Sunovion has submitted two separate supplements to the original NDA (S26 and S27; for Latuda, lurasidone oral tablets) both as a Prior Approval Supplement (PAS) and a Submission of Pediatric Study Reports-Exclusivity Determination. The two supplements included the same pharmacokinetic (PK) study report in children and adolescents 6-17 years (Study D1050300). The PK study was submitted to fulfill the post-marketing requirement (PMR) listed as 1701-1 in the original approval letter (dated 10/28/2010). The PK study is also used to satisfy the written request (WR) issued by the agency (dated 04/20/2012). In addition, the following studies were submitted in each supplement.

- Study D1050301 was submitted in S26, which provides clinical efficacy and safety information to support the approval of lurasidone in the treatment of adolescent patients with schizophrenia.
- Study D1050325 was submitted in S27, which provides clinical efficacy and safety information in children and adolescents with irritability associated with autistic disorder.

The office of Clinical Pharmacology finds that the supplements are acceptable from the clinical pharmacology’s point of view. The design and conduct of the pediatric pharmacokinetic study (Study D1050300) are consistent with the requirements listed under the issued WR and this study has fulfilled the PMR. There are no additionally identified PMR studies at this time.
The PK study indicated that:

- The exposure of lurasidone (i.e., steady-state Cmax and AUC: Figure 1 and Figure 2) was similar in children and adolescents 10 – 17 years and adult patients for doses from 40 mg to 160 mg without adjusting for body weight.
- For the younger children (i.e., 6-9 year), the exposure of lurasidone (i.e., steady-state Cmax and AUC) was found to be similar to adult patients for doses from 40 mg to 80 mg, even though there seemed to be similar exposures (steady-state Cmax and AUC) in younger children (i.e., 6- 9 years) both at the 20 mg and at 120 mg dose level.

Based on these results, the intended doses of 40 mg and 80 mg for the treatment of schizophrenia in adolescents yielded similar exposure to adults, and hence are acceptable from the OCP’s point of view.

**Labeling Recommendations:**

Label language change to section 12.3:

- **Sponsor’s version:**

- **Reviewer recommendation:**

The LATUDA exposure (i.e., steady-state Cmax and AUC) in children and adolescent patients (10 to 17 years of age) was generally similar to in adults when administered the same dose from 40 to 160 mg without adjusting for body weight.
Figure 1: Lurasidone Exposure (C\textsubscript{max}) in Pediatric Subjects (Different Age Strata’s) compared to Adult Subjects for Various Doses (20 mg to 160 mg)
Figure 2: Lurasidone Exposure (AUC) in Pediatric Subjects (Different Age Strata’s) compared to Adult Subjects for Various Doses (20 mg to 160 mg)
Appendix: Review of Individual Study Report
8. STUDY OBJECTIVES

This study evaluated the PK profiles of lurasidone administered at doses of 20, 40, 80, 120, and 160 mg/day to pediatric subjects aged 6 to 17 years. The safety and tolerability of these doses were also assessed.

8.1. Primary Objective

The primary objective was to characterize the PK and assess safety and tolerability of single and multiple oral doses of 20, 40, 80, 120, or 160 mg/day lurasidone in subjects 6 to 17 years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders.

8.2. Secondary Objective

The secondary objective was to characterize the PK for metabolites of lurasidone (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) following single and multiple oral doses of 20, 40, 80, 120, or 160 mg/day lurasidone in subjects 6 to 17 years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders.

Study Design:

- Open label, single-dose and multiple-dose lurasidone PK study.
- Male and female subjects from 6 to 17 year years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders.
- Sequential escalating doses of lurasidone (20, 40, 80, 120, or 160 mg/day) were administered to the four age groups (6 to 9, 10 to 12, 13 to 15, and 16 to 17 years) of subjects.
- Thus, all dose levels (i.e., 20 mg to 160 mg) were dosed to all age groups except the highest dose of 160 mg which was not dosed to the youngest cohort of 6-9 year subjects.
This was a Phase 1, open-label, multicenter, single- and multiple-ascending lurasidone dose study in subjects from 6 to 17 years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders. Sequential escalating doses of lurasidone (20, 40, 80, 120, or 160 mg/day) were administered to 4 age groups (6 to 9, 10 to 12, 13 to 15, and 16 to 17 years) of subjects. All subjects received a single dose of lurasidone followed by a 2-day washout period, then once-daily dosing of lurasidone for 7 days (20 mg through 120 mg cohorts) or 9 days (160 mg cohort).

Approximately 100 subjects were planned to be enrolled to obtain 80 completed subjects in the 4 age groups. To reach 20 completed subjects per age group (i.e., 4 subjects/age group/dose level × 5 doses), clinical sites were to collectively enroll approximately 25 subjects per age group.

For subjects in the 20 to 120 mg cohorts, there was a screening period (Day -28 to Day -2), followed by a study period (Day -1 to Day 11), and a follow-up period (7 [±3] days after discharge on Day 11, i.e., Day 18 [±3]). During the study period, subjects had 2 inpatient visits (Day -1 to Day 2, and Day 9 to Day 11) for dosing and study assessments, 3 outpatient visits (Days 3, 5 and 7), and a telephone contact (Day 6) for assessment of safety and study drug compliance. At the discretion of the investigator, subjects were allowed to remain inpatient from Day -1 through Day 11. Subjects who met study entry criteria but were not enrolled into the study could have been rescreened once more for possible enrollment into this study.

The total study participation for subjects in the 20 to 120 mg cohorts could have lasted up to approximately 49 days.

For subjects in the 160 mg cohort only, there was a screening period (Day -28 to Day -2), followed by a study period (Day -1 to Day 13), and a follow-up period (7 [±3] days after discharge on Day 13, i.e., Day 20 [±3]). During the study period, subjects had 2 inpatient visits (Day -1 to Day 2, and Day 11 to Day 13) for dosing and study assessments, 3 outpatient visits (Days 3, 5 and 7), and a telephone contact (Day 6) for assessment of safety and study drug compliance. At the discretion of the investigator, subjects were allowed to remain inpatient from Day -1 through Day 13.

The total study participation for subjects in the 160 mg cohort could have lasted up to approximately 51 days.

Dosing was initiated at the 20 mg cohort for each age group. Dosing of subsequent dose cohorts in each age group did not occur until a review of safety data from the prior dose level for each age group had been completed (see Section 9.1.2). Dosing was initiated and maintained at the same dose for each dose cohort (e.g., the 20 mg/day dose cohort was initiated and continued at 20 mg/day) except for the 120 and 160 mg cohorts.

For the 120 mg cohort, the following dosing scheme was used: Day 1, 80 mg; Days 4 to 5, 80 mg; and Days 6 to 10, 120 mg.

For the 160 mg cohort, the following dosing scheme was used: Day 1, 80 mg; Days 4 to 5, 80 mg; Days 6 to 7, 120 mg; and Days 8 to 12, 160 mg.
**Administration**

Oral

**Sampling Times**

Blood was collected for measurement of luradione and its metabolite concentrations at predose and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours post Day 1 dose administration, and predose and at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post Day 10 dose administration.
Pharmacokinetic assessments for serum lurasonide and its metabolite concentrations included the following: 48 hour serial blood sampling following Day 1 dose administration (predose, 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose); and 24 hour serial blood sampling following Day 10 (or Day 12) dose administration (predose, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose). Collected serum samples were analyzed by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

Pharmacokinetic parameters were derived using noncompartmental methods with WinNonlin® Professional version 5.2 (Pharsight Corp., Mountain View, California, US). All PK computations were performed using WinNonlin Professional 5.2 or SAS® version 9.2 (SAS Institute, Inc., Cary, North Carolina, US). Graphics were prepared with SAS version 9.2; SigmaPlot® 9.0 (Systat Software, Inc., San Jose, California, US); or WinNonlin Professional 5.2.

The following PK parameters for lurasonide and its metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) were estimated by noncompartmental methods using actual elapsed time from dosing on Day 1 and Day 10 (or Day 12 for the 160 mg cohort). If actual times were not available, nominal times were used.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$</td>
<td>Maximum concentration in the sampled matrix (ng/mL), obtained directly from the observed concentration versus time data.</td>
</tr>
<tr>
<td>$t_{max}$</td>
<td>Time of maximum concentration (h), obtained directly from the observed concentration versus time data.</td>
</tr>
<tr>
<td>$C_{trough}$</td>
<td>Concentration in the sampled matrix (ng/mL) at 24 hours postdose on Day 10 (or Day 12 for the 160 mg cohort), obtained directly from the observed concentration versus time data.</td>
</tr>
<tr>
<td>AUC$_{0-24}$</td>
<td>Area under the concentration-time curve in the sampled matrix from zero (predose) to 24 hours (ng·h/mL), calculated by linear up/log down trapezoidal summation.</td>
</tr>
</tbody>
</table>
Blood samples were collected and processed to obtain serum samples for the concentration measurements of lurasidone and its major metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220).

Pharmacodynamics were not assessed for this study.

Pharmacodynamics were not assessed for this study.
9.5.1.6.1.2. Collecting and Recording Adverse Events

Adverse events were collected and recorded for each subject from the date informed consent/assent was signed until the end of their participation in the study, ie, the subject discontinued or completed the study.

Following the end of the subject’s participation in the study, the investigator or an authorized delegate reported SAEs ‘spontaneously’ if considered at least possibly related to study drug (see Section 9.5.1.6.1.4).

Adverse events were volunteered spontaneously by the study subject, or discovered by the study staff during physical examinations or by asking an open, nonleading question such as ‘How have you been feeling since you were last asked?’ All AEs and any required remedial action were recorded in the subject’s source documentation and transcribed onto the appropriate eCRF page for the treatment period indicated. The nature of the AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken of the AE were documented together with the investigator’s (or a physician listed on the Form FDA 1572) assessment of the seriousness of the AE and causal relationship to study drug and/or study procedure (at the time of assessment).

All AEs were recorded individually in the study subject’s own words (verbatim) unless, in the opinion of the investigator, the AEs constituted components of a recognized condition, disease or syndrome. In the latter case, the condition, disease, or syndrome was named rather than each individual sign and/or symptom. Rashes were identified as type, extent, and location.

9.5.1.6.1.3. Assessment of Adverse Events

The investigator or a physician listed on the Form FDA 1572 assessed all AEs for severity, relationship with study drug, and for whether it met the criteria for classification as an SAE, requiring immediate notification to the sponsor (see Section 9.5.1.6.1.3). These assessments were made in accordance with the standard ratings detailed in Table 6 (severity) and Table 7 (causality).

<table>
<thead>
<tr>
<th>Table 6: Severity Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
</tbody>
</table>

When changes in the intensity of an AE occurred more frequently than once a day, the maximum intensity for the event was noted for that day. Any change in severity of signs and symptoms over a number of days was captured by recording a new AE, with the amended severity grade, and the date (and time, if known) of the change.
Analytical Method

<table>
<thead>
<tr>
<th>Method Type</th>
<th>LC/MS/MS</th>
<th>Matrix</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytes</td>
<td>Lurasidone and its major metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Validation

- Method validated prior to use ✔ Yes □ No
- Method validation acceptable ✔ Yes □ No

Study Sample Analysis

- Samples analyzed within the established stability period ✔ Yes □ No
- Quality control samples range acceptable ✔ Yes □ No
- Chromatograms provided ✔ Yes □ No
- Accuracy and precision of the calibration curve acceptable ✔ Yes □ No
- Accuracy and precision of the quality control samples acceptable ✔ Yes □ No
- Overall performance acceptable ✔ Yes □ No

Study Population

A total of 105 subjects (males and females patients between the age of 6-17 year) participated in the study and received at least 1 dose of study drug; therefore, 105 subjects were included in the safety population. Of these, 90 (85.7%) subjects completed all study procedures per protocol and received all planned doses of study drug.

Summary of demographics

Table 1: Demographics and baseline characteristics of all subjects (ages 6-17 year)
Table 2: Primary psychiatric history by dose cohorts for all subjects (ages 6-17 year)

<table>
<thead>
<tr>
<th>Reported Term*</th>
<th>Dose Cohort - All Age Groups (6-17 Years) Combined</th>
<th>All Subjects: N=105</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg N=20</td>
<td>40 mg N=25</td>
</tr>
<tr>
<td>ADHD with Conduct Disorder/DDB, NOS</td>
<td>16 (80.0)</td>
<td>16 (64.0)</td>
</tr>
<tr>
<td>Bipolar Spectrum Disorder, Bipolar I</td>
<td>2 (10.0)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Bipolar Spectrum Disorder, NOS</td>
<td>1 (5.0)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>PDD/ASD, Autistic Disorder</td>
<td>1 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Schizophrenia Spectrum Diagnosis Schizoaffective</td>
<td>0</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Schizophrenia Spectrum Diagnosis Schizophrenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tourette’s Syndrome</td>
<td>0</td>
<td>1 (4.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD = attention-deficit hyperactivity disorder; ADI-R = Autism Diagnostic Interview, Revised; ASD = autistic spectrum disorder; DBD = Disruptive Behavior Disorder; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision; MINI-Kid = Mini-International Neuropsychiatric Interview-Kid; N = number of subjects enrolled; n = number of subjects in category; NOS = Not Otherwise Specified; PDD = pervasive developmental disorder.

Notes: Subjects are counted only once per reported term.
Note: Psychiatric disorders are coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0.
* Diagnosis was via clinical interview using MINI-Kid and diagnostic interview, and the DSM-IV-TR as a reference. Autistic disorder was confirmed by the ADI-R.
Results

Pharmacokinetic Results

**Figure 2:** Mean (SD) Lurasidone Serum Concentration-time Profiles on Day 1

**Figure 3:** Mean (SD) Lurasidone Serum Concentration-time Profiles on Day 10 (or Day 12 for the 160 mg cohort)

**Table 3:** Summary of Lurasidone Key Pharmacokinetics Parameters for All Age Groups on Day 1
Table 4: Summary of Lurasidone Key Pharmacokinetics Parameters for All Age Groups on Day 10 (or Day 12 for 160 mg)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Statistic</th>
<th>AUC_{tot} \ (ng \ h/mL)</th>
<th>AUC_{ unchanged} \ (ng \ h/mL)</th>
<th>C_{max} \ (ng/mL)</th>
<th>t_{max} \ (h)</th>
<th>t_{1/2} \ (h)</th>
<th>CL/F \ (L/h)</th>
<th>V_{z/F} \ (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>n</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>78.0</td>
<td>83.8</td>
<td>24.4</td>
<td>1.97</td>
<td>16.2</td>
<td>346</td>
<td>6940</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>44.9</td>
<td>48.3</td>
<td>14.1</td>
<td>0.94</td>
<td>4.68</td>
<td>245</td>
<td>3030</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>18.5</td>
<td>19.5</td>
<td>4.63</td>
<td>0.50</td>
<td>6.27</td>
<td>104</td>
<td>2630</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>64.8</td>
<td>69.1</td>
<td>22.8</td>
<td>2.00</td>
<td>17.2</td>
<td>290</td>
<td>5930</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>179</td>
<td>192</td>
<td>53.8</td>
<td>4.00</td>
<td>25.4</td>
<td>1020</td>
<td>11800</td>
</tr>
<tr>
<td>40 mg</td>
<td>n</td>
<td>24</td>
<td>19</td>
<td>24</td>
<td>24</td>
<td>20</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>140</td>
<td>153</td>
<td>38.4</td>
<td>1.83</td>
<td>21.3</td>
<td>317</td>
<td>8700</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>65.4</td>
<td>69.8</td>
<td>22.4</td>
<td>0.82</td>
<td>7.26</td>
<td>144</td>
<td>3500</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>36.8</td>
<td>58.1</td>
<td>5.10</td>
<td>1.00</td>
<td>11.1</td>
<td>134</td>
<td>4740</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>128</td>
<td>134</td>
<td>32.9</td>
<td>2.00</td>
<td>18.8</td>
<td>299</td>
<td>7740</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>292</td>
<td>299</td>
<td>94.2</td>
<td>4.00</td>
<td>38.4</td>
<td>689</td>
<td>17300</td>
</tr>
<tr>
<td>80 mg</td>
<td>n</td>
<td>54</td>
<td>50</td>
<td>55</td>
<td>55</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>300</td>
<td>328</td>
<td>68.2</td>
<td>2.16</td>
<td>16.8</td>
<td>324</td>
<td>7640</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>140</td>
<td>163</td>
<td>37.5</td>
<td>1.01</td>
<td>5.42</td>
<td>240</td>
<td>5390</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>47.8</td>
<td>51.6</td>
<td>6.33</td>
<td>0.50</td>
<td>8.17</td>
<td>82.3</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>276</td>
<td>299</td>
<td>58.3</td>
<td>2.00</td>
<td>16.4</td>
<td>269</td>
<td>6490</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>770</td>
<td>972</td>
<td>197</td>
<td>6.00</td>
<td>32.7</td>
<td>1550</td>
<td>31800</td>
</tr>
</tbody>
</table>

Abbreviations: SD = standard deviation; Min = minimum; Max = maximum.
Source: Table 14.2.7.
The observed lurasidone pediatric pharmacokinetic exposures following multiple-dose administration (Cmax and AUC0-tau) across the dose range studied (20-160 mg) were generally within the simulated adult exposure ranges for the same dose and durations in adults.
Figure 4: Lurasidone Exposure (Cmax) in Pediatric Subjects (different age strata’s) compared to Adult Subjects for various doses (20 mg to 160 mg)
Figure 5: Lurasidone Exposure (AUC) in Pediatric Subjects (different age strata’s) compared to Adult Subjects for various doses (20 mg to 160 mg)

Therefore, the overall exposure (i.e., both Cmax and AUC values) for lurasidone remain similar in all age strata (i.e., across all age groups from 6 years up to adults) when they get administered the same dose in mg. Thus, no dose adjustment based on weight was required to match the exposures in efficacy studies conducted in children and adolescents.

Safety Results
Was there any death or serious adverse events? □ Yes  □ No  □ NA
Overall Sponsor Conclusions

The observed lurasidone pediatric PK exposures (C\textsubscript{max} and AUC\textsubscript{0-24}) following multiple dose administration, in subjects age 6 to 17 years, across the daily dose range studied (20 to 160 mg) were generally similar to adult exposures previously observed at steady state. Overall, lurasidone was generally tolerated by all age groups at daily doses of up to 80 mg with an adverse event profile that was similar to prior studies in adults.
1. **Study Design:**
   An open label single and multiple dose PK study in subjects from 6 to 17 years old with schizophrenia spectrum, bipolar spectrum, autistic spectrum disorder, or other psychiatric disorders was an appropriate study design to assess the PK of lurasidone (and its metabolites) in the patients of various age strata (i.e., 6 to 17 years). The study provided PK on both day 1 as well as on steady state (day 10) for children and adolescents. The sequential escalating doses of lurasidone made the design safe and prudent design in children.
   - **Dose:** Sequential escalating doses of lurasidone (20, 40, 80, 120, or 160 mg/day) were administered to the four age groups (6 to 9, 10 to 12, 13 to 15, and 16 to 17 years) of subjects. Thus, all dose levels (i.e., 20 mg to 160 mg) were dosed to all age groups except the highest dose of 160 mg which was not dosed to the youngest cohort of 6-9 year subjects.
   - **Sample Size:** A total of 105 subjects (males and females patients between the ages of 6-17 year) participated in the study, which is considered acceptable to assess the PK.
   - **Age range and gender representation of the patients:** The study included 20 or more patients in each of the age strata’s: 6-9 year, 10-12 year, 13-15 year and 16-17 year. It had representation from both genders: 65% males and 35% female and included 78% whites and 22% blacks/African Americans.
   - **PK samples:** Complete PK profiles were obtained on day 1 as well as at steady state at all dose levels for all age strata’s.
   - **Restrictions on co-medication that may affect PK:** Excluded use of inhibitors or inducers of CYP3A4’s.
   - **Restrictions on organ dysfunction patients:** Excluded any subjects with hepatic impairments.
   - **Moieties measured:** lurasidone and its major metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) are all measured in the pediatric PK study.
   - **Data Analysis:** NCA analysis was performed. Major PK parameters including Cmax, Tmax, AUC0-24 (at steady state and Day 1) and AUC 0-inf are all assessed.

2. **Protocol deviation:**
   No significant deviations were observed which could impact the quality of PK data.

3. **Subject Exclusion:**
   Three subjects (Subjects 300013225, 300013226, and 300013251) were excluded from the pharmacokinetic analysis for Study D1050300. Blood samples for these 3 subjects were collected but not analyzed due to the samples being stored at inappropriate condition. We agree that the samples that are inappropriately handled may yield inaccurate results. Given that the storage issue occurred randomly in the three subjects, we do not expect the final conclusion on PK should be affected in any way after the three subjects are excluded.

4. **Bioanalytical Method:**
   An acceptable and validated LC/MS/MS methodology with rigorous quality control and calibration data for all moieties of interest provides assurance for the quality of the PK data.

5. **Pharmacokinetic findings:**
   The PK study indicated that:
   - The exposure of lurasidone (i.e., steady-state Cmax and AUC: Figure 4 and Figure 5) was similar in children and adolescents 10 – 17 years and adult patients for doses from 40 mg to 160 mg without adjusting for body weight.
   - For the younger children (i.e., 6-9 year), the exposure of lurasidone (i.e., steady-state Cmax and
AUC) was found to be similar to adult patients for doses from 40 mg to 80 mg, even though there seemed to be a higher exposures (steady-state Cmax and AUC) in younger children (i.e., 6-9 years) both at the 20 mg and at 120 mg dose level.

Based on these results, the intended doses of 40 mg and 80 mg for the treatment of schizophrenia in adolescents yielded similar exposure to adults, and hence are acceptable from the OCP’s point of view.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRAVEEN BALIMANE
12/23/2016

HAO ZHU
12/23/2016

Reference ID: 4033257