provided. This study enrolled subjects who had completed the acute efficacy study D1050326. The latter study was conducted from March 2014 through October 2016. (DelBello MP, Goldman R, Phillips D, Deng L, Cucchiaro J, Loebel A. Efficacy and Safety of Lurasidone in Children and Adolescents With Bipolar I Depression: A Double-Blind, Placebo-Controlled Study. J Am Acad Child Adolesc Psychiatry. 2017 Dec;56(12) :1015-1025.) Consequently, the long-term safety database should by now be considerably more comprehensive. In our view, safety data from the open-label study should be submitted and assessed as part of this procedure. If the final study report is not yet available, then an up-to date 'interim' analysis should be provided.

We concur with the Rapporteur's comments (sections 4.2 and 5.1). A paediatric subheading should also be included in section 4.8 in our view.

Assessor's comment:

In the previous procedure (EMEA/H/C/002713/P46/008) the CHMP did not recommend changes in Section 4.8 of the SmPC before further data are available based on a more extensive exposure in number of patients and duration.

As the studies are not sufficient for a new indication in pediatric population to be approved, it is the Rapporteur's opinion that there is no need to require an extra interim analysis of the open study D1050302 at this stage, considering also that the final report of this study is expected in June 2019.

However, the rapporteur recommends to include a short sentence about safety based on the short-term study in section 5.1 of the SmPC for the completeness: "**The safety profile of lurasidone in children included in this short-term study is in line with that in adults treated within the approved indication.**"

# 12. Request for supplementary information (20th Sep 2018)

## *12.1. Other concerns*

### *Clinical aspects*

1. The proposed changes of SmPC section 5.1 to include the data from the D1050326 study in children and adolescent patients (10-17 years of age) with bipolar I disorder, need to be revised as indicated in the attached PI-document.

# 13. Assessment of the responses to the request for supplementary information (26th Sep 2018)

## *13.1. Other concerns*

### *Clinical aspects*

**Question 1**

The proposed changes of SmPC section 5.1 to include the data from the D1050326 study in children and adolescent patients (10-17 years of age) with bipolar I disorder, need to be revised as indicated in the attached PI-document.

**Summary of the MAH's response**

The MAH has submitted revised SmPCs (25 Sep 2018) following the Rapporteur's comments

**Assessment of the MAH's response**

The MAH has submitted revised SmPCs following the Rapporteur's comments. However, the Rapporteur's recommendations have not been followed appropriately and further revision is needed. See also the comments as indicated in the attached PI-document.

In summary,

1. The MAH did not delete the sentence regarding NNT as requested by the Rapporteur and without providing any further clarification. The Rapporteur is still of the opinion that "Endpoints presented in SmPC section 5.1 are the primary and key secondary endpoints. The responder endpoint is not considered of such importance to the prescribers that it warrants inclusion. In addition, as mentioned in the previous sentence of the proposed SmPC text, the primary and key secondary efficacy endpoint was not met in younger patients (below 15 years of age), the calculated NNT contains uncertainties. Therefore, the proposed text by the MAH is not considered acceptable and should be deleted."

2. The MAH included detailed safety data in section 5.1 which was not intended in the Rapporteur's recommendation. It is considered sufficient with the included sentence stating that the safety profile in children being consistent with that in adults ("The safety profile of lurasidone in children included in this short-term study is consistent with that observed when treated within the approved indication in adults."). The MAH proposed text with detailed safety data and table 2.2 are therefore not accepted and should be removed.

# 14. Assessment of the MAH responses (dated 3 Oct 2018) to the request for supplementary information

## *14.1. Other concerns*

### *Clinical aspects*

1. The proposed changes of SmPC section 5.1, need to be revised as indicated in the attached PI-document.

**Summary of the MAH's response**

The MAH has submitted revised SmPCs (3 Oct 2018) following the Rapporteur's comments.

**Assessment of the MAH's response**

The MAH has in the revised SmPCs accepted the Rapporteur's comments. However, a part was missing in the clean version of the 5.1 text, which should be included (see Attached Product Information).

# 15. Member State comments

MS1:

We agree with Rapporteur's assessment report.

MS2:
We have reviewed the Rapporteur's report and comments on the PI.
We agree with the Rapporteur's proposals as regards the representation of efficacy data, but note that the incidence of nausea in adults is listed as 'common' (i.e. ≥ 1/100 to < 1/10) in section 4.8 whilst it is 16%, i.e. 'very common' in the paediatric depression study. The safety profile of lurasidone in children included in this short-term study is therefore not entirely consistent with that observed when treated within the approved indication in adults. Differences in frequency and severity of adverse effects across populations should be reflected in the SmPC.

Assessor's comment on the MS1 comments:

The comments by MS1 are endorsed.

According to the safety table provided by the MAH for paediatric patients (10-17 years) and comparing with SPC section 4.8 information in adults, the following difference in frequency of adverse reactions was noted:

| | Adults | Children | Ying's Comment |
|---|---|---|---|
| GI disorders:<br>Nausea | Common | Very common | Could be reflected. |
| GI disorders:<br>Diarrhea | Unknown | Common | Could be reflected. |
| Metabolism and nutrition disorders:<br>Decreased appetite | Uncommon | Common | Could be reflected. |
| Psychiatric disorders: | Nightmare Uncommon | Abnormal dreams – common | Different terms were used. Abnormal dreams occurred equally (2%) in placebo and Lurasidone groups in Children. No need to specify. |

Therefore, the following amendment to the proposed wording in SmPC section 5.1 (in **bold**) regarding safety profile based on the short-term study is recommended:

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

# 16. Assessment of the MAH responses (dated 12 Oct 2018) to the request for supplementary information

## *16.1. Other concerns*

### *Clinical aspects*

1. The proposed changes of SmPC section 5.1, need to be revised as indicated in the attached PI-document.

**Summary of the MAH's response**

The MAH has submitted revised SmPCs following the Rapporteur's comments (11th Oct 2018).

**Assessment of the MAH's response**

The MAH has accepted the Rapporteur's comments in the revised SmPC (see Attached Product Information).

The procedure is recommended for approval.