

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**200603**

**OTHER REVIEW(S)**

Medical Officer's Consult Review of NDA 200-603  
Ophthalmology Consultation

Submission date: December 30, 2009  
Review date: October 23, 2010  
Sponsor: Sepracor, Inc.  
Drug: Lurasidone HCl

Pharmacologic Category: Antipsychotic with high affinities to D2 and 5HT2 receptors

Proposed Indication: Acute treatment of schizophrenia in adults

Requested Consult: The NDA for lurasidone was submitted to our Division (NDA 200603 [IND 61,292]) in December 2009 and the 120-day safety update submitted April 29, 2010. Lurasidone is an antipsychotic agent with high affinities to D2 and 5HT2 receptors as well as melanin-binding properties. Due to the melanin-binding, the Sponsor was advised to obtain ophthalmologic examinations in one of their long-term clinical trials. The Sponsor incorporated ophthalmologic examinations at specific timepoints (baseline, 6 months, 12 months, 18+ months) in study D1050237 and D1050237E. Study D1050237 was a randomized, double-blind, 12 month study evaluating the safety of lurasidone (flexible dose) and risperidone (flexible dose) and Study D1050237E was a 6-month open-label extension to the double-blind study (lurasidone flexible dose). A subset of subjects were to undergo ophthalmologic examinations including visual acuity, dilated funduscopy examination, slit-lamp examination and external eye examination. In the NDA, the Sponsor had reported these findings as either "normal" or "abnormal" and the Division requested that more information regarding abnormal findings be submitted. The 120-day safety update includes additional clinical data for these ophthalmologic findings.

Please evaluate the ophthalmologic examination findings with regard to overall risk of ophthalmologic adverse events with lurasidone.

It is understood that conclusions may be hampered by lack of a placebo group and by the low numbers of available assessments - ~38 lurasidone-treated patients had baseline and post-baseline assessments and data for 85 patients with baseline and post-baseline assessments are still blinded at this time.

The EDR link for the 120-day safety update: <\\CDSESUB1\EVSPROD\NDA200603\0008>

|   | Unblinded Subjects <sup>a</sup>                  |  | Blinded Subjects <sup>d</sup> |
|---|--|--|-------------------------------|
|   | Lurasidone <sup>b</sup><br>(D1050237/ D1050237E) | Risperidone <sup>c</sup><br>(D1050237) |                               |
| <b>Number of Subjects with One or More Ophthalmologic Assessments</b>                   | <b>115</b>                                       | <b>46</b>                              | <b>158</b>                    |
| Baseline Assessment Only  | 77   | 31                                     | 73                            |
| Baseline and Post-baseline Assessments  | 38 <sup>e</sup>                                  | 15 <sup>e</sup>                        | 85                            |
| <b>Number of Subjects with ANY Ophthalmologic Abnormality<sup>f</sup></b>               | <b>51</b>  | <b>21</b>                              | <b>79</b>                     |
| Baseline Assessment Only  | 33   | 15                                     | 27                            |
| Baseline and Post-baseline Assessments  | 18   | 6                                      | 52                            |
| <b>Number of Subjects with Post-baseline Assessment and ANY Abnormality<sup>f</sup></b> | <b>18</b>  | <b>6</b>                               | <b>52</b>                     |
| Subjects with No Clinically Significant Findings <sup>i</sup>                           | 15   | 5                                      | 48                            |
| New Post-Baseline Abnormality   | 4  | 2                                      | 15                            |
| No change from Baseline   | 7  | 2                                      | 28                            |
| Improved from Baseline  | 2  | 1                                      | 4                             |
| Incomplete Assessment at Baseline or Post-Baseline                                      | 2 <sup>g,h</sup>                                 | 0                                      | 1 <sup>j</sup>                |
| Subjects with Clinically Significant Findings <sup>i</sup>                              | 3  | 1                                      | 4                             |
| New Post-Baseline Abnormality   | 1 <sup>k</sup>                                   | 1 <sup>l</sup>                         | 1 <sup>m</sup>                |
| No change from Baseline   | 1  | 0                                      | 3                             |
| Improved from Baseline  | 1  | 0                                      | 0                             |

a Unblinded subjects are subjects who discontinued or completed Study D1050237 double-blind phase as of 01 Jul 2009.

b Subjects who took at least one dose of lurasidone in Study D1050237 and/or D1050237E (open-label extension).

c Subjects who took at least one dose of risperidone in Study D1050237.

d Blinded subjects are subjects who discontinued or completed Study D1050237 after 01 Jul 2009 or who are ongoing as of 01 Dec 2009.

e Four subjects received risperidone in the double-blind core phase (D1050237) and lurasidone in the extension phase (D1050237E) but are only counted once in the total (n = 315). These subjects did not have any ophthalmologic abnormalities.

f At least one clinically significant finding on any test.

g Subject D1050237-0014-00005 did not have an assessment for extra-ocular eye movement (EOM) performed at baseline, but did have abnormal not clinically significant finding of exotropia noted in the right eye at Visit 11 which was classified as "incomplete assessment at Baseline or Post-baseline", and was therefore not assessed for change (ophthalmologic abnormality reported at Visit 11 only for this subject).

h Subject D1050237-0033-0006 did not have assessment for contrast sensitivity performed at baseline but did have an abnormal not clinically significant finding at Visit 11 noted in both eyes which was classified as "incomplete assessment at Baseline or Post-baseline", and was therefore not assessed for change (ophthalmologic abnormality reported at Visit 11 only for this subject).

i For subjects with multiple abnormalities, tabulations were based on the most severe change.

j Subject D1050237-0033-0010 did not have assessment for contrast sensitivity performed at baseline but did have an abnormal not clinically significant finding at Visit 11 noted in both eyes which was classified as "incomplete assessment at Baseline or Post-baseline", and was therefore not assessed for change (ophthalmologic abnormality reported at Visit 11 only for this subject).

**Reviewer's Comments:** *Few subjects in the study have had post-baseline ophthalmic examinations. Of the lurasidone group, only 38 subjects have had a post-baseline exam and 18 of them had an ophthalmic abnormality. The majority of these, 15 are reported as being clinically insignificant. The three reported as clinically significant are cataracts, however, there were cataracts present at baseline and it is not possible to determine whether there was any change.*

*Of the patients remaining masked to treatment. Only 85 have had a post-baseline ophthalmic examination. Most of these have had a reported ophthalmic abnormality (n=52), but the abnormality is reported as being clinically insignificant (n=48). The four reported as clinically significant are reports of either a cataract or optic nerve changes consistent with glaucoma in patients with pre-existing cataracts or glaucoma respectively.*

*There is a single report of bilateral crystalline deposits in the central macular bilaterally in patient D1050237-0018-00032/48/B/F. Visual acuity of the subject is not reported. If this subject received lurasidone, further follow-up is warranted.*

**Summary/Recommendations:**

- 1. There are no ophthalmic findings reported to date which need to be considered in a benefit-to-risk decision of the use of lurasidone in the treatment of acute treatment of schizophrenia in adults.*
- 2. It is recommended that additional ophthalmic follow-up as currently planned be obtained and reported.*
- 3. Additional follow-up on patient D1050237-0018-00032/48/B/F is warranted.*

Wiley A. Chambers, M.D.  
Supervisory Medical Officer, Ophthalmology

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WILEY A CHAMBERS  
10/23/2010

**MEMORANDUM**  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** October 22, 2010

**To:** Ann Sohn  
Regulatory Project Manager  
Division of Psychiatry Products (DPP)

**From:** Jessica Cleck Derenick, PhD  
Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** **DDMAC Comments on LATUDA® (lurasidone HCl) label**  
NDA# 200603

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DDMAC has reviewed the proposed product labeling (PI) for LATUDA® (lurasidone HCl) tablets submitted for DDMAC review on August 24, 2010.

The following comments, using the proposed PI sent via email on October 20, 2010 by Ann Sohn, are provided directly on the marked up version of the label attached below.

If you have any questions about DDMAC's comments, please do not hesitate to contact us.

**General Comments:**

1.  (b) (4)

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JESSICA N CLECK DERENICK  
10/22/2010

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: October 21, 2010

To: Thomas Laughren, MD, Director  
Division of Psychiatry Products

Through: Melina Griffis RPh, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Richard Abate, RPh, MS, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Latuda (Lurasidone HCl) Tablets 40 mg, 80 mg, and 120 mg

Application Type/Number: NDA 200603

Applicant/sponsor: Sunovion Pharmaceuticals

OSE RCM #: 2010-64-1

## **1 INTRODUCTION**

This review evaluates the revised container labels and carton labeling for Latuda (Lurasidone HCl) Tablets in NDA 200603 dated August 9, 2010 and the container labels and blistercards dated October 15, 2010. The Applicant submitted revised labels and labeling August 9, 2010 with revisions based on comments DMEPA made in our July 1, 2010 review and included a new proposed proprietary name, (b) (4). DMEPA has since notified the Applicant the proposed name, (b) (4), is unacceptable. The container labels and blistercards submitted October 15, 2010 included a proposed revision to the color scheme.

## **2 MATERIAL REVIEWED**

Using Failure Mode and Effects Analysis,<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the revised product labels and labeling submitted August 9, 2010 and the proposed color scheme changes provided October 15, 2010 to identify vulnerabilities that may lead to medication errors. See Appendices A and B for samples of the proposed color changes.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

Per our previous recommendations, the Applicant satisfactorily revised the proposed container labels and carton labeling. However, the proposed color changes provided in the October 15, 2010 submission introduces vulnerability to confusion that could lead to medication errors. The color used for the 120 mg strength is difficult to read and the proprietary name is presented in a color of one of the proposed strengths. The use of similar colors can lead to product selection errors. Thus, we request the Applicant revise their labels as outlined below.

Please copy the DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sandra Griffith, project manager, at 301-796-4264.

### **3.1 COMMENTS TO THE APPLICANT**

#### **A. General Comment**

1. Revise the presentation of the established name on the container labels, carton labeling, and blistercard so that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2. Revise the color used in the presentation of the proprietary name to one that is not used in the strength differentiation color scheme (ie., no blue, green, or yellow).
- B. Container Labels and Carton Labeling Color Scheme (40 mg, 80 mg, and 120 mg)

(b) (4)

#### **4 REFERENCES**

OSE review 2010-64, Label and Labeling Review for Lurasidone HCl Tablets, July 1, 2010;  
Abate, R.

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RICHARD A ABATE  
10/21/2010

MELINA N GRIFFIS  
10/21/2010

CAROL A HOLQUIST  
10/21/2010

## Memorandum of Consultation

**To:** Caro Alfaro, M.D., ODE I/Division of Psychiatry Products

**Through:** George S. Benson, M.D., Deputy Division Director, DRUP  
Theresa Kehoe, M.D., Team Leader, DRUP

**From:** Marcea Whitaker, M.D., Medical Officer, DRUP

**Date:** September 22, 2010

**Re:** **Lurasidone**  
**Indication: Schizophrenia**  
**Reason for Consult: Review of BMD results from NDA 200603/N000 (December 30, 2009)**

**Sponsor:** **Dainippon Sumitomo Pharma America, Inc.**

**Related INDs:** **IND 61,292 (November 15, 1000)**

**Submissions Reviewed:** **NDA 200603/eCTD0000/ December 30, 2009**  
**NDA 200603/eCTD0011/April 28, 2010/Safety Update**  
**NDA 200603/eCTD0024/July 19, 2010/Response to FDA**

**Executive Summary:** Due to the limited BMD data available (twelve subjects with 12-month BMD data) and the absence of a placebo arm, it is difficult to make any definitive assessment of lurasidone's effect on BMD. From what is available, it appears that the effect of lurasidone on BMD at the lumbar spine and hip over 12 months is similar to risperidone. Therefore, similar risperidone bone loss language should be included in lurasidone labeling. Additional data will be needed to adequately define lurasidone's effect on BMD.

### **Recommendation:**

- The sponsor's proposed labeling regarding bone loss, Section 5.6 Hyperprolactinemia, appears acceptable.

**Background:** Lurasidone (previously referred to as SM-13496 or MK-3756) is a novel anti-psychotic with high affinity for dopaminergic (D2) serotonergic (5-HT<sub>7</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>1A</sub>), and noradrenaline  $\alpha_2C$  receptors. Lurasidone has a unique chemical structure that differs from conventional and atypical antipsychotic agents.

The proposed indication for lurasidone is the acute treatment of adult patients with schizophrenia. The efficacy of lurasidone in schizophrenia is purported to be mediated

through a combination of central dopamine Type 2 (D<sub>2</sub>) and serotonin Type 2 (5-HT<sub>2A</sub>) receptor antagonism. Based on its pharmacologic profile, lurasidone is expected to be associated with fewer extrapyramidal symptoms (EPS) than conventional agents and be effective in ameliorating a broad range of schizophrenia symptoms.

Nonclinical BMD effects: Based on Pharmacology/Toxicology review (dated 11/27/2002 by Lois Freed), decreased bone densities were observed in the 3-month rat studies. The sponsor agreed that the bone density findings in rat “would be problematic” and indicated that “review of the 3- and 6-month animal data suggest that those that received higher doses did indeed have accelerated bone loss.” The sponsor tentatively attributed this finding to hyperprolactinemia, although the sponsor acknowledged that a direct drug-related effect on bone was possible. A DMEP consult, dated September 2, 2003, recommended that the sponsor obtain DXA scans at discrete time points instead of relying on the proposed bone biomarkers. At that time, the proposed study was 6 weeks in duration with a 6-month extension to monitor for bone changes.

Total exposure: To date, over 2600 subjects have been treated with lurasidone in 43 studies (39 completed and four ongoing).

#### Risperidone and BMD effects

As a class, antipsychotics have been associated with bone loss which has been thought to be due to elevated prolactin levels and subsequent hypogonadism. Risperidone is used as the active control in the study under review. The Risperdal® label contains the following Warning and Precaution:

#### Under Warnings and Precautions (5.6) Hyperprolactinemia

“Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.”

There is no further mention of BMD data elsewhere in the label. A literature search of antipsychotics and bone loss resulted in the following studies:

- A study by Calarge, et al. (2010) in schizophrenic adolescent boys (7-17 years) showing a negative association of serum prolactin and trabecular volumetric BMD at the ultradistal radius (after adjusting for sexual development).
- A study by Meaney and Keane (2007) in schizophrenic premenopausal women showed an overall loss in the prolactin-raising subgroup (that included risperidone) (p=0.02). The mean percent change/year BMD at lumbar spine was 0.26% (prolactin raising) vs 1.30% (prolactin-sparing group), and at the hip was 0.08% (prolactin raising) and 1.20% (prolactin-sparing group).

**Reviewer's comment: Results may be difficult to interpret since a large majority of these subjects were taking prolactin –raising antipsychotics prior to study entry and had either osteoporosis or osteopenia at baseline.**

**Current Submission:**

On December 30, 2009, the sponsor submitted an NDA 200603 for lurasidone for the treatment of schizophrenia. The submission (N000) and 120-day safety update (eCTD 0008/April 29, 2010), included interim data from clinical study D1050237, a 12-month randomized double blind study evaluating safety of lurasidone compared to risperidone, and a 6-month open-label extension study D1050237E (lurasidone only). During these studies, DXA scans were obtained at screening, 6 months, 12 months and 18 months, in addition to bone biomarkers and other measures of bone metabolism. Pre-NDA meeting minutes (May 28, 2009) highlight agreements allowing the sponsor to forego submission of interim study reports.

Items reviewed:

- NDA 200603, December, 30, 2010 submission: Containing summary data for BMD findings at the time of datalock (01 July 2009), selected narratives, case report forms (CRFs), and preliminary interim datasets
- 120-day safety update: Containing narratives, CRFs, and interim datasets, submitted 4/29/2010

|   |
|---|
| <b>Review of Study D1050237 and D1050237E</b> |
|---|

**Title:** Long-Term Safety, Tolerability, and Effectiveness of Lurasidone in Subjects with Schizophrenia or Schizoaffective Disorder: A Randomized, Active Comparator-Controlled Trial

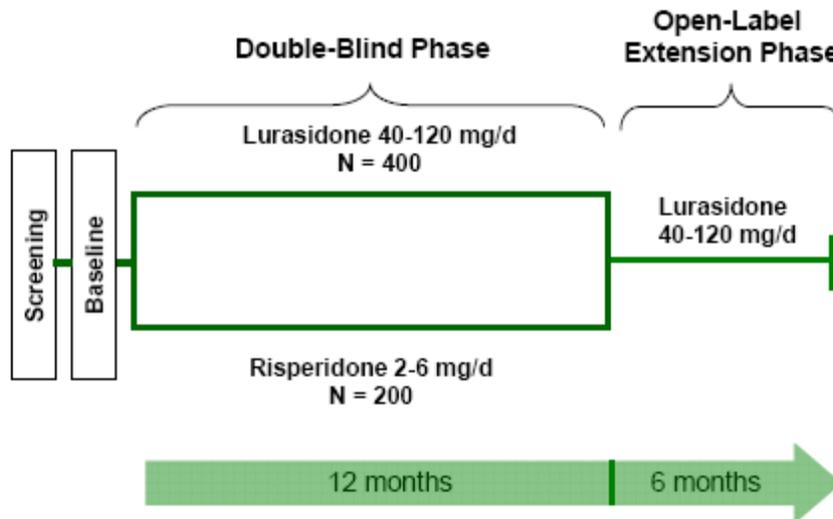
**Study Rationale:** Similar to other antipsychotic drugs that bind to the dopamine D<sub>2</sub> receptor, lurasidone has been shown to elevate serum prolactin levels in preclinical animal models. This study will assess changes in bone mineral density in subjects treated with lurasidone and risperidone after 6, 12, and 18 (lurasidone only) months using dual-energy x-ray absorptiometry (DXA) scans as well as changes in blood and urine markers of bone metabolism (osteocalcin, bone alkaline phosphatase, N-telopeptide, parathyroid hormone). The study will also include a cognition sub-study.

**Study Conduct:** This is a Phase 3, 12-month, multicenter, double-blind treatment study followed by a 6-month open-label extension period in outpatients with chronic schizophrenia or schizoaffective disorder. A total of 600 subjects will be randomized 2:1 to receive lurasidone or risperidone.

Following a washout period up to 7 days, subjects will be randomized to receive either lurasidone (80 mg/day) or starting doses of risperidone. Flexible dosing up to 120 mg of lurasidone and up to 6 mg of risperidone will be allowed beginning in Week 2 (Day 8).

At the completion of the 12 month double-blind treatment phase, subjects may enroll in the extension study after a 3-day placebo washout, and then will receive lurasidone 80 mg/day in an open-label fashion, with titration in weekly increments, if needed. See Figure 1 for a schematic of the study.

**Figure 1: Study Schematic**



**Major Inclusion Criteria** include subjects between 18 to 75 years of age who meet the DSM-IV criteria for schizophrenia or schizoaffective disorder subtypes; and have been judged to be “clinically stable” (non-acute phase of illness) for at least 8 weeks prior to baseline.

**Major Exclusion Criteria** include subjects resistant to antipsychotic treatment; treatment with risperidone within 6 weeks prior to baseline; history of poor response or intolerability to risperidone; history of treatment with clozapine for refractory psychosis and/or subject has been treated with clozapine within 4 months of baseline visit. Subjects who do not require chronic treatment with an antipsychotic drug or those with a history of hypersensitivity to risperidone or an allergic reaction to more than 2 chemical classes of drugs (prescription or non-prescription) are also excluded. Subjects who routinely use anabolic or who require oral or inhaled steroids (>5 mg/day prednisone or equivalent) are excluded.

**Reviewer’s comment:** In the general protocol, there were no exclusionary criteria for subjects with osteoporosis/osteopenia or those taking bone-active drugs. Per the Final Study Protocol (p.29), “the following additional exclusion criteria only applied to those participating in the cognition sub-study:”

35. Subjects who are diagnosed with osteoporosis for the first time based on the screening DXA scan may not participate in this study until or unless

**they have consulted with a primary care physician (or specialist) regarding treatment options for osteoporosis and issues related to the use of antipsychotic medication. Subjects must provide written documentation clearing them for participation in the study.**

- 36. Subjects who have been taking the following medications (which may affect bone density) for less than the specified times: oral contraceptives (3 months), hormone replacement therapy (3 months), thyroid supplements (3 months), calcitonin (3 months), Fosamax® or other bisphosphonates (1 year), or raloxifene (1 year).**

**In the reviewed data, one subject was identified as being postmenopausal who was also taking hormone replacement therapy. (See addendum for Response from Sponsor regarding postmenopausal status of other subjects.)**

**Bone and other selected safety measures include:**

- Adverse event monitoring,
- Physical examination, including vital signs, weight, height, BMI, and waist circumference.
- Laboratory evaluations: serum  $\beta$ -hCG, urine  $\beta$ -hCG, complete blood count (CBC), serum chemistry (including creatinine phosphokinase), routine urinalysis, urine drug screen, serum prolactin, serum total and free testosterone, serum PTH, lipid profile (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides), fasting plasma glucose, HbA<sub>1c</sub>, and blood sampling for analysis of serum lurasidone and its hydroxyl metabolite;
- Markers of bone turnover and laboratory measures related to bone turnover or density: CTx, serum calcium and phosphorus, vitamin D, prolactin, parathyroid hormone, 25-hydroxyvitamin D<sub>3</sub>, free and total testosterone, osteocalcin, bone alkaline phosphatase, and NTx
- Menstrual cyclicity; premenopausal female subjects will be given a calendar to mark beginning and end of menses. This calendar will be reviewed at each visit. In addition, history of menstrual cyclicity and irregularities will be collected at Visit 1
- 12-lead ECG
- DXA

Bone mineral density (BMD) will be measured by Hologic or Lunar DXA machines. Bone mineral density will be obtained at the Screening Visit and at 6 and 12 months in the double-blind phase and at 18 months in the open-label extension phase. Wherever possible, all measurements will utilize the left hip and the average of L1 through L4 vertebrae. Furthermore, total body scans will be obtained for the assessment of fat, lean body tissue mass (body composition), and total body BMD.

**Endpoints:** The endpoints will be the mean percentage change from baseline for the following:

1. Average of L1-L4 lumbar spine BMD;
2. Total hip and femoral neck BMD;
3. Total body fat in grams;

4. Total body fat in percentage;
5. Total bone mineral content.

## Study Results

**Disposition** (data from NDA Original Submission, Dec 2010): Of the 600 subjects planned for this study, 190 have received lurasidone and 85 have received risperidone. Only subjects who had completed the double-blind study period or discontinued from the study by the database cutoff of 01 July 2009, have been included in the submitted dataset and analyses. The premature discontinuation rate was high for both study groups with 91% discontinuations for lurasidone and 87% for risperidone. Adverse events were the most common reason for discontinuation in both the lurasidone and risperidone groups (35% and 28%, respectively).

Of the 275 subjects currently enrolled in the study D1050237 (also referred to as P23LTC), 39 subjects had a baseline BMD and at least one post-baseline BMD assessment at the lumbar spine and total hip. Only twenty-one (21) subjects had a post baseline assessment at 6 months or beyond.

**Reviewer's comment: The sponsor has 38 subjects (using LOCF) in their tabular summary vs. the 39 subjects found in the datasets by this reviewer. Based on previous agreements, the sponsor was not required to submit an interval study report with this submission.**

**Demographics:** The lurasidone group was comprised of 18 men (ages 18-61, mean 39.8) and 9 women (ages 25-54, mean 42.6). The risperidone group was composed of 9 men (ages 18-56, mean 38.3) and 3 women (ages 27-45, mean 34.0). One subject was identified by the sponsor as postmenopausal. This subject was on hormone replacement and was also taking calcium 500 mg tablets containing vitamin D. Three subjects were taking Prevacid and one subject was taking medrol dose pak for "cough". Mean baseline T scores or Z scores were not reported.

Sponsor's Table 1 (from Table 15.1.1.1) shows an overall BMD result (percent change from baseline) at the lumbar spine of 0.9% for lurasidone and 0.5% for risperidone; and overall BMD change at the hip of -0.5% for lurasidone and -0.6% for risperidone.

**Table 1: BMD results: Lurasidone vs Risperidone (% change from baseline)**

|   | Lurasidone                         | Risperidone                        |
|---|------------------------------------|------------------------------------|
| <b>Lumbar spine (L1-L4)</b>                                     | <b>0.9</b><br>(-2.8, 4.1)<br>N=27  | <b>0.5</b><br>(-7.6, 5.7)<br>N=11  |
| <b>Total Hip and Femoral Neck</b>                               | <b>-0.5</b><br>(-4.0, 3.6)<br>N=27 | <b>-0.6</b><br>(-4.7, 1.4)<br>N=11 |
| <b>Total body fat (g)</b>                                       | -1.1<br>(-35.2, 51.1)<br>N=25      | 15.0<br>(-27.3, 70.5)<br>N=11      |
| <b>Total body fat (%)</b>                                       | -0.5<br>(-25.5, 48.6)<br>N=25      | 10.0<br>(-22.4, 55.0)<br>N=11      |
| <b>Total body BMC</b>   | -0.2<br>(-5.9, 7.2)<br>N=25        | -1.4<br>(-18.5, 4.1)<br>N=11       |
| Source: Sponsor Table 15.1.1.1, Original NDA submission, p.5421 |                                    |                                    |

The sponsor concludes that there were no important differences between the lurasidone and the risperidone treatment groups.

**Reviewer’s comment: As 40% of subjects were ≤30 years of age and may not have reached peak bone mass, additional BMD analyses by time point and by age and sex were performed. Younger subjects would be expected to gain bone and therefore, smaller increases or small decreases in BMD may be significant.**

**FDA analysis by time point (Month 6, 12, 18):**

**Lumbar spine results:**

Summary BMD data for lumbar spine changes are shown in Table 2.

For all subjects with at least one post baseline BMD (n=39), the mean maximum change in LS BMD at any time point from baseline was +1.4% in the lurasidone group compared to +0.9% in the risperidone group. In the lurasidone group, outlier LS BMD values of +4.1% and +7.9% occurred in a 28 year-old male taking concomitant Prevacid (#018-00011) and a 54 year-old female (#0032-00001) on hormone replacement therapy, calcium and vitamin D, respectively. In the risperidone group, outlier LS BMD values of +5.7, +5.8 and -7.6 occurred in 30 year-old female, 40 year-old male, and 45 year-old female, respectively.

In the twenty (20) subjects with LS BMD data at 6 months, the mean change from baseline at 6 months in the lurasidone group was +2.9%, compared to 0.4% in the risperidone group. In the lurasidone group, there was an increase of +4.1% in a 28 year-old male. In the risperidone group, there was a decrease in BMD of -7.6 in a 45 year-old female and a BMD increase of 5.7% in a 30 year-old female.

In the ten (10) subjects with LS BMD data at 12 months, the mean change from baseline at 12 months was +0.4% in the lurasidone group, compared to +3.5% in the risperidone group. There were no notable outliers.

The two lurasidone subjects with LS BMD readings at 18 months had mean change from baseline values of -0.1% and -0.5% (mean -0.3%)

**Table 2: Lumbar spine mean percent change**

|  | <b>Lurasidone</b>                      | <b>Risperidone</b>                     |
|--|--|--|
| <b>LS Mean maximum change (Range)</b>      | <b>+1.4%</b><br>(-1.7 to +7.9)<br>N=27 | <b>+0.9%</b><br>(-7.6 to +5.8)<br>N=12 |
| <b>LS Mean change at 6 months (Range)</b>  | <b>+2.9%</b><br>(-0.2 to 7.9)<br>N=11  | <b>+0.4%</b><br>(-7.6 to +5.7)<br>N=9  |
| <b>LS Mean change at 12 months (Range)</b> | <b>+0.4%</b><br>(-2.5 to +2.1)<br>N=6  | <b>+3.5%</b><br>(+2.5 to 3.7)<br>N=4   |
| <b>LS Mean change at 18 months (Range)</b> | <b>-0.3%</b><br>(-0.4 to -0.1)<br>N=2  | ---                                    |
| Source: Data calculated from BM dataset    |  |  |

**Reviewer’s comment:** These data suggest that overall there was no clinically significant difference in mean maximum change between the two treatment groups. These results are similar to the sponsor’s values. No consistent changes were noted over the time course of 6-18 months but there was a possible trend toward an increase in BMD at 6 months in the lurasidone group that reversed over time.

**Total Femur results:**

Summary BMD data for total femur changes are shown in Table 3.

**Table 3: Total Femur mean percent changes**

|   | <b>Lurasidone</b>                      | <b>Risperidone</b>                     |
|---|--|--|
| <b>Hip Mean maximum change (Range)</b>      | <b>-0.6%</b><br>(-3.9 to +3.7)<br>N=12 | <b>-0.4%</b><br>(-3.8 to +1.4)<br>N=10 |
| <b>Hip Mean change at 6 months (Range)</b>  | <b>+0.2%</b><br>(-2.6 to +3.7)<br>N=12 | <b>-0.4%</b><br>(-3.8 to 2.0)<br>N=10  |
| <b>Hip Mean change at 12 months (Range)</b> | <b>-0.9%</b><br>(-3.9 to +2.8)<br>N=7  | <b>-1.0%</b><br>(-4.7 to +1.1)<br>N=5  |
| <b>Hip Mean change at 18 months (Range)</b> | <b>-0.7%</b><br>(-1.3 to +0.2)<br>N=2  | ---                                    |
| Source: Data calculated from BM dataset     |  |  |

For all subjects with at least one post baseline BMD (n=39), the mean maximum change in hip BMD at any time point from baseline was -0.6% in the lurasidone group compared to -0.4% in the risperidone group. There were no significant outliers.

In the twenty-two (22) subjects with hip BMD data at 6 months, the mean change from baseline at 6 months in the lurasidone group was +0.2%, compared to -0.4% in the risperidone group. One subject in the risperidone group had a decrease in BMD of -4.7%.

In the twelve (12) subjects with hip BMD data at 12 months, the mean change from baseline at 12 months was -0.9% in the lurasidone group, compared to -1.0% in the risperidone group. A 61 year-old male on lurasidone had a decrease of -4.0%.

Two lurasidone subjects had hip BMD readings at 18 months, mean -0.7%.

**Reviewer’s comment: Results for the overall change in BMD are similar to the sponsor’s values. Overall, there was no clinically significant difference between treatment groups over time.**

**FDA analysis by age and sex:**

Summary data for mean percent change in BMD (total femur and lumbar spine) by age and sex are presented in Table 4 (lumbar spine) and Table 5 (total femur).

**Table 4: Mean % change in Lumbar Spine BMD by age and sex at Months 6, 12, and 18**

|                | Month 6     |              | Month 12     |             | Month 18     |     |
|----------------|-------------|--------------|--------------|-------------|--------------|-----|
|                | LUR         | RIS          | LUR          | RIS         | LUR          | RIS |
| <b>Males</b>   |             |              |              |             |              |     |
| <b>18-29</b>   | 3.3%<br>N=2 | 2.4%<br>N=1  | 2.1%<br>N=1  | 4.1%<br>N=1 | --           | --  |
| <b>30-39</b>   | --          | --           | 1.6%<br>N=1  | --          | --           | --  |
| <b>40-49</b>   | 0.8%<br>N=1 | 1.3%<br>N=3  | 0.4%<br>N=2  | 4.0%<br>N=2 | -0.4%<br>N=1 | --  |
| <b>50-59</b>   | 2.3%<br>N=1 | -0.1%<br>N=1 | 0.8%<br>N=1  | --          | -0.1%<br>N=1 | --  |
| <b>60-69</b>   | 1.3%<br>N=1 | --           | -2.5%<br>N=1 | --          | --           | --  |
| <b>Females</b> |             |              |              |             |              |     |
|                | Month 6     |              | Month 12     |             | Month 18     |     |
|                | LUR         | RIS          | LUR          | RIS         | LUR          | RIS |
| <b>18-29</b>   | --          | 2.3%<br>N=1  | --           | 2.4%<br>N=1 | --           | --  |
| <b>30-39</b>   | --          | 5.7%<br>N=1  | --           | 3.8%<br>N=1 | --           | --  |
| <b>40-49</b>   | --          | --           | ---          | --          | --           | --  |
| <b>50-59</b>   | --          | --           | 1.2%<br>N=1  | --          | --           | --  |
| <b>60-69</b>   | --          | --           | --           | --          | --           | --  |

BMD change at Lumbar Spine: Overall, the subsets by age were small (n=1-2). For male subjects treated with lurasidone who also had comparative risperidone data, BMD changes at the spine were similar at 6 months. At 12 months BMD increases were more pronounced in the risperidone group suggesting a beneficial effect or absence of effect on BMD at the lumbar spine in the 18-29 and 40-49 age groups for risedronate. For female subjects, no comparative data between treatment groups were available. There were minimal data at 18 months for both sexes. (Note: All subjects were on lurasidone at the 18 month time point).

**Table 5: Mean % change in Femur Total BMD by age and sex at Months 6, 12, and 18**

|                | Month 6      |              | Month 12     |              | Month 18     |     |
|----------------|--------------|--------------|--------------|--------------|--------------|-----|
|                | LUR          | RIS          | LUR          | RIS          | LUR          | RIS |
| <b>MALES</b>   |              |              |              |              |              |     |
| 18-29          | 0.3%<br>N=3  | -1.9%<br>N=2 | 2.7%<br>N=1  | 1.1%<br>N=1  | --           | --  |
| 30-39          | 1.3%<br>N=1  | --           | -1.1<br>N=1  | --           | --           | --  |
| 40-49          | 0.5%<br>N=2  | 0.3%<br>N=2  | -0.7%<br>N=1 | 0.3%<br>N=2  | -1.3%<br>N=1 | --  |
| 50-59          | -0.6%<br>N=2 | 0.9%<br>N=1  | -0.8%<br>N=1 | --           | 0.3%<br>N=1  | --  |
| 60-69          | -0.4%<br>N=1 | --           | -4.0%<br>N=1 | --           | --           | --  |
| <b>FEMALES</b> |              |              |              |              |              |     |
|                | Month 6      |              | Month 12     |              | Month 18     |     |
|                | LUR          | RIS          | LUR          | RIS          | LUR          | RIS |
| 18-29          | 2.7%<br>N=1  | 2.0%<br>N=1  | --           | 0.1%<br>N=1  | --           | --  |
| 30-39          | --           | -3.8%<br>N=1 | --           | -2.9%<br>N=1 | --           | --  |
| 40-49          | --           | -0.7%<br>N=1 | --           | --           | --           | --  |
| 50-59          | -0.2%<br>N=1 | --           | -1.6%<br>N=1 | --           | --           | --  |
| 60-69          | --           | --           | --           | --           | --           | --  |

BMD change at Femur: Overall, the subsets by age were small (n=1-3). For male subjects treated with lurasidone who had comparative risperidone data, changes were similar at 6 and 12 months. For female subjects, only one subject had comparative data (at 6 months) but no differences were noted. Again, there were minimal data at the 18-month time point for both sexes. (Note: All subjects were on lurasidone at the 18 month time point).

**Reviewer comments: The sparsity of the data does not allow conclusions based on postmenopausal status.**

**Biomarkers: The following biomarkers were obtained:**

- CTx: measured at Day 0 and 12 months
- NTx, BSAP, osteocalcin and PTH: Measured at prescreening, day 0, Month 6, Month 9, and Month 12,
- serum calcium and phosphorus,
- vitamin D,
- prolactin,
- parathyroid hormone,
- 25-hydroxyvitamin D3,
- free and total testosterone,

- osteocalcin,
- bone alkaline phosphatase, and

**Reviewer's comment: Only line listings for the listed biomarkers were provided. The sponsor will be asked to submit summary tables containing these data.**

**Other Events of Interest:**

**Fractures:** A total of 21 fractures have occurred in the lurasidone program. Sixteen (16) fractures (in various locations) were reported in the Safety Update (data cut-off 01 Dec 2009). Two fracture cases occurred in study D1050237. Narratives for the two cases were reviewed.

- 0011-00002: A 63 year-old male who on Study Day 63 fell and broke his right ankle after missing the curb while walking to his car in the dark.
- 0037-00007: A 48 year-old male who on Study Day 111 who had a "severe accidental fall" and sustained a left wrist fracture.

**Label Review:**

The sponsor's proposed labeling includes the following:

## 5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D<sub>2</sub> receptors, (b) (4) elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients [see Adverse Reactions (6)].

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a (b) (4) carcinogenicity study conducted in rats and mice [see Nonclinical Toxicology(13)]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

In short-term placebo-controlled studies, the mean change from baseline to endpoint in prolactin levels for (b) (4)-treated patients was an increase of (b) (4) compared to a decrease of (b) (4) ng/mL in the placebo-treated patients. (b) (4)

**Reviewer’s comment: The underlined section is similar to that found in the risperidone label. This is acceptable.**

**Addendum**

The following Information Request were sent to the sponsor on June 22, 2010. Sponsor’s Responses (submitted July 15, 2010, received July 19, 2010) are also provided.

1. **FDA Question:** Please determine the menopausal status for the following subjects from study D1050237:

| Subject #  | Postmenopausal? |
|------------|-----------------|
| 0011-00001 |                 |
| 0011-00018 |                 |
| 0014-00018 |                 |
| 0024-00004 |                 |
| 0024-00005 |                 |
| 0024-00034 |                 |
| 0032-00001 |                 |
| 0053-00001 |                 |
| 0055-00003 |                 |
| 0018-00008 |                 |
| 0028-00001 |                 |
| 0046-00012 |                 |

**Sponsor’s Response:**

| Unique Subject ID   | Treatment   | Post- Menopausal |
|---------------------|-------------|------------------|
| D1050237-0011-00001 | Lurasidone  | No               |
| D1050237-0011-00018 | Lurasidone  | No               |
| D1050237-0014-00018 | Lurasidone  | No               |
| D1050237-0018-00008 | Risperidone | No               |
| D1050237-0024-00004 | Lurasidone  | No               |
| D1050237-0024-00005 | Lurasidone  | No               |
| D1050237-0024-00034 | Lurasidone  | Yes              |
| D1050237-0028-00001 | Risperidone | No               |
| D1050237-0032-00001 | Lurasidone  | Yes              |
| D1050237-0046-00012 | Risperidone | No               |
| D1050237-0053-00001 | Lurasidone  | Yes              |
| D1050237-0055-00003 | Lurasidone  | No               |

**Reviewer’s comment: In the study, there were three postmenopausal subjects with post-baseline BMD assessments. Maximum change in BMD at the lumbar spine and hip for these subjects are shown below. All three subjects were in the lurasidone treatment group. The greatest change occurred at the lumbar spine**

(+7.9%) at Month 6 in a subject also taking HRT and calcium therapy. All subjects lost BMD at the hip with one subject losing 2% BMD over 1 month. The remaining subjects had modest BMD decreases over 3-6 months. No conclusions can be drawn from these limited data. The 2% loss at the hip deserves further investigation.

|            |      | Lumbar spine |                      | Hip   |         |
|------------|------|--------------|----------------------|-------|---------|
| 0024-00034 | 50 F | +0.9%        | Month 1              | -2.0% | Month 1 |
| 0032-00001 | 54 F | +7.9%        | Month 6,<br>HRT/Ca2+ | -0.3% | Month 6 |
| 0053-00001 | 44 F | -1.9%        | Month 3              | -0.3% | Month 3 |

2. Using available unblinded data from study D1050237:

- Provide individual line listings and summary tables for CTx, NTx, BSAP, osteocalcin and PTH. Data should be summarized by treatment group and include the following timepoints: Baseline, Month 3, Month 6, and Month 12. These tables can be limited to subjects with post-baseline values.
- Provide individual line listings and summary tables for the mean change from baseline in calcium, phosphorus, vitamin D, prolactin, 25-hydroxyvitamin D3, and free and total testosterone, by treatment group.

**Sponsor’s Response:**

**Mean Change from baseline LOCF**

| Laboratory Parameter  | Lurasidone    | Risperidone  |
|---|---------------|--------------|
| Serum CTX (pg/mL)   | 22.8 (n=44)   | -30.8 (n=16) |
| NTX   | 1.6 (n=116)   | -0.8 (n=52)  |
| BSAP  | -0.15 (n=117) | -0.16 (n=56) |
| Osteocalcin   | -0.16 (n=116) | -0.29 (n=55) |
| PTH   | 5.0 (n=114)   | -3.3 (n=56)  |
| Source: From Table 16.7.1.1.4 Information Request 7/15/2010 |               |              |

**Reviewer’s comment:** The submitted laboratory/biomarker data represent all subjects enrolled in Study D1050237 and are not limited to subjects with post baseline BMD readings (n=39 subjects). The increases in CTX and smaller increases in NTX in the lurasidone group compared to risperidone suggest increased bone resorption in the lurasidone group. Overall increases in PTH in the lurasidone group was seen compared to risperidone. There were no clinical difference in BSAP and OC. The sponsor’s results reflect short term changes as the majority of subjects did not complete the study.

**Reviewer’s comment: On further review of CTX data in subjects with post-baseline BMD values, no subject in the either treatment group had both baseline and 12 month CTX values. In the lurasidone group, 14/27 (52%) subjects with post baseline CTX readings prematurely discontinued the study with only 6 of the 14 having a baseline value. No conclusions can be made from the available data.**

Table A: Lurasidone Group CTX

| Subject ID | Age | Sex | Tx                                 | Baseline | Value | Day | Value | Day |
|------------|-----|-----|------------------------------------|----------|-------|-----|-------|-----|
| 0011-001   | 35  | F   | LUR 80                             | --       | 103   | 30  |       |     |
| 0011-018   | 37  | F   | LUR 80, 120                        | 126      | 252   | 38  |       |     |
| 0011-019   | 54  | M   | LUR 80,120                         | 144      | 187   | 49  |       |     |
| 0014-005   | 60  | M   | LUR 80                             | ---      | ---   | --  |       |     |
| 0014-013   | 50  | M   | LUR80                              | ---      | 232   | 68  | 141   | 152 |
| 0014-018   | 32  | F   | LUR80                              | 57       | --    | --  |       |     |
| 0014-026   | 48  | M   | LUR 80, 120                        | 182      | 218   | 42  |       |     |
| 0018-009   | 41  | M   | LUR 80                             | --       | --    | --  | 197   | 350 |
| 0018-011   | 28  | M   | LUR 80                             | --       | 462   | 244 |       |     |
| 0020-002   | 61  | M   | LUR 80, 40                         | --       | --    | --  | 547   | 369 |
| 0024-004   | 34  | F   | LUR 80                             | --       | --    | --  |       |     |
| 0024-005   | 44  | F   | LUR 80                             | --       | --    | --  |       |     |
| 0024-006   | 20  | M   | LUR 80                             | --       | --    | --  |       |     |
| 0024-019   | 50  | M   | LUR 80                             | --       | 247   | 103 |       |     |
| 0024-034   | 50  | F   | LUR 80, 120                        | 341      | 237   | 23  |       |     |
| 0028-002   | 51  | M   | LUR 80, 120<br>PLA, LUR 80,<br>120 | --       | --    | --  | 196   | 363 |
| 0032-001   | 54  | F   | LUR 80<br>PLA, LUR 80              | --       | --    | --  | 161   | 354 |
| 0033-001   | 30  | M   | LUR 80, 40                         | --       | --    | --  | 133   | 369 |
| 0033-006   | 39  | M   | LUR 80                             | --       | 115   | 174 |       |     |
| 0034-014   | 50  | M   | LUR 80                             | 640      | 488   | 15  |       |     |
| 0046-001   | 45  | M   | LUR 80 PLA,<br>LUR 80              | --       | --    | --  | 218   | 360 |
| 0046-002   | 28  | M   | LUR 80, 120                        | --       | 392   | 142 |       |     |
| 0051-001   | 19  | M   | LUR 80, PLA<br>LUR 40              | --       | 516   | 166 | 479   | 355 |
| 0051-006   | 18  | M   | LUR 80                             | 718      | 703   | 98  |       |     |
| 0053-001   | 44  | F   | LUR 80                             | --       | 97    | 80  |       |     |
| 0055-003   | 26  | F   | LUR 80                             | --       | 224   | 223 |       |     |
| 0055-009   | 54  | M   | LUR 80, 40                         | --       | --    | --  |       |     |

From Subset of LB\_CTX values.JMP

Table B: Risperidone Group CTX

| Subject ID | Age | Sex | Tx                                    | Baseline | Value | Study Day | Value | Study Day |
|------------|-----|-----|---------------------------------------|----------|-------|-----------|-------|-----------|
| 0014-008   | 48  | M   | RIS 4, 6                              | --       | --    | --        |       |           |
| 0018-002   | 46  | M   | RIS 4, PLA                            | --       | --    | --        | 121   | 352       |
| 0018-008   | 27  | F   | RIS 4, 2, PLA,<br>LUR80,40,80         | --       | --    | --        | 96    | 353       |
| 0018-015   | 46  | M   | RIS 2                                 |          | 474   | 201       |       |           |
| 0024-008   | 22  | M   | RIS 4, 2                              | --       | --    | --        | 917   | 359       |
| 0028-001   | 30  | F   | RIS 6, 4<br>PLA, LUR 80,<br>120       | --       | --    | --        | 271   | 364       |
| 0032-002   | 30  | M   | RIS 4, 6                              |          | 2904  | 64        |       |           |
| 0046-005   | 40  | M   | RIS 4, 6, 4, 6<br>PLA,<br>LUR 80, 120 |          |       |           | 336   | 369       |
| 0046-012   | 45  | F   | RIS 4, 6                              | --       | --    | --        | 124   | 301       |
| 0051-003   | 18  | M   | RIS 4                                 | ---      | --    | --        | 688   | 359       |
| 0055-004   | 39  | M   | RIS 4                                 | --       | --    | --        |       |           |
| 0055-008   | 56  | M   | RIS 4, 2                              |          | >6000 | 147       |       |           |

From Subset of LB\_CTX values.JM

Table C: Lurasidone Group PTH (nl range 14-72 pg/ml)

| Subject ID | Age/<br>Sex | Screening | Day<br>-1 | #   | D   | #  | D   | #  | D   | #  | D   | #  | D   | Change<br>LOCF |
|------------|-------------|-----------|-----------|-----|-----|----|-----|----|-----|----|-----|----|-----|----------------|
| 0011-001   | 35F         | 42        | 36        | --  | --  |    |     |    |     |    |     |    |     | --             |
| 0011-018   | 37F         | 32        | 37        | 45  | 38  |    |     |    |     |    |     |    |     | 8              |
| 0011-019   | 54M         | 38        | 32        | 31  | 49  |    |     |    |     |    |     |    |     | -1             |
| 0014-005   | 60M         | 44        | 46        | 41  | 113 |    |     |    |     |    |     |    |     | 67             |
| 0014-013   | 50M         | 49        | 93        | 63  | 68  | 54 | 152 |    |     |    |     |    |     | -39            |
| 0014-018   | 32F         | 45        | 27        | 32  | 94  |    |     |    |     |    |     |    |     | -5             |
| 0014-026   | 48M         | 25        | 15        | 26  | 42  |    |     |    |     |    |     |    |     | 11             |
| 0018-009   | 41M         | 26        | 22        | 40  | 168 | 19 | 263 | 33 | 350 | 54 | 452 |    |     | 32             |
| 0018-011   | 28M         | 28        | 19        | 29  | 167 | 67 | 244 |    |     |    |     |    |     | 48             |
| 0020-002   | 61M         | 40        | 55        | 45  | 167 | 36 | 266 | 50 | 369 |    |     |    |     | -5             |
| 0024-004   | 34F         | 38        | 47        | 36  | 10  |    |     |    |     |    |     |    |     | -11            |
| 0024-005   | 44 F        | 53        | 41        | 35  | 11  |    |     |    |     |    |     |    |     | -6             |
| 0024-006   | 20M         | 20        | 25        | 24  | 22  |    |     |    |     |    |     |    |     | -1             |
| 0024-019   | 50M         | 28        | 35        | 23  | 103 |    |     |    |     |    |     |    |     | -12            |
| 0024-034   | 50 F        | 38        | 34        | 29  | 23  |    |     |    |     |    |     |    |     | -5             |
| 0028-002   | 51M         | --        | 26        | 18  | 173 | 33 | 266 | 27 | 363 | 20 | 455 | 27 | 544 | 1              |
| 0032-001   | 54F         | 45        | 41        | 37  | 167 | 35 | 252 | 47 | 354 | 40 | 447 |    |     | -1             |
| 0033-001   | 30M         | --        | --        | 47  | 173 | 29 | 369 |    |     |    |     |    |     | --             |
| 0033-006   | 39M         | 16        | 17        | --  | --  |    |     |    |     |    |     |    |     | --             |
| 0034-014   | 50<br>M     | 36        | 34        | 30  | 15  |    |     |    |     |    |     |    |     | -4             |
| 0046-001   | 45M         | 70        | 26        | 50  | 176 | 50 | 253 | 53 | 360 | 59 | 449 | 51 | 549 | 25             |
| 0046-002   | 28M         | 33        | 22        | 30  | 142 |    |     |    |     |    |     |    |     | 8              |
| 0051-001   | 19M         | 33        | 39        | 29  | 166 | 56 | 250 | 34 | 355 |    |     |    |     | -5             |
| 0051-006   | 18M         | 28        | 53        | 25  | 98  |    |     |    |     |    |     |    |     | -28            |
| 0053-001   | 44F         | 53        | 54        | 76  | 80  |    |     |    |     |    |     |    |     | 22             |
| 0055-003   | 26F         | 54        | 77        | 132 | 167 | 83 | 223 |    |     |    |     |    |     | 9              |
| 0055-009   | 54M         | 46        | 76        | 66  | 45  |    |     |    |     |    |     |    |     | -10            |

From Subset of LB\_PTH values.JMP

**Reviewer's comment: Using LOCF analysis for the subjects with BMD readings post baseline, the mean change in PTH from baseline (using Day -1 values) to LOCF was +4.1 pg/ml in the lurasidone group compared to -4.2 pg ml in the risperidone group. Note: For the risperidone group, only values while on risperidone were used (<12 months). The greater increase in PTH in the lurasidone group does not appear to be clinically relevant.**

Table D: Risperidone Group PTH

| Subject ID | Age/<br>Sex | Screening | Day<br>-1 | #  | D   | #  | D   | #  | D   | #  | D   | #  | D   | Δ   |
|------------|-------------|-----------|-----------|----|-----|----|-----|----|-----|----|-----|----|-----|-----|
| 0014-008   | 48M         | 53        | 34        | 46 | 173 | 59 | 260 |    |     |    |     |    |     | 25  |
| 0018-002   | 46M         | 39        | 30        | 24 | 168 | 22 | 252 | 27 | 352 | 19 | 443 | 24 | 539 | -6  |
| 0018-008   | 27F         | 33        | 13        | 31 | 168 | 21 | 266 | 23 | 353 | 22 | 450 |    |     | 10  |
| 0018-015   | 46M         | 34        | 27        | 26 | 168 | 32 | 201 |    |     |    |     |    |     | 5   |
| 0024-008   | 22M         | 90        | 58        | 23 | 174 | 36 | 266 | 37 | 359 |    |     |    |     | -21 |
| 0028-001   | 30F         | 62        | 62        | 82 | 168 | 67 | 191 | 91 | 267 | 62 | 364 | 56 | 463 | 0   |
|            |             |           |           |    |     |    |     |    |     |    |     | 66 | 539 |     |
| 0032-002   | 30M         | --        | 22        | 13 | 64  |    |     |    |     |    |     |    |     | -9  |
| 0046-005   | 40M         | 34        | 38        | 35 | 159 | 53 | 238 | 38 | 369 | 43 | 446 |    |     | 5   |
| 0046-012   | 45F         | 24        | 28        | 21 | 168 | 30 | 264 | 36 | 301 |    |     |    |     | 8   |
| 0051-003   | 18M         | 25        | 42        | 25 | 170 | 36 | 254 | 33 | 359 |    |     |    |     | -9  |
| 0055-004   | 39M         | 31        | 36        | 5  | 42  |    |     |    |     |    |     |    |     | -31 |
| 0055-008   | 56M         | 50        | 70        | 43 | 147 |    |     |    |     |    |     |    |     | -27 |

From Subset of LB\_PTH values.JMP

**Mean Change from baseline LOCF**

| <b>Laboratory Parameter</b>                                 | <b>Lurasidone</b> | <b>Risperidone</b> |
|---|-------------------|--------------------|
| Calcium   | -0.02 (n=158)     | -0.03 (n=67)       |
| Phosphorus  | -0.02 (n=157)     | -0.03 (n=67)       |
| Prolactin   | 3.9 (n=156)       | 18.1 (n=66)        |
| Free Testosterone   | -0.47 (n=91)      | -2.42 (n=39)       |
| Total Testosterone  | -10.6 (n=95)      | -74.5 (n=40)       |
| Source: From Table 16.7.1.1.5 Information Request 7/15/2010 |                   |                    |

**Reviewer’s comment: No relevant changes in calcium or phosphorus were noted. More pronounced increases in prolactin and decreases in testosterone (free and total) were seen in the risperidone group.**

3. Provide clarification on your method of BMD correction.

**Sponsor’s Response: The sponsor provided general information regarding BMD correction.**

**Reviewer’s comment: The sponsor did not provide specific information regarding BMD correction in clinical study D1050237. No additional analyses are planned, therefore, the response is adequate.**

**References:**

Calarge, C., Zimmerman, B., Kuperman, S. and Schlechte, J. (2010). A cross-sectional evaluation of the effect of risperidone and selective serotonin reuptake inhibitors on bone mineral density in boys. *J Clin Psychiatry*, 71(3):338-347.

Meaney, A. and Keane, V. (2007). Bone Mineral density changes over a year in young females with schizophrenia: Relationship to medication and endocrine variables. *Schizophrenia Research*, 93:136-143.

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/s/

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MARCEA B WHITAKER  
09/22/2010

THERESA E KEHOE  
09/22/2010

GEORGE S BENSON  
09/22/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: September 9, 2010

FROM: Hue (Hyojong) Kwon, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau Ph.D. Mart = K. Yau 9/9/10  
Acting Team Leader, Bioequivalence  
Division of Scientific Investigations (HFD-48)

SUBJECT: Addendum to the EIR Covering NDA 200603, Lurasidone  
HCl Tablets, Sponsored by Sepracor Inc. (Dainippon  
Sumitomo Pharma America Inc.)

TO: Thomas P. Laughren, M.D.  
Director  
Division of Psychiatry Products (DPP)  
Office of New Drugs

At the request of the review division (DPP), the Division of Scientific Investigations (DSI) conducted an audit of the following bioequivalence study:

**Protocol Number:** D1001053 (Study Number P09-1922)

**Study Title:** An Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Determine the Bioequivalence of Two Different SM-13496 Formulations of 40 mg tablet (b)(4) drug load) and 20 mg tablet (b)(4) drug load) in Healthy Young Adult Subjects

DSI inspection summary memo for the above study was sent to DPP on August 16, 2010. DSI recommended that the study not be accepted for agency review based on the significant inspectional findings.

On August 31, 2010, (b)(4) (analytical site, refer as (b)(4) submitted their written response to THE Form FDA 483 (Attachment 1). Our evaluation on the firm's written response is summarized below:

1. (b)(4) planned to submit the results of the following experiments by January 2011: (1) evaluation of dilution

factors of 10-fold and 20-fold, (2) freeze/thaw stability below  $-65^{\circ}\text{C}$  and (3) matrix effect (483 items 3 and 6).

2. (b) (4) acknowledged that QCs were not treated under the same conditions as study samples (483 item 4) but the firm's 12-month frozen sample stability data at  $-20^{\circ}\text{C}$  and  $-80^{\circ}\text{C}$  support that there is no significant difference between freshly prepared QC and frozen QC. (b) (4) response is acceptable.
3. In response to 483 item 5, (b) (4) explained that the observation had no impact on integrity of study samples, because (1) the duration between the sample extraction and completion of analysis did not exceed established sample stability under the same condition in the validation study. The firm suggested SOP be revised for better documentation of sample handling. (b) (4) response is acceptable.
4. In response to 483 item 6(b), (b) (4) requested DSI to review the results of bench-top stability and stock-solution stability experiments that (b) (4) conducted under the same analysis condition in the sponsor's submission. As the validation report from (b) (4) was not provided, DSI can not comment on the (b) (4) study data submitted by the sponsor.
5. In response to 483 item 6(c) and 8, (b) (4) acknowledged that recovery of SM-13496 and incurred sample reproducibility (ISR) were not appropriately evaluated. The firm planned to revise their SOPs to implement appropriate study procedures. (b) (4) should conduct the following experiments to support accuracy of the data: (1) recovery of SM-13496 and (2) ISR.
6. In response to 483 item 7, (b) (4) submitted re-calculated concentrations of subject samples in batch 090804a using its own calibration curve (Table 3 in the written response to Form FDA 483, Attachment 1). (b) (4) response is acceptable.

### Conclusion

DSI's recommendation provided in the previous EIR cover memo (dated August 16, 2010) to DPP remains unchanged as the results from the following experiments: dilution integrity, freeze/thaw stability, matrix effect, recovery of SM-13496 and ISR, are

still not available. The sponsor should be informed of the above.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

  
Hue (Hyojong) Kwon, Ph.D.

**DSI Final Classification:**

**VAI** - Kitasato University East Hospital, Kanagawa, Japan

**VAI** - [REDACTED] (b) (4)

cc:

CDER DSI PM TRACK

HFD-48/Kwon/Rivera-Lopez/Ball/Haidar/CF

OND/DPP/Ann Sohn/Kofi Kumi/Raman Baweja (HFD-860)

Draft: HK 9/8/2010

Edit: MYK 9/8/2010

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FACTS [REDACTED] (b) (4)

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name   |
|-------------------------|------------------------|----------------|----------------|
| NDA-200603              | ORIG-1                 | SEPRACOR INC   | Lurasidone HCl |

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/s/

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HYOJONG KWON

09/09/2010

This memo is an addendum to the previous EIR cover memo. The firm's revised SOP is not included in the addendum due to large file size.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: August 16, 2010

FROM: Hue (Hyojong) Kwon, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 8/16/10*  
Acting Team Leader, Bioequivalence  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 200603, Lurasidone HCl  
Tablets, Sponsored by Sepracor Inc. (Dainippon  
Sumitomo Pharma America Inc.)

TO: Thomas P. Laughren, M.D.  
Director  
Division of Psychiatry Products (DPP)  
Office of New Drugs

The review division (DPP) requested that the Division of Scientific Investigations (DSI) conduct an audit of the clinical and bioanalytical portions of the following bioequivalence study.

**Protocol Number:** D1001053 (Study Number P09-1922)

**Study Title:** An Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Determine the Bioequivalence of Two Different SM-13496 Formulations of 40 mg tablet (b)(4) drug load) and 20 mg tablet (b)(4) drug load) in Healthy Young Adult Subjects

The clinical and analytical portions of the study D1001053 were conducted at Kitasato University East Hospital (refer as 'Kitasato'), Kanagawa, Japan and (b)(4)

Following the inspections at Kitasato (7/26-7/30/2010) and at (b)(4), Forms FDA 483 were issued. The written response from (b)(4) has not been received as of 8/11/2010. DSI will provide an amendment if there is any disagreement to 483 observations by (b)(4) in their written response. The objectionable items, Kitasato's written response (dated 7/30/2010, Attachment 2) and our evaluations follow:

Kitasato University East Hospital, Kanagawa, Japan:

1. Investigational product retention samples from the test and reference drug products used in the bioequivalence study were not maintained at the clinical research site as follows:

Test formulation: SM-13496 40 mg tablets  
Reference formulation: SM-13496 20 mg tablets

The clinical site failed to randomly select and retain reserve samples of test and reference products, as required under 21 CFR 320.38. In the firm's written response to Form FDA 483, they explained that the study was conducted to comply with the Japanese regulation, which did not require the retention of reserve samples at the site. However, DSI cannot assure the authenticity of the test and reference products used in Study D1001053 without the reserve samples.

(b) (4)

2. The quality control samples (QCs) (0.04, 0.5, 8 ng/mL) and calibration standards (0.02, 0.05, 0.1, 0.2, 0.5, 1, 2, 5 and 10 ng/mL) for SM-13496 (lurasidone HCl) used in the analytical runs were not representative of SM-13496 concentrations observed in study samples.
  - The maximum observed concentration of SM-13496 was 111.98 ng/mL after 20-fold dilution.

(b) (4) selected a calibration range of 0.02 to 10 ng/mL, and QC concentrations at 0.04, 0.5 and 8 ng/mL. The subjects mean C<sub>max</sub> range was about 48-55 ng/mL with a maximum observed C<sub>max</sub> value of 111.98 ng/mL before 20-fold dilution. During the inspection, (b) (4) acknowledged that the calibration curve and QCs were not representative of concentrations of study samples, which required 10-fold or 20-fold dilution of all samples at 0.5, 1, 1.5, 2, 4, 6 hr. DSI cannot assure the accuracy of the concentration data without a validation of accuracy of dilution; see also the following observation (483 item 3).

3. Failure to evaluate integrity of dilution applied to study samples.
  - Approximately 47% (378 out of 792) study samples were diluted 10-fold or 20-fold but there was no dilution QC in a run or evaluation of dilution factors (10 or 20) in method validation.

The calibration range was not representative of concentrations of study samples and therefore, (b) (4) diluted approximately 47% of study samples. The firm evaluated dilution integrity for 100-fold dilution using 800 ng/mL, however this dilution factor was not used in the analysis of study samples and the concentration, 800 ng/mL is not representative of the study samples. DSI cannot assure the accuracy of the data cannot be assured as the firm used inappropriate calibration range and did not evaluate the dilution factors (10- or 20-fold) used in the study nor included dilution QCs to ensure the dilution integrity.

**4. QCs were not treated under the same conditions as study samples.**

- Study samples were stored below 65°C prior to extraction, whereas QCs were freshly prepared on the day of extraction.

The firm prepared QCs and calibrators freshly on the day of extraction of each batch. Under this condition, subject sample and QCs went through different freeze/thaw cycles. In order to assure the accuracy of the data, QCs and study samples should be treated under the same conditions.

**5. Lack of documentation to ensure the condition of processed samples prior to analysis.**

- Specifically, the processed samples (extracts) were transferred to a different building for analysis, however there was no record documenting the duration and range of storage conditions between completion of processing (extraction) and analysis.

The firm did not document the duration and range of storage conditions of the extracts from the completion of extraction until analysis. Sample processing was performed in a different building from where the samples were analyzed. DSI cannot assure the accuracy of the concentration data without verification of the condition of the processed samples prior to analysis.

**6. Failure to conduct appropriate method validation experiments.**

- For example:
  - (a) Freeze/thaw stability was evaluated at -20 °C, whereas study samples were stored below -65°C

**(b) Bench-top stability, stock solution stability and matrix effect for SM-13496 were not evaluated**

**(c) Recovery of SM-13496 was excessive (mean recovery was over 150%) in a validation experiment but the experiment was not investigated or repeated.**

**(d) Failure to prepare independent stock solutions for calibrators and QCs**

**(e) Dilution linearity was not evaluated. A dilution factor of 100 was evaluated in pre-study method validation, whereas study samples were diluted 10- and 20-fold before analysis**

**(f) Manual chromatogram integration was applied to all pre-study method validation, except for partial validation conducted in 2008 to evaluate precision/accuracy, selectivity, LLOQ and post-preparative stability**

The firm did not evaluate (1) the actual range of conditions for samples storage and handling and (2) the complete accuracy of the assay method in pre-study method validation.

Stock solutions were prepared in bulk and frozen prior to extraction. Study samples were stored frozen below -65°C and thawed prior to extraction. However, the firm did not evaluate stability of SM-13496 in serum during freeze/thaw cycles below -65°C to room temperature, and stability of the stock solution. The experimental extraction recovery of SM-13496 was over 150%, however there was no repeated experiment or investigation to explain this result.

The firm did not demonstrate accuracy of the assay using independent stock solutions for calibrators and QCs.

Approximately 47% of subject samples were diluted 10- or 20-fold during the analysis, however dilution factors (10- or 20-fold) used in the subject samples were not evaluated in the pre-study method validation. Dilution QCs were not used to ensure accuracy of dilution in each run.

The firm applied manual integration of chromatograms of all runs in the pre-study method validation in 1999, however there were no objective criteria or procedures to ensure consistency of the manual integration. During the inspection, the firm stated that the method validation was conducted in 1999 and they updated the SOP for validation experiments in 2009.

DSI cannot assure the accuracy of concentration data without evaluating the necessary elements of the assay in the method validation.

**7. Failure to use an acceptable calibration curve in batch 090804a.**

**- Specifically, the batch 090804a was calculated with the calibration curve from batch 090803a.**

According to the correspondence, the sponsor asked (b) (4) to analyze each subject's samples from period I and II together. This sponsor's request was made after completing analysis of batch 090803 containing period I samples and 090804a containing period II samples from this subject. Because of this request, (b) (4) calculated concentrations of samples in batch 090804a using the calibration curve from the batch 090803. During the inspection, DSI requested the firm to re-calculate the concentrations of subject samples from the batch 090804a using its own calibration curve. DSI recommends that the re-calculated data (Attachment 2) should be used in bioequivalence evaluation.

#### **8. Failure to evaluate assay reproducibility in incurred samples**

According to (b) (4)'s SOP for evaluating "incurred sample reproducibility" (ISR), ISR experiment would be conducted upon a sponsor's request. At the time of the study, the sponsor did not request to evaluate ISR, so there was no ISR evaluation. DSI cannot assure the reproducibility of incurred samples' measurements without data from appropriate ISR experiment.

#### **Conclusion**

Following our evaluation of the inspectional findings and the firm's response during the inspection, DSI recommends the following:

1. The authenticity of the test and reference products used in Study D1001053 cannot be assured as the clinical site failed to randomly select and retain the reserve samples. Therefore, Study D1001053 fails to meet the regulatory requirements for the retention of reserve samples for bioequivalence study [21 CFR 320.38 and 63]. Also, the identification of the lot for test drug product used in Study D1001053 cannot be assured (483 Item 1).
2. The accuracy of study sample concentrations cannot be assured, as (b) (4) used inappropriate concentrations for calibrators and QCs, and did not validate the accuracy of dilution factors used in the study (483 Items 2, 3, 4, 5).

3. The accuracy of reported SM-13496 concentrations in Study D1001053 cannot be assured, as the assay method was not validated for all aspects of study conduct (483 Item 6).
4. The reviewer should replace the concentrations for subject samples in batch 090804a with the re-calculated concentrations in the Attachment 2 (483 Item 7).
5. The reproducibility of incurred samples cannot be assured, as the firm did not evaluate reproducibility of the assay using random subject samples (483 Item 8).

Due to the above inspectional findings, DSI recommends that the bioequivalence study, D1001053 not be accepted for review. Study samples should be analyzed with appropriate calibrators representing study sample concentrations and QC samples serving as controls for each analytical run. If samples were diluted during analysis, appropriate experiments should be conducted to evaluate dilution integrity with dilution factors applied in the study or dilution QCs should be included to represent integrity of diluted samples.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

 8/16/2010  
Hyojong (Hue) Kwon, Ph.D.

**DSI Final Classification:**

**VAI** - Kitasato University East Hospital, Kanagawa, Japan

**VAI** - [REDACTED] (b) (4)

cc:

CDER DSI PM TRACK

HFD-48/Kwon/Rivera-Lopez/Ball/Haidar/CF

OND/DPP/Ann Sohn/Kofi Kumi/Raman Baweja (HFD-860)

Draft: HK 8/10/2010

Edit: MFS 8/11/2010, MYK 8/11/2010

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FACTS (b) (4)

| Application Type/Number | Submission Type/Number | Submitter Name                                 | Product Name   |
|-------------------------|------------------------|--|----------------|
| NDA-200603              | ORIG-1                 | DAINIPPON<br>SUMITOMO<br>PHARMA AMERICA<br>INC | Lurasidone HCl |

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/s/

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HYOJONG KWON  
08/16/2010  
Dr. Yau signed the hard copy on 8/16/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

DATE: August 9, 2010

TO: Ann J. Sohn, Regulatory Project Manager  
Cara Alfaro, PharmD, Clinical Analyst  
Ni Aye Khin, MD, Medical Officer  
Division of Psychiatry Products, HFD-130

THROUGH: Tejashri Purohit-Sheth, MD  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

FROM: Anthony Orenca, MD, FACP  
Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 200-603

APPLICANT: Dainippon Sumitomo Pharma America, Inc.

DRUG: lurasidone (b) (4)

THERAPEUTIC CLASSIFICATION: Standard Review (New Molecular Entity)

INDICATIONS: treatment of schizophrenia

CONSULTATION REQUEST DATE: February 25, 2010

DIVISION ACTION GOAL DATE: September 4, 2010

PDUFA DATE: October 30, 2010

## **I. BACKGROUND:**

Schizophrenia is a severe psychotic disorder associated with substantial morbidity and mortality, but available treatments that are partially effective in alleviating acute and chronic symptoms. Lurasidone is a novel drug for the treatment of schizophrenia. This new molecular entity possesses high affinities for dopamine D2, serotonin 5-HT7, 5-HT2A, 5-HT1A, and noradrenaline alpha 2C receptors. Lurasidone exhibits little or no affinity for histamine H1 or acetylcholine M1 receptors.

The results of three adequate and well-controlled studies were submitted in support of the application.

### **STUDY Protocol D1050006**

Study Protocol D1050006 was a multicenter, randomized, fixed dose (lurasidone 40 mg or lurasidone 120 mg p.o. daily), double-blind, parallel-group, placebo-controlled trial of 6 weeks' duration in subjects hospitalized with acute exacerbation of schizophrenia. The primary objective of the study was to evaluate efficacy of lurasidone versus placebo in the treatment of subjects with schizophrenia (diagnosed by DSM-IV criteria), as measured by reductions from baseline on total score of the Brief Psychiatric Rating Scale (BPRS), as extracted from the Positive and Negative Symptom Scale (PANSS).

The study included subjects aged 18 to 64 years, who satisfied DSM-IV criteria for schizophrenia, had been hospitalized with acute or relapsing schizophrenia within 3 weeks of screening, had demonstrated sufficient psychiatric symptoms at baseline (defined by BPRS total score of 42), and who were not judged treatment-resistant were eligible for randomization. The primary efficacy variable was based on the BPRS. Secondary efficacy variables were based on the PANSS and the Clinical Global Impressions scale (CGI). The study was conducted in 15 centers throughout the U.S. The first patient was enrolled on February 6, 2001. The last patient completed follow-up on December 18, 2001.

### **Study D1050231**

Study D1050231 was a randomized, placebo and active comparator controlled clinical trial to study the safety and efficacy of two doses of lurasidone in acutely psychotic patients with schizophrenia. The primary study objective was to evaluate the efficacy of lurasidone (40 mg/day or 120 mg/day) compared with placebo in subjects with acute schizophrenia (DSM-4 criteria) as measured by the mean change from Baseline in the PANSS total score at Week 6. The primary efficacy parameter was the mean change from Baseline in PANSS total score at Week 6.

This study was conducted in 52 study centers: 5 centers in Colombia, 14 centers in India, 4 centers in Lithuania, 4 centers in the Philippines, and 25 centers in the United States. The first subject was enrolled on January 31, 2008. The last subject completed (acute phase) on June 16, 2009.

### **Study D1050229**

Study D1050229 was a randomized, placebo-controlled study of three doses of lurasidone in acutely psychotic patients with schizophrenia. The primary study objective was to

evaluate the efficacy of lurasidone (40, 80, or 120 mg/day) compared with placebo in the treatment of subjects with acute schizophrenia (DSM-4 criteria) as measured by the mean change from Baseline in the PANSS total score at Week 6. The primary efficacy parameter was the change from Baseline in PANSS total score at Week 6.

This study was conducted in 48 study centers: 1 study center in France; 6 study centers in India; 2 study centers in Malaysia; 5 study centers in Romania; 7 study centers in Russia; 6 study centers in Ukraine; and 21 study centers in the United States. The first subject was enrolled on October 26, 2007. The last subject completed (Double-blind phase) on December 15, 2008.

**Study D1050196 (Not part of DPP consult to DSI, but part of ORA’s sponsor audit)**

D105096 was a double-blind, multicenter (22 U.S. sites), randomized, parallel-group study with a 3- to 7-day single-blind placebo washout, followed by 6 weeks of double-blind treatment with 80 mg SM-13496 or placebo. The primary objective was to evaluate the efficacy of SM-13496 versus placebo in the treatment of subjects with schizophrenia (diagnosed by DSM-IV criteria) as measured by reductions from baseline on the total score of the BPRS, as extracted from the PANSS survey instrument. Study D105096 was conducted over a period of 27 weeks. The first subject was randomized on May 28, 2004, and the last subject completed the study on December 6, 2004. The primary efficacy was the mean change from baseline to study endpoint on the BPRS total score.

For the domestic clinical inspection sites, sites 14 and 15 in Study Protocol D1050006 randomized nearly 40% of the total number of study subjects enrolled in this study. Further, Clinical Investigators Riesenbergs and Tran-Johnson enrolled subjects in 3 or 4 of the adequate and well-controlled clinical trials for lurasidone. It is important to evaluate the reliability of data generated by these sites.

For the foreign sites, Colombian clinical sites were selected primarily due to their significant contribution to the overall efficacy “signal” in this multicenter trial. Geographic analyses showed significant results favoring the Sponsor drug over placebo consistently in the Colombia, and not other regions (e.g., U.S. or India) in Study Protocol D1050231.

**II. RESULTS (by protocol/site):**

| Name of CI                        | City, State   | Protocol/<br>Site #  | Insp. Date         | EIR<br>Received<br>Date | Final<br>Classification |
|-----------------------------------|---------------|--|--------------------|-------------------------|-------------------------|
| Tram K. Tran-Johnson, PharmD, PhD | San Diego, CA | D1050006<br>Site #15<br>D1050231<br>Site #37                         | 4/12-4/30/<br>2010 | 5/10/2010               | NAI                     |
| Robert A. Riesenbergs, MD         | Atlanta, GA   | D1050006<br>/Site 15<br>D1050231<br>Site #17<br>D1050229<br>Site #17 | 5/11-5/26/<br>2010 | 7/9/2010                | NAI                     |

|                             |                     |                             |               |           |     |
|-----------------------------|---------------------|-----------------------------|---------------|-----------|-----|
| Laura Giraldo<br>Ospina, MD | Bogota,<br>COLOMBIA | D1050231<br>Site #464       | 6/14-/16/2010 | 7/15/2010 | NAI |
| Rodrigo Cordoba,<br>MD      | Bogota,<br>COLOMBIA | D1050231<br>Site #465       | 6/9-10/2010   | 7/15 2010 | NAI |
| Sepracor/SPONSOR            | Fort Lee, NJ        | D1050006<br>and<br>D1050196 | 5/11-6/8/2010 | 7/13/2010 | VAI |

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The EIR has not been received and findings are based on preliminary communication with the field.

## **CLINICAL SITE INVESTIGATOR**

### **1. Tram K. Tran-Johnson, PharmD, PhD**

CNRI-San Diego, LLC  
446 26<sup>th</sup> Street 6<sup>th</sup> Floor  
San Diego, CA 92102

## **PROTOCOL D1050006**

### **a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from January 18 to February 4, 2010. For Protocol D105006, a total of 43 subjects were screened, 29 were enrolled, and 13 subjects completed the study. An audit of 29 enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

### **b. Limitations of inspection**

None.

### **c. General observations/commentary**

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

### **d. Data acceptability/reliability for consideration in the NDA review decision.**

The data, in support of clinical efficacy and safety from this site, appear acceptable for this specific indication.

### PROTOCOL D1050231

#### **a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from January 18 to February 4, 2010. For Protocol D1050231, a total of 33 subjects were screened, 16 subjects were enrolled, and 5 subjects completed the study. An audit of 16 subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

#### **b. Limitations of inspection**

None.

#### **c. General observations/commentary**

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

#### **d. Data acceptability/reliability for consideration in the NDA review decision.**

The data, in support of clinical efficacy and safety from this site, appear acceptable for this specific indication.

### **2. Robert A. Riesenber, MD**

Atlanta Center for Medical Research  
811 Juniper St. NE  
Atlanta, GA 30308

### PROTOCOL D1050006

#### **a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from May 11 to 26, 2010. For Protocol D1050006, a total of 34 subjects were screened, 7 were screen failures, 27 were enrolled, and 6 subjects completed the study. Informed consents were obtained properly on all 34 subjects. An audit of 14 enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

**b. Limitations of inspection**

None.

**c. General observations/commentary**

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

**d. Data acceptability/reliability for consideration in the NDA review decision.**

The data, in support of clinical efficacy and safety from this site, appear acceptable for this specific indication.

**PROTOCOL D1050231**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from May 11 to 26, 2010. For Protocol D1050231, a total of 10 subjects were screened and enrolled, 4 were screen failures, and 2 subjects completed the study. An audit of 10 enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

**b. Limitations of inspection**

None.

**c. General observations/commentary**

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

**d. Data acceptability/reliability for consideration in the NDA review decision.**

The data, in support of clinical efficacy and safety at this clinical site, appears acceptable for this specific indication.

**PROTOCOL D1050229**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from May 11 to 26, 2010. For protocol D1050229, a total of 26 subjects were screened, 15 subjects were enrolled, and none completed the entire study (acute and extension phase). There were 13 subjects who completed the acute phase of the study. An audit of 16 enrolled study subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

**b. Limitations of inspection**

None.

**c. General observations/commentary**

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

**d. Data acceptability/reliability for consideration in the NDA review decision.**

The data, in support of clinical efficacy and safety from this site, appear acceptable for this specific indication.

**3. Laura Giraldo Ospina, MD**

CESAME, S.A. Calle 103A #21-49  
Bogota, Colombia

**PROTOCOL D1050231**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from June 14 to 16, 2010. For Protocol D1050231, a total of 20 subjects were screened, 12 subjects were enrolled and randomized, and 7 subjects completed the study. An audit of 12 subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Ethics Committee documents and Sponsor-generated correspondence were also inspected.

**b. Limitations of inspection**

None.

**c. General observations/commentary**

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

**d. Data acceptability/reliability for consideration in the NDA review decision.**

The data, in support of clinical efficacy and safety from this site, appear acceptable for this specific indication.

**4. Rodrigo Cordoba, MD**

GRUPO CISNE LTDA-UIC Campo Abierto  
Carrera 69 #170-40/70  
Bogota, Colombia

**PROTOCOL D1050231**

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from June 9 to 10, 2010. For protocol D1050231, a total of 19 subjects were screened, 14 subjects were enrolled and randomized, and 4 subjects completed the study. An audit of 14 subjects was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Ethics Committee documents and Sponsor-generated correspondence were also inspected.

**b. Limitations of inspection**

None.

**c. General observations/commentary**

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

**d. Data acceptability/reliability for consideration in the NDA review decision.**

The data, in support of clinical efficacy and safety from this site, appear acceptable for this specific indication.

**5. SPONSOR**

**Sepracor, Inc. (Dainippon Sumitomo, Inc.)**

1 Bridge Plaza N Suite 150  
Fort Lee, NJ 07024-7102

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.810, from May 11 to June 8, 2010. Protocols D1050006 and D1050196 were inspected.

**b. Limitations of inspection**

None.

**c. General observations/commentary:**

For Protocols D1050006 and D1050196, organization and personnel; standard operating procedures; selection and training of clinical trial monitors; monitoring procedures and activities; drug integrity or accountability; quality assurance; recorded retention and annual reporting were evaluated during the course of the inspection. No discrepancies or deficiencies were noted in the selection and training of clinical investigators, IRB processes, or firm's responsibilities to contract research organizations.

At the end of the inspection, the ORA field investigator issued a three-observation Form FDA 483 on June 8, 2010.

(A) Failure to ensure that the study was conducted in accordance with protocol or investigational plan. For Study D1050006, the Study Monitor changed the Study Protocol screening requirements for the female patients of childbearing age from a Urine Pregnancy Test to a Serum Pregnancy Test; however, the protocol was not updated by the sponsor.

(B) Failure to maintain adequate written records of the disposition of an investigational drug in accordance with 21 CFR Part 312.57. Specifically, for Study D1050006, study drug and placebo return documentation for Sites 4, 6, and 9 could not be located.

(C) Lack of adequate records covering receipt and disposition of an investigational drug. Specifically, for D1050006, drug accountability records could not account for the use or destruction of 40,464 tablets of mixed, active and placebo study medication, and for D1050196, drug accountability records could not account for the use or destruction of 1,952 tablets of mixed active and placebo study medication.

Sepracor responded in a letter on July 2, 2010. The sponsor clarified adequately the disposition and destruction of the tablets for study drug lurasidone and placebo. Specifically, drug accountability for D1050006 and D100196 were based on study drug kits rather than individual tablet counts. Per sponsor, a kit consisted of pre-packaged, sealed blisters of 672 tablets in study D1050006 (thus, properly accounting for the 40,464 tablets) and 114 tablets in study D100196 (thus, properly accounting for the 1,952 tablets). Sepracor has implemented measures to improve standard of monitoring and record keeping to account disposition of investigational drug in accordance with 21 CFR 312.57(a). An "Investigational Product Return Form," signed by site coordinator and monitor, was implemented for all trials in calendar year 2007, accompanying every drug return shipment that accounts for tablets contained in each kit.

The other observations noted by the ORA field investigator are considered regulatory deficiencies, however, with no significant impact on data integrity and human subjects protection. For the other observations on the Form FDA 483, Sepracor was committed to implement corrective actions.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

Although regulatory violations were noted, it is unlikely that these would impact data reliability. Data appear reliable to support the schizophrenia indication.

### **III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Two U.S. clinical investigator sites, two foreign clinical investigator sites, and the sponsor site were inspected in support of this application for the pivotal protocols. No discrepancies were noted with the data listings provided in the NDA and source documents for the clinical investigator sites. No significant deficiencies were noted at any of the clinical sites, and the regulatory violations noted at the sponsor inspection are unlikely to importantly impact data integrity. Data appear acceptable in support of the application.

*{See appended electronic signature page}*

Anthony Orenca, M.D.  
Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

| Application Type/Number | Submission Type/Number | Submitter Name                                 | Product Name   |
|-------------------------|------------------------|--|----------------|
| NDA-200603              | ORIG-1                 | DAINIPPON<br>SUMITOMO<br>PHARMA AMERICA<br>INC | Lurasidone HCl |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ANTHONY J ORENCIA  
08/09/2010

TEJASHRI S PUROHIT-SHETH  
08/09/2010

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

|                                    |   |
|------------------------------------|---|
| <b>NDA</b>                         | 200603  |
| <b>Brand Name</b>                  | (b) (4)   |
| <b>Generic Name</b>                | Lurasidone (MK-3756)  |
| <b>Sponsor</b>                     | Danippon sumitomo pharma america, Inc.                                    |
| <b>Indication</b>                  | Schizophrenia   |
| <b>Dosage Form</b>                 | 120 mg  |
| <b>Drug Class</b>                  | Antipsychotic/ treatment of schizophrenia                                 |
| <b>Therapeutic Dosing Regimen</b>  | Starting dose: 40 or 80 mg once daily,<br>Maximum dose: 120 mg once daily |
| <b>Duration of Therapeutic Use</b> | Chronic   |
| <b>Maximum Tolerated Dose</b>      | 400 mg once daily in schizophrenic patients                               |
| <b>Submission Number and Date</b>  | SDN 001 & SDN 007. February 24, 2010                                      |
| <b>Review Division</b>             | DPP / HFD 130   |

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

The QT study results are inconclusive due to the following reasons:

- The primary endpoint was inadequately defined. The QT study used time-matched mean changes from baseline in QTcI (i.e.,  $\Delta QTcI$ ) as the primary endpoint. The primary variable is inappropriate because it does not account for between-day shifting for ECG signals, which can be pronounced with an 11 day difference between the observation day and baseline day. A time-matched, baseline-corrected, and placebo-adjusted QTc ( $\Delta\Delta QTc$ ) should be used as the primary variable in a parallel thorough QT study. However, this variable cannot be derived from the current trial because of the absence of the placebo arm.
- Assay sensitivity was not established in the trial. The QT study used ziprasidone as active control. The results from ziprasidone arm has two limitations:
  - The results were described by using  $\Delta QTc$  rather than  $\Delta\Delta QTc$ .
  - At the tested dose level, the QTc interval change appears to be larger than the small changes defined by ICH E14 guidance.

In this randomized, double-blind, three-arm, multiple-dose, parallel study, 87 subjects (29 in each arm) received lurasidone 120 mg, lurasidone 600 mg, or ziprasidone (80 mg titrated to 160 mg per day) as active control. A total of 67 subjects (23 in lurasidone 120 mg arm, 20 for lurasidone 600 mg, and 24 for ziprasidone) were included in the ECG analyses. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates And The 90% CIs Corresponding To The Largest Upper Bounds For Lurasidone (Therapeutic 120 mg Dose And Supratherapeutic 600 mg Dose) And The Largest Lower Bound for Ziprasidone (FDA Analysis)**

| Treatment                                   | Time (hour) | $\Delta$ QTcI (ms) | 90% CI (ms)  |
|---|-------------|--------------------|--------------|
| <b>Lurasidone 120 mg</b>                    | 2           | 7.5                | (3.3, 11.7)  |
| <b>Lurasidone 600 mg</b>                    | 4           | 4.6                | (-0.2, 9.5)  |
| <b>Ziprasidone 80 mg titrated to 160 mg</b> | 6           | 16.3               | (12.3, 20.3) |

The 120-mg lurasidone dose represents the highest anticipated therapeutic dose. The 600-mg dose is the maximum tolerated dose and is 5-fold higher than the intended clinical dose. The supratherapeutic dose produces lurasidone mean  $C_{max}$  values 3.6-fold higher than the mean lurasidone  $C_{max}$  for the therapeutic dose. The highest clinical exposure scenarios include severe hepatic impairment (1.3-fold increase in  $C_{max}$ ), renal impairment (1.9-fold increase in  $C_{max}$ ) and drug interaction with a moderate CYP3A4 inhibitor such as diltiazem (2.1-fold increase in  $C_{max}$ ). The exposures observed in this study following the 600-mg dose cover these scenarios. Potent CYP3A4 inhibitors such as ketoconazole are contraindicated as they are expected to cause a 6.9-fold increase in  $C_{max}$ .

## 1.2 QT INTERDISCIPLINARY REVIEW TEAM’S COMMENTS

- Repeating the thorough QT study (TQT) should be considered. The sponsor should submit the TQT study protocol for QT-IRT to review prior to conducting the study. If the sponsor is unwilling to conduct another TQT study, as an alternative, the sponsor may choose to perform intensive ECG monitoring in their on-going and future clinical trials. The recommended time points include baseline,  $T_{max}$  of parent compound and major metabolites after the first dose and at steady state, and periodically during the treatment.
- If there is an intention to use ziprasidone as positive control in a future thorough QT study, we recommend that the sponsor identify appropriate dose of ziprasidone that is associated with the small changes in QTc interval defined by ICH E14 guidance. In addition, the sponsor should collect PK information and establish the concentration-QT relationship of ziprasidone, which can be used to establish the assay sensitivity.

## 2 PROPOSED LABEL

*We have used red strike out for suggested test to be deleted. QT-IRT recommendations for labeling are suggestions only; we defer final decisions related to labeling to the review division.*

(b)  
(4)

[REDACTED]

(b) (4)

[REDACTED]

[REDACTED]

### **3 BACKGROUND**

#### **3.1 PRODUCT INFORMATION**

Lurasidone hydrochloride (lurasidone, formerly referred to as MK-3756), is a candidate antipsychotic agent for the treatment of schizophrenia. It possesses high affinities for dopamine D2, serotonin 5-HT7, 5-HT2A, and 5HT1A receptors. Lurasidone has been studied in several Phase 2 clinical trials where the compound demonstrated antipsychotic efficacy and a generally favorable safety profile.

Lurasidone has a unique chemical structure that differs from conventional antipsychotic therapies such as the phenothiazine-, butyrophenone-, and benzamide-classes of antipsychotic agents. Because of its serotonin 5-HT2 blocking and 5-HT1A agonist activity, lurasidone is expected to be associated with fewer extrapyramidal symptoms (EPS) than conventional therapeutic agents.

#### **3.2 MARKET APPROVAL STATUS**

Lurasidone is currently not marketed in any country.

### 3.3 PRECLINICAL INFORMATION

It was shown in HEK293 that SM-13496 concentration-dependently inhibits rapidly activating delayed rectifier potassium currents in HEK293 cells with an estimated  $IC_{50}$  of 0.7-0.8  $\mu$ M.

Results showed that ID-14326 hydrochloride and ID-14283 hydrochloride, metabolites of SM-13496, concentration-dependently inhibit rapidly activating delayed rectifier potassium currents in HEK293 cells, with an estimated  $IC_{50}$  of  $6.76 \times 10^{-7}$  and 0.7-0.8  $\mu$ M, respectively. It was concluded that SM-13496 depressed hERG current and the effect was equal to risperidone, which is an analog of SM-13496.

A safety pharmacology study concerning the cardiovascular effects of SM-13496 at relatively high doses on blood pressure, heart rate, electrocardiogram parameters, and toxicokinetics (TK) were investigated in conscious dogs using a telemetry system.

SM-13496 at 100 and 300 mg/kg, sotalol as a positive control at 30 mg/kg, or vehicle alone (0.5 w/v %methyl cellulose) were administered orally to four female beagle dogs with the latin square method at a 1 or 2-week intervals and cardiovascular parameters were continuously recorded for 24 hours after administration.

No marked effects were observed on systolic, diastolic, or mean blood pressure up to 24 hours after administration of SM-13496 at 100 and 300 mg/kg, but slight increases in heart rate were observed at both doses.

With regard to ECG parameters, SM-13496 did not cause prolongation of the QT interval at 100 and 300 mg/kg. Moreover, prolongation of the QTc was only apparent at 300 mg/kg. Shortening of the PQ and RR intervals was observed at 100 and 300 mg/kg, but there were no effects at any dose on QRS duration. In contrast, sotalol at 30 mg/kg, the positive control, caused remarkable prolongation of the QT interval and QTc.

From the above results, SM-13496 was adjudged to produce no effects on blood pressure, QT interval, QTc and QRS duration in conscious dogs at a dose of 100 mg/kg ( $C_{max}$ : 1.903  $\mu$ g/mL) which result in serum concentration about 11 times as high as that in human serum in a clinical study. While slight increase in heart rate and shortening of PQ and RR intervals were observed at both 100 and 300 mg/kg, at the dose of 300 mg/kg ( $C_{max}$ : 2.780  $\mu$ g/mL) with a serum concentration about 17 times that in human serum in a clinical study, no marked effects were evident with regard to blood pressure, QT interval and QRS duration, and slight prolongation of the QTc was observed.

*Reviewer's comments: Lurasidone and its metabolites blocked hERG currents with high affinity. In vivo, lurasidone prolongs QTc but at very high exposures (10,000-fold the clinical  $C_{max}$  exposure).*

### 3.4 PREVIOUS CLINICAL EXPERIENCE

From the Integrated Summary of Safety and IB

“The mean duration of exposure in Phase 1 non-schizophrenic studies was 2.5 days for the "all lurasidone" group and 4.3 days for the placebo group. There was no clinically meaningful difference in mean duration of exposure among lurasidone dosing groups (2.0, 2.8, and 2.8 days for  $\leq 30$ , 40, and 60-100 mg, respectively). Based on cumulative exposure, 10.5% of subjects receiving any

dose of lurasidone had 7 or more days of exposure and 38.4% of subjects in the placebo group had 7 or more days of exposure.

“Single oral doses of lurasidone 10, 20, 40, and 80 mg were found to be well-tolerated when administered to young healthy male Caucasian subjects; however, a single dose of 100 mg resulted in dose-limiting AEs of subjective restlessness. At the 100 mg dose level, five of the six subjects receiving lurasidone reported restlessness as a drug-related AE. This was of moderate severity in three of the subjects, with two of the subjects expressing their reluctance to receive the study drug again.

“No SAEs were observed during the study. The most commonly reported drug-related AEs were restlessness, irritability, myalgia, and nausea.

“Multiple oral doses of lurasidone were well-tolerated by healthy male Caucasian subjects at the 40 mg, BID, dose regimen. Lurasidone was not well-tolerated at multiple doses of 80 mg, OD. Four subjects receiving 80 mg, OD, were withdrawn from the study (one on Day 1, 2 on Day 5, and one on Day 7) due to drug-related AEs. Three subjects were self withdrawals for personal reasons. No SAEs were reported during the study. All AEs were mild to moderate in severity. The most commonly reported drug-related AEs were psychiatric and nervous system related events of restlessness, anxiety, insomnia, disturbance in attention, and fatigue

“The mean duration of exposure in phase 1 schizophrenic studies was 10.8 days for the “all lurasidone” group, 6.0 days for the placebo group, and 10.7 days for the ziprasidone group. Based on cumulative exposure, 90.1% of subjects in the lurasidone 120 mg group, 27.1% of subjects in the > 120 mg group, 6.3% of subjects in the placebo group, and 96.6% of subjects in the ziprasidone group had 7 or more days of exposure.

“In phase 1 schizophrenic patients studies, the most frequently reported TEAEs, as a percentage of the Safety Population, at the primary SOC level were Nervous System Disorders (83.7% of all lurasidone-treated subjects). The proportion of subjects reporting Nervous System Disorders were 90.7% of subjects in the 120 mg group, 71.9% of subjects in the > 120 mg group, 43.8% of subjects in the placebo group, and 75.9% of subjects in the ziprasidone group. The most common TEAEs (>10% of subjects in the “all lurasidone” group) for lurasidone-treated subjects were: somnolence (57.8%), akathisia (32.6%), anxiety (26.4%), insomnia (18.6%), nausea (16.3%), headache (15.1%), dystonia (14.0%), sedation (13.2%), vomiting (13.2%), restlessness (12.8%), and dyspepsia (12.4%). The most common TEAEs (>1.0% of subjects in the “all lurasidone” group) leading to study discontinuation in lurasidone-treated subjects from the P1SCH studies were nausea (1.6%), vomiting (1.6%), sedation (1.6%), akathisia (1.2%), and dystonia (1.2%). Most of the TEAEs leading to study discontinuation occurred in subjects taking lurasidone > 120 mg.

“For the parameter of supine diastolic BP, nine (4.9%) of 182 lurasidone-treated subjects experienced markedly abnormally low values. Of these, eight (of 138;

5.8%) were in the lurasidone 120 mg treatment group and one (of 44; 2.3%) was in the lurasidone > 120 mg group.

“ECG in phase 1 schizophrenic patients. Mean change from Baseline to LOCF for HR was  $4.7 \pm 10.1$  bpm for “all lurasidone” treatment group,  $4.7 \pm 9.7$  bpm for the lurasidone 120 mg dose group, and  $4.7 \pm 10.8$  bpm for the lurasidone > 120 mg dose group. Mean change from Baseline to LOCF for HR was  $2.6 \pm 13.1$  bpm for the placebo group and  $4.3 \pm 9.4$  bpm for ziprasidone 160 mg treated-subjects.

“Mean change from Baseline to LOCF for QTcF was  $1.0 \pm 13.9$  msec for the “all lurasidone” treatment group,  $0.3 \pm 14.2$  msec for the lurasidone 120 mg dose group, and  $2.2 \pm 13.5$  msec for lurasidone > 120 mg-treated subjects. The mean change from Baseline to LOCF for QTcF was  $-3.4 \pm 19.3$  ms for placebo and  $5.8 \pm 15.1$  ms subjects treated with ziprasidone 160 mg.

“QTcB > 450 ms occurred in 9.3% (24 of 257) of subjects in the “all lurasidone” treatment group and 17.2% (five of 29) of subjects in the ziprasidone 160 mg treatment group; zero of 16 subjects in the placebo group had QTcB > 450 ms. The lowest percentage of QTcB > 450 ms occurred in the lurasidone > 120 mg group (5.2%, five of 96). The percentage of QTcF > 450 ms was 6.3% (one of 16) in the placebo group, 3.5% (nine of 257) for “all lurasidone” treatment group, and 3.4% (one of 29) for ziprasidone 160 mg-treated subjects.

**Table 2: Incidence of Prolonged QTc—Safety Population: P1SCH Studies**

| Prolongation Criteria/Parameter                 | n/m (%) of Subjects |                   |                     |                |                    |
|---|---------------------|-------------------|---------------------|----------------|--------------------|
|   | Placebo             | Lurasidone 120 mg | Lurasidone > 120 mg | All Lurasidone | Ziprasidone 160 mg |
|   | N = 16              | N = 162           | N = 96              | N = 258        | N = 29             |
| Male QTc > 450 msec or<br>Female QTc > 470 msec |                     |                   |                     |                |                    |
| QTcB  | 0/16                | 12/161 (7.5)      | 4/96 (4.2)          | 16/257 (6.2)   | 4/29 (13.8)        |
| QTcF  | 1/16 (6.3)          | 7/161 (4.3)       | 0/96                | 7/257 (2.7)    | 1/29 (3.4)         |
| Any QTc > 450 msec                              |                     |                   |                     |                |                    |
| QTcB  | 0/16                | 19/161 (11.8)     | 5/96 (5.2)          | 24/257 (9.3)   | 5/29 (17.2)        |
| QTcF  | 1/16 (6.3)          | 9/161 (5.6)       | 0/96                | 9/257 (3.5)    | 1/29 (3.4)         |
| Any QTc > 500 msec                              |                     |                   |                     |                |                    |
| QTcB  | 0/16                | 3/161 (1.9)       | 0/96                | 3/257 (1.2)    | 0/29               |
| QTcF  | 0/16                | 2/161 (1.2)       | 0/96                | 2/257 (0.8)    | 0/29               |
| Increase from Baseline ≥ 30 msec                |                     |                   |                     |                |                    |
| QTcB  | 1/16 (6.3)          | 29/161 (18.0)     | 18/96 (18.8)        | 47/257 (18.3)  | 10/29 (34.5)       |
| QTcF  | 1/16 (6.3)          | 24/161 (14.9)     | 7/96 (7.3)          | 31/257 (12.1)  | 7/29 (24.1)        |
| Increase from Baseline ≥ 60 msec                |                     |                   |                     |                |                    |
| QTcB  | 0/16                | 4/161 (2.5)       | 1/96 (1.0)          | 5/257 (1.9)    | 1/29 (3.4)         |
| QTcF  | 0/16                | 3/161 (1.9)       | 0/96                | 3/257 (1.2)    | 0/29               |

Abbreviations: QTcB = QTc using Bazett’s correction, QTcF = QTc using Fridericia’s correction, n = number of subjects satisfying the prolongation criteria at least once post-Baseline, m = number of subjects with at least one post-Baseline value, % = percentage of subjects meeting the predefined criteria.

Note: Grouping includes Studies [D1050160](#), [D1050217](#), [D1050247](#), [D1050249](#), [D1050263](#), [D1050269](#), and [D1050279](#).

Source: [ISS Table 10.2.1.2](#)

Source: *ISS Table 31.*

“QTcB > 500 ms occurred in no placebo subjects and three of 257 subjects (1.2%) in the “all lurasidone” treatment group. QTcF > 500 ms occurred in no placebo subjects and two of 257 subjects (0.8%) in the “all lurasidone” treatment group; both subjects were in the lurasidone 120 mg treatment group.

**Table 3: Incidence of Abnormal Electrocardiogram Values —Safety Population: P1SCH Studies**

| ECG Parameter (unit)/<br>Abnormality Criteria/Visit | n/m (%) of Subjects |                      |                        |                |                       |
|---|---------------------|----------------------|------------------------|----------------|-----------------------|
|   | Placebo             | Lurasidone<br>120 mg | Lurasidone<br>> 120 mg | All Lurasidone | Ziprasidone<br>160 mg |
|   | N = 16              | N = 162              | N = 96                 | N = 258        | N = 29                |
| Heart Rate (bpm)/ Abnormal<br>(≥ 100 bpm)           |                     |                      |                        |                |                       |
| Baseline  | 0/16                | 0/162                | 2/96 (2.1)             | 2/258 (0.8)    | 0/29                  |
| LOCF Endpoint                                       | 1/16 (6.3)          | 3/161 (1.9)          | 2/96 (2.1)             | 5/257 (1.9)    | 1/29 (3.4)            |
| Overall Post-Baseline                               | 1/16 (6.3)          | 7/161 (4.3)          | 6/96 (6.3)             | 13/257 (5.1)   | 4/29 (13.8)           |
| PR Interval (msec)/ Abnormal<br>(≥ 210 msec)        |                     |                      |                        |                |                       |
| Baseline  | 0/16                | 2/162 (1.2)          | 1/96 (1.0)             | 3/258 (1.2)    | 0/29                  |
| LOCF Endpoint                                       | 0/16                | 2/161 (1.2)          | 1/96 (1.0)             | 3/257 (1.2)    | 0/29                  |
| Overall Post-Baseline                               | 0/16                | 14/161 (8.7)         | 2/96 (2.1)             | 16/257 (6.2)   | 1/29 (3.4)            |
| QRS Interval (msec)/ Abnormal (≥<br>120 msec)       |                     |                      |                        |                |                       |
| Baseline  | 0/16                | 2/162 (1.2)          | 0/96                   | 2/258 (0.8)    | 0/29                  |
| LOCF Endpoint                                       | 0/16                | 2/161 (1.2)          | 0/96                   | 2/257 (0.8)    | 0/29                  |
| Overall Post-Baseline                               | 0/16                | 5/161 (3.1)          | 0/96                   | 5/257 (1.9)    | 0/29                  |
| QT Interval (msec)/ Abnormal<br>( > 500 msec)       |                     |                      |                        |                |                       |
| Baseline  | 0/16                | 0/162                | 0/96                   | 0/258          | 0/29                  |
| LOCF Endpoint                                       | 0/16                | 1/161 (0.6)          | 0/96                   | 1/257 (0.4)    | 0/29                  |
| Overall Post-Baseline                               | 0/16                | 4/161 (2.5)          | 0/96                   | 4/257 (1.6)    | 0/29                  |
| Interpretation/ Abnormal                            |                     |                      |                        |                |                       |
| Baseline  | 4/16 (25.0)         | 87/162 (53.7)        | 43/96 (44.8)           | 130/258 (50.4) | 12/29 (41.4)          |
| LOCF Endpoint                                       | 9/16 (56.3)         | 74/161 (46.0)        | 36/96 (37.5)           | 110/257 (42.8) | 14/29 (48.3)          |
| Overall Post-Baseline                               | 12/16 (75.0)        | 143/161 (88.8)       | 67/96 (69.8)           | 210/257 (81.7) | 27/29 (93.1)          |

Abbreviations: ECG = Electrocardiogram; LOCF = Last Observation Carried Forward.

Note: Grouping includes Studies [D1050160](#), [D1050217](#), [D1050247](#), [D1050249](#), [D1050263](#), [D1050269](#), and [D1050279](#).

Note: Baseline is defined as the last measurement prior to treatment administration. If there are multiple measurements at the Baseline visit, the average of the measurement is considered Baseline. LOCF Endpoint is the last post-Baseline measurement during the study period or within 7 days after treatment discontinuation (excluding scheduled follow-up visits). If there are multiple measurements at endpoint, the average of the measurements is considered endpoint.

Note: n = Number of subjects satisfying the abnormality criteria at least once, m = number of subjects with a non-missing result at the specified time point, % = percentage of subjects meeting the predefined criteria.

Source: [ISS Table 10.3.1.2](#)

Source: *ISS Table 32*

*Reviewer's comments: In phase 1, approximately 320 healthy subjects received lurasidone at single doses ranging from 0.1 to 100 mg. In study D1050001 at the 100-mg dose level, five of the six subjects receiving lurasidone reported restlessness as a drug-related AE. This was of moderate severity in three of the subjects, with two of the subjects expressing their reluctance to receive the study drug again. Lurasidone was not well-tolerated in healthy subjects at multiple doses of 80 mg, OD.*

*Overall, schizophrenic patients (N = 258) received doses ranging from 120 to 600 mg/day. Lurasidone, administered in schizophrenic patients without titration at doses of 120, 140, and 160 mg, OD, intermittently over an 8-day period (five days consecutively), was safe and well-tolerated. The most commonly reported drug-related AEs were somnolence and restlessness. One patient in the 120-mg arm had a prolonged QTcF (Day -1: 405 ms; Day 7, period 1: 713.00 ms) that was considered adverse and mild in severity and resulted in the subject discontinuing from the study. There were more PR abnormal ( $\geq 210$  ms) in the "all lurasidone" arm than in the placebo and ziprasidone arm. However, no dose-dependent trend was observed.*

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of lurasidone's clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT did not review the protocol prior to conducting this study.

### **4.2 TQT STUDY**

#### **4.2.1 Title**

A double-blind, double-dummy, active controlled, randomized, 3-arm, parallel study to evaluate the effects of therapeutic and suprathreshold doses of MK-3756 on QTc interval in male and female schizophrenic or schizoaffective patients

#### **4.2.2 Protocol Number**

D1050249

#### **4.2.3 Study Dates**

April 24, 2006 – August 31, 2006

#### **4.2.4 Objectives**

**Primary:** To evaluate effects of a therapeutic (120 mg) dose of lurasidone on the QT interval corrected for heart rate (QTc), and to evaluate effects of a suprathreshold (600 mg) dose of lurasidone on the QTc interval.

**Secondary:** To demonstrate sensitivity of this QTc assay using ziprasidone as a positive control.

## 4.2.5 Study Description

### 4.2.5.1 Design

This was a double-blind, double-dummy, randomized, three-arm, parallel study.

### 4.2.5.2 Controls

The Sponsor used positive control (ziprasidone) with no placebo.

### 4.2.5.3 Blinding

This was a double-blind study.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

- Lurasidone 120 mg
- Lurasidone 600 mg
- Ziprasidone (80 mg titrated to 160 mg)

### 4.2.6.2 Sponsor's Justification for Doses

“The therapeutic dose was 120 mg based on the highest anticipated therapeutic dose. The suprathreshold dose was 600 mg (titrated over 6 days with 5 additional days at 600 mg to reach approximate steady-state plasma concentrations) was selected based upon results of the MTD study in schizophrenic patients. This dose provided a five-fold margin in exposure over the highest dose planned for Phase 3.”

*Reviewer's Comment: The 120-mg lurasidone dose represents the highest anticipated therapeutic dose. The 600-mg dose is the maximum tolerated dose and is 5-fold higher than the intended clinical dose. The suprathreshold dose produces lurasidone mean  $C_{max}$  values 3.6-fold higher than the mean lurasidone  $C_{max}$  for the therapeutic dose. The highest clinical exposure scenarios include severe hepatic impairment (1.3-fold increase in  $C_{max}$ ), renal impairment (1.9-fold increase in  $C_{max}$ ) and drug interaction with a moderate CYP3A4 inhibitor such as diltiazem (2.1-fold increase in  $C_{max}$ ). The exposures observed in this study following the 600-mg dose cover these scenarios. Potent CYP3A4 inhibitors such as ketoconazole are contraindicated as they are expected to cause a 6.9-fold increase in  $C_{max}$ .*

### 4.2.6.3 Instructions with Regard to Meals

Doses were administered after a standardized meal.

*Reviewer's Comment: Administration of doses with food is acceptable. Previous studies have shown a 3-fold increase in  $C_{max}$  and 2.2-fold increase in AUC when doses were administered in the fed state.*

#### **4.2.6.4 ECG and PK Assessments**

ECG measurements for assessment of QTc were obtained on Day 0 and Day 11 at 1, 2, 4, 6 and 8 hours post-dose. Blood samples for measurement of lurasidone concentrations were collected on Day 11 at 1, 2, 3, 4, 6, 8 and 24 hours post-dose. Additional trough concentrations were also obtained from Day 2 to Day 11.

*Reviewer's Comment: The PK and ECG assessments are adequate to capture the QT effect at peak concentrations of lurasidone ( $T_{max} \sim 1$  to 4 hours) and its metabolites ( $T_{max} \sim 1.5$  to 4 hours).*

#### **4.2.6.5 Baseline**

Day 0 time-matched baseline was used for the analysis.

#### **4.2.7 ECG Collection**

Twelve-lead ECGs were performed at protocol-specified timepoints (Table 5). A baseline 12-lead safety ECG was performed prior to time zero on Day 0. The Mortara H-12 Holter recorder was affixed to the subject prior to time zero on Day 0 (baseline). Subjects rested quietly in a supine position for 20 minutes prior to the first timepoint, and the Holter monitor began recording 10 minutes prior to the first timepoint. The safety ECGs were measured during this time. Special care was taken for proper lead placement. If there was a change in a subject's ECG, measurements were repeated 2 more times and an average of the 3 measurements was used for determination of eligibility for study continuation.

Replicate ECGs were extracted by [REDACTED] (b) (4) laboratory according to a pre-specified study protocol algorithm. Subjects rested quietly in a supine position at least 10 minutes prior to and 5 minutes following each additional prescribed ECG timepoint. Subsequently, as requested by DSPA, the ECGs were re-extracted by eResearch Technology at the prespecified timepoint. It is unknown whether the subjects were supine during the 1, 3, 5, and 7 hour timepoints. Subjects were prohibited from drinking any liquids 10 minutes prior to and 5 minutes following each protocol-prescribed ECG timepoint.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

A total of 87 subjects (67 male and 20 female) were enrolled in this study and received at least one dose of study drug.

Of these, 73 subjects received all doses of study drug and completed all study procedures.

**Table 4: Demographic Characteristics**

| Demographic Variable  | Lurasidone 120 mg<br>N=29 | Lurasidone 600 mg<br>N=29 | Ziprasidone 160 mg<br>N=29 | Overall<br>N=87       |
|---|---------------------------|---------------------------|----------------------------|-----------------------|
| Mean age in years (range)   | 38 ( 22 to 55)            | 40 (18 to 56)             | 38 (19 to 54)              | 39 (18 to 56)         |
| Mean weight in kg (range)   | 83.0 (54.5 to 110.7)      | 84.0 (50.4 to 172.7)      | 86.6 (55.0 to 117.9)       | 84.5 (50.4 to 172.7)  |
| Mean height in cm (range)   | 173.1 (160.0 to 190.5)    | 170.3 (82.1 to 193.8)     | 176.2 (157.5 to 190.5)     | 173.2 (82.1 to 193.8) |
| BMI in kg/m <sup>2</sup> (range)  | 27.7 (19.3 to 35.0)       | 24.9 (18.5 to 256.3)      | 27.8 (19.7 to 35.8)        | 30.7 (18.5 to 256.3)  |
| Gender [n (%)]  |                           |                           |                            |                       |
| Female  | 6 (20.7)                  | 7 (24.1)                  | 7 (24.1)                   | 20 (23.0)             |
| Male  | 23 (79.3)                 | 22 (75.9)                 | 22 (75.9)                  | 67 (77.0)             |
| Race [n (%)]  |                           |                           |                            |                       |
| Hispanic  | 4 (13.8)                  | 1 (3.4)                   | 2 (6.9)                    | 7 (8.0)               |
| Black   | 11 (37.9)                 | 19 (65.5)                 | 11 (37.9)                  | 41 (47.1)             |
| White   | 14 (48.3)                 | 7 (24.1)                  | 16 (55.2)                  | 37 (42.5)             |
| Asian   | ---                       | 2 (6.9)                   | ---                        | 2 (2.3)               |
| Note(s): BMI = body mass index; bid = twice daily.<br>Study drug administered daily for 11 days: lurasidone 120 mg x 1 day; titrated lurasidone 600 mg = lurasidone (120 mg x 1 day, 200 mg x 1 day, 400 mg x 2 days, 520 mg x 2 days, and 600 mg x 5 days); titrated ziprasidone 160 mg = ziprasidone (40 mg [bid] x 4 days and 80 mg [bid] x 7 days).<br>Height and weight data was missing from Listing 16.2.4.1 for Subject 12. Entries for height (82.1 cm) and weight (172.7 kg) in CRF for Subject 40 appeared to be incorrect, but were used as recorded in weight and demographic listings and demographic summary tables.<br>Source: Table 14.1.3.1.1 and Listing 16.2.4.1. |                           |                           |                            |                       |

Source: Table 10, CSR.

All subjects were using medications, including antipsychotics at study screening.

**Table 5: Number (%) of Subjects with Most frequently Administered Therapeutic Class of Concomitant Medications**

| Therapeutic Class of Concomitant Medication   | Lurasidone 120 mg<br>N = 29 | Lurasidone 600 mg<br>N=29 | Ziprasidone 160 mg<br>N=29 | Overall<br>N=87 |
|---|-----------------------------|---------------------------|----------------------------|-----------------|
| D07AA – Weak corticosteroids, (Group 1)   | 3 (10.3)                    | 3 (10.3)                  | 3 (10.3)                   | 9 (10.3)        |
| M01AE – Propionic acid derivatives  | 4 (13.8)                    | 4 (13.8)                  | 1 (3.4)                    | 9 (10.3)        |
| N02BE - Anilides  | 13 (44.8)                   | 12 (41.4)                 | 11 (37.9)                  | 36 (41.4)       |
| N04AC – Ethers of tropine derivatives   | 7 (24.1)                    | 9 (31.0)                  | 10 (34.5)                  | 26 (29.9)       |
| N05AH – Diazepines, oxazepines, and thiazepines   | 9 (31.0)                    | 12 (41.4)                 | 11 (37.9)                  | 32 (36.8)       |
| N05AX – Other antipsychotics  | 11 (37.9)                   | 9 (31.0)                  | 10 (34.5)                  | 30 (34.5)       |
| N05BA – Benzodiazepine derivatives  | 28 (96.6)                   | 28 (96.6)                 | 28 (96.6)                  | 84 (96.6)       |
| N05CF – Benzodiazepin-related drugs   | 25 (86.2)                   | 23 (79.3)                 | 22 (75.9)                  | 70 (80.5)       |
| Note(s): bid = twice daily.<br>Study drug administered daily for 11 days: lurasidone 120 mg x 1 day; titrated lurasidone 600 mg = lurasidone (120 mg x 1 day, 200 mg x 1 day, 400 mg x 2 days, 520 mg x 2 days, and 600 mg x 5 days); titrated ziprasidone 160 mg = ziprasidone (40 mg [bid] x 4 days and 80 mg [bid] x 7 days).<br>Source: Table 14.1.3.3.1. |                             |                           |                            |                 |

Source: Table 11, CSR.

## 4.2.8.2 Statistical Analyses

### 4.2.8.2.1 Primary Analysis

The primary analysis assessed the effect of a therapeutic dose of lurasidone on cardiac repolarization on Day 11, as measured by the time-matched mean changes from baseline in QTcI on-drug (Day 11), relative to baseline (Day 0) at the same scheduled time. Specifically, a linear mixed model for time-matched change from baseline in QTcI was estimated with fixed effects for study arm (120 mg and 600 mg lurasidone, ziprasidone), prior therapy (on aripiprazole, not on aripiprazole within 30 days prior to the first dose of

study medication), gender (male, female), time (hour), the interaction of study arm and time (hour) plus the baseline value of QTcI as a covariate (time matched), with time as a repeated measure on each subject. The within-subject covariance structure was pre-specified as unstructured. In case of a non-convergence problem, a robust sandwich estimator for the standard error of the fixed effects and a spatial exponential anisotropic covariance pattern model was to be used. The mean and two-sided 90% CI for the mean change from baseline in QTcI were reported at each timepoint. The effect of a therapeutic dose (120 mg daily) of lurasidone on QTcI was determined as the mean corresponding to the largest upper bound of the CI for these values. The same analysis was completed for the supratherapeutic level (600 mg QD).

#### **4.2.8.2.2 Assay Sensitivity**

To demonstrate assay sensitivity, the secondary hypothesis was that administration of ziprasidone was associated with an increase in QTc interval. The two-sided 90% CI for the mean QTcI change from baseline was computed from the model of the primary analysis. The least-squares (LS) means and two-sided 90% CI for the mean change from baseline in QTcI were reported at each timepoint. If the mean change was greater than 5 ms and the CI excluded zero on the lower end for at least one of the timepoints, it was concluded that assay sensitivity is established.

*Reviewer's Comments: It is unclear whether the ziprasidone at the tested dose is associated with the small changes in QTc interval as defined by ICH E14 guidance.*

#### **4.2.8.2.3 Categorical Analysis**

Data for QT/QTc were categorized based on guidelines for prolongation given in the E14 guidance document. The categorical analysis was performed to summarize the total counts and percentages of clinically noteworthy ECG events for subjects on each study arm. These analyses were performed on the absolute ECG intervals as well as the time-matched change from baseline. The following categories were specified for clinically noteworthy events: QT/QTcI/QTcB/QTcF

- QT/QTc > 450 ms (Day 0 and Day 11)
- QT/QTc > 480 ms (Day 0 and Day 11)
- QT/QTc > 500 ms (Day 0 and Day 11)
- Time-matched change-from-baseline QT/QTc  $\geq$  30 ms (Day 11)
- Time-matched change-from-baseline QT/QTc  $\geq$  60 ms (Day 11)

The categorical analysis for QT/QTc values and change from baseline were conducted based on the mean of the replicates for the individual subject. All events were summarized for each study arm on the basis of subject incident rates, with the denominator being the number of subjects in the ECG population. The summary tables included total number of subjects and the number and percentage of subjects meeting the specified criteria for the clinically noteworthy event. Subjects may have been counted in multiple categories, and therefore subject counts could not be added across categories.

#### **4.2.8.2.4 Additional Analyses**

Additionally, since it has been documented that drug-induced changes in HR (or RR) can inflate the false positive rate in thorough QT studies, a supportive analysis of the effect of lurasidone on heart-rate corrected QT was assessed using a model-based QT correction. This linear mixed model for change-from-baseline QT was identical to that of the primary analysis but included, in addition, a fixed effect and random coefficient for change in RR. This coefficient acted as a model-based individual correction for any drug-induced changes in RR. The within-subject covariance structure was pre-specified as spatial exponential anisotropic. Two additional fixed effects allowing the correction factor (change in RR covariate) to vary by treatment (study arm), were added to the above model and tested at the 5% significance level. If statistically significant, these effects were also included in this model. Two-sided 90% CI for the mean QTc values for each study arm and timepoint were computed.

#### 4.2.8.3 Safety Analysis

There were 14 subjects who prematurely withdrew from the study. Four subjects (#s 6, 43, 101, and 102) were excluded from the randomized subject population because the dates of randomization were missing. A total of 87, 67, and 47 subjects were included in the safety, ECG, and PK analyses, respectively. No deaths were reported.

**Table 6: Disposition of Randomized and Safety Study Population**

| Disposition                            | Randomized and Safety Population Study Arm |                            |                             |                |
|--|--|----------------------------|-----------------------------|----------------|
|  | Lurasidone 120 mg<br>N (%)                 | Lurasidone 600 mg<br>N (%) | Ziprasidone 160 mg<br>N (%) | Total<br>N (%) |
| Randomized                             | 29 (100.0)                                 | 29 (100.0)                 | 29 (100.0)                  | 87 (100.0)     |
| Completed Study                        | 25 (86.2)                                  | 22(75.9)                   | 26 (89.7)                   | 73 (83.9)      |
| Withdrawal                             | 4 (13.8)                                   | 7 (24.1)                   | 3 (10.30)                   | 14 (16.1)      |
| Laboratory Adverse Event               | ---  | ---                        | ---                         | ---            |
| Lost to Follow-up                      | ---  | ---                        | 1 (3.4)                     | 1 (1.1)        |
| Subject Withdrew Consent               | 3 (10.3)                                   | 5 (17.2)                   | 1 (3.4)                     | 9 (10.3)       |
| Protocol Deviation                     | ---  | 1 (3.4)                    | ---                         | 1 (1.1)        |
| Subject Discontinued for Other Reasons | 1 (3.4)                                    | 1 (3.4)                    | 1 (3.4)                     | 1 (3.4)        |

Note(s): bid = twice daily.  
Study drug administered daily for 11 days: lurasidone 120 mg = lurasidone 120 mg x 1 day; titrated lurasidone 600 mg = lurasidone (120 mg x 1 day, 200 mg x 1 day, 400 mg x 2 days, 520 mg x 2 days, and 600 mg x 5 days); titrated ziprasidone 160 mg = ziprasidone (40 mg [bid] x 4 days and 80 mg [bid] x 7 days.  
Source: Tables 14.1.2.1 and Table 14.1.2.2.

Source: table 7, CSR

**Table 7: Listing of Subjects Who Discontinued from the Study**

| Study Arm Prior to Discontinuation <sup>a</sup> | Subject No | Sex | Age | Date of Last Dose | Duration of Study Drug (Days) | Reason for Discontinuation            |
|---|------------|-----|-----|-------------------|-------------------------------|---------------------------------------|
| Lurasidone 120 mg                               | 3          | M   | 44  | 31 May 2006       | 6                             | Subject withdrew consent              |
| Lurasidone 120 mg                               | 4          | M   | 42  | 27 May 2006       | 2                             | Subject withdrew consent              |
| Lurasidone 600 mg                               | 5          | M   | 38  | 28 May 2006       | 3                             | Subject withdrew consent              |
| Lurasidone 600 mg                               | 12         | F   | 39  | 28 May 2006       | 3                             | Subject withdrew consent              |
| Ziprasidone 160 mg                              | 20         | M   | 32  | 20 Jun 2006       | 11                            | Lost to follow-up                     |
| Ziprasidone 160 mg                              | 32         | M   | 28  | 02 Jul 2006       | 6                             | Subject discontinued for other reason |
| Lurasidone 600 mg                               | 34         | M   | 41  | 06 Jul 2006       | 7                             | Subject discontinued for other reason |
| Ziprasidone 160 mg                              | 37         | F   | 31  | 27 Jun 2006       | 8                             | Subject withdrew consent              |
| Lurasidone 600 mg                               | 40         | F   | 32  | 18 Jul 2006       | 5                             | Subject withdrew consent              |
| Lurasidone 600 mg                               | 45         | M   | 45  | 11 Aug 2006       | 4                             | Protocol deviation                    |
| Lurasidone 120 mg                               | 107        | M   | 28  | 26 Jun 2006       | 7                             | Subject discontinued for other reason |
| Lurasidone 600 mg                               | 108        | M   | 53  | 23 Jun 2006       | 4                             | Subject withdrew consent              |
| Lurasidone 120 mg                               | 114        | M   | 38  | 05 Jul 2006       | 9                             | Subject withdrew consent              |
| Lurasidone 600 mg                               | 127        | M   | 42  | 29 Jul 2006       | 5                             | Subject withdrew consent              |

Note(s): bid = twice daily.  
 Study drug administered daily for 11 days: lurasidone 120 mg x 1 day; titrated lurasidone 600 mg = lurasidone (120 mg x 1 day, 200 mg x 1 day, 400 mg x 2 days, 520 mg x 2 days, and 600 mg x 5 days); titrated ziprasidone 160 mg = ziprasidone (40 mg [bid] x 4 days and 80 mg [bid] x 7 days.  
 Source: [Listing 16.2.4.1](#), [Listing 16.2.5.1](#), and [Listing 16.2.1.1.2](#).

Source: Table 9, CSR

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 8. C<sub>max</sub> and AUC values in the thorough QT study were 3.6-fold and 4.4-fold higher, respectively, following administration of 600 mg

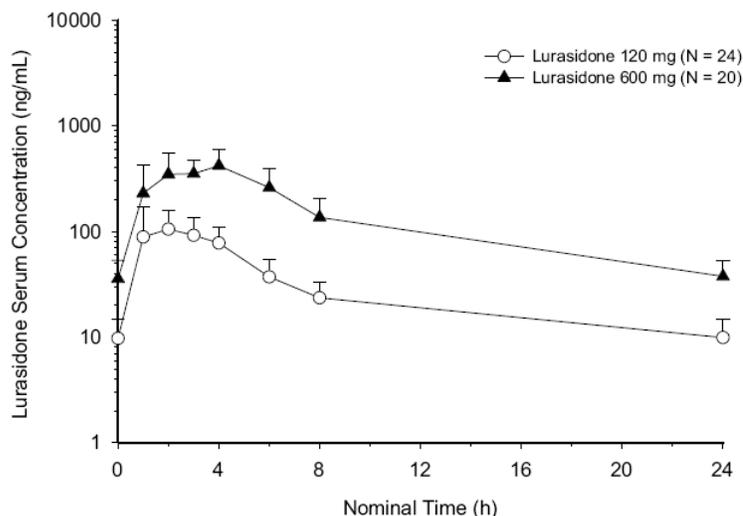
lurasidone compared with 120 mg lurasidone, the intended clinical dose. The time course of lurasidone concentrations on Day 11 is illustrated in Figure 1.

**Table 8: Arithmetic Mean (CV%) of Key Pharmacokinetic Parameters of Lurasidone**

| Parameter (units)  | Lurasidone 120 mg        | Lurasidone 600 mg        |
|--|--------------------------|--------------------------|
| C <sub>max</sub> (ng/mL)   | n=25<br>129 (58.3)       | n=22<br>470 (49.8)       |
| AUC <sub>(0-24)</sub> (ng.h/mL)  | n=23<br>713 (45.4)       | n=21<br>3110 (43.9)      |
| t <sub>max</sub> (h)   | n=25<br>2.17 (1.08-4.25) | n=22<br>4.00 (1.17-6.00) |
| CL <sub>ss</sub> /F (L/h)  | n=23<br>674 (346.8)      | n=21<br>415 (172.8)      |
| C <sub>trough</sub> (ng/mL)  | n=15<br>9.72 (55.7)      | n=18<br>31.7 (60.5)      |
| <p>Note(s): t<sub>max</sub> is expressed as median (range); PK = pharmacokinetic.<br/> AUC<sub>(0-24)</sub> and CL<sub>ss</sub>/F were not reported for Subjects 11 and 38 (120-mg lurasidone) due to missing time of collection of 24 hour PK sample, and Subject 53 (600-mg lurasidone) due to missing 24 hour PK sample. C<sub>trough</sub> values were excluded if % time deviation for trough samples on Day 11 exceeded 5%. Pharmacokinetic parameters from Subjects 19 (600 mg Lurasidone), 27 (600 mg Lurasidone) and 121 (120 mg Lurasidone) were included.<br/> Source: <a href="#">Table 14.2.26.2</a>.</p> |                          |                          |

Source: *Clinical Study Report P-81 Table 13*

**Figure 1: Mean (+SD) Lurasidone Concentration versus Nominal Time (Day 11)**



Notes: Serum concentrations from Subjects 19 (600 mg Lurasidone), 27 (600 mg Lurasidone) and 121 (120 mg Lurasidone), were excluded from the mean profile due to anomalously low concentrations.

Source: [Table 14.2.24](#).

Source: *Clinical Study Report P-77 Figure 1*

*Reviewer's Comment: The sponsor noted that concentration-time profiles for three subjects were anomalously low (25-200-fold lower  $C_{max}$  compared to other subjects). This finding is unexpected because noncompliance, concomitant drugs and adverse events (vomiting) were ruled out as causes.*

#### **4.2.8.4.2 Exposure-Response Analysis**

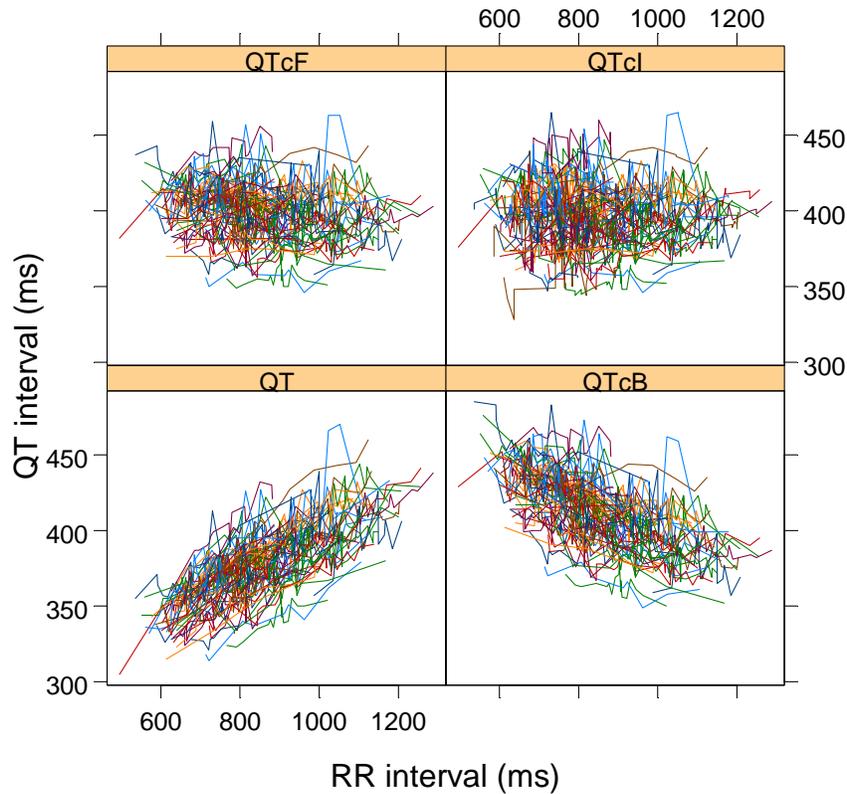
*Reviewer's Analysis: A plot of  $\Delta QTcI$  vs. lurasidone concentrations is presented in Figure 4.*

## **5 REVIEWERS' ASSESSMENT**

### **5.1 EVALUATION OF THE QT/RR CORRECTION METHOD**

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Ideally, a good correction QTc would result in no relationship of QTc and RR intervals. The relationship between different correction methods and RR is also graphically presented in Figure 2.

**Figure 2: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



We calculated the Mean Sum of Squared Slopes (MSSS) from each individual regression of QTc versus RR. The smaller this value is, the better the correction method. Based on the results listed in Table 9, it appears the difference between QTcF and QTcI is small and both of them are better than QTcB. To be consistent with the sponsor's proposed primary endpoint, this reviewer also used QTcI for the primary statistical analysis.

**Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

| Treatment Group    | Correction Method |        |      |        |      |        |
|--------------------|-------------------|--------|------|--------|------|--------|
|                    | QTcB              |        | QTcF |        | QTcI |        |
|                    | N                 | MSSS   | N    | MSSS   | N    | MSSS   |
| Lurasidone 120 mg  | 23                | 0.0219 | 23   | 0.0229 | 23   | 0.0243 |
| Lurasidone 600 mg  | 20                | 0.0080 | 20   | 0.0022 | 20   | 0.0067 |
| ZAll               | 67                | 0.0169 | 67   | 0.0117 | 67   | 0.0142 |
| Ziprasidone 160 mg | 24                | 0.0194 | 24   | 0.0088 | 24   | 0.0107 |

## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for Lurasidone

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcI effect. The analysis results are listed in Table 10.

**Table 10: Analysis Results of  $\Delta$ QTcI for Lurasidone and Ziprasidone**

| Time (hr) | $\Delta$ QTcI: Lurasidone 120 |      |     |             | $\Delta$ QTcI: Lurasidone 600 |      |     |             | $\Delta$ QTcI: Ziprasidone |      |     |              |
|-----------|-------------------------------|------|-----|-------------|-------------------------------|------|-----|-------------|----------------------------|------|-----|--------------|
|           | N                             | Mean | SD  | 90% CI      | N                             | Mean | SD  | 90% CI      | N                          | Mean | SD  | 90% CI       |
| 1         | 23                            | 1.0  | 2.6 | (-3.4, 5.4) | 19                            | 3.2  | 2.9 | (-1.6, 8.0) | 24                         | 12.3 | 2.6 | (8.0, 16.6)  |
| 2         | 23                            | 7.5  | 2.5 | (3.3, 11.7) | 20                            | 3.3  | 2.7 | (-1.2, 7.8) | 24                         | 13.6 | 2.4 | (9.5, 17.7)  |
| 4         | 23                            | 5.4  | 2.7 | (0.9, 9.8)  | 19                            | 4.6  | 2.9 | (-0.2, 9.5) | 23                         | 15.1 | 2.7 | (10.6, 19.5) |
| 6         | 23                            | 2.3  | 2.4 | (-1.7, 6.2) | 19                            | 3.9  | 2.6 | (-0.5, 8.3) | 23                         | 16.3 | 2.4 | (12.3, 20.3) |
| 8         | 21                            | 1.5  | 2.3 | (-2.4, 5.3) | 19                            | 5.2  | 2.4 | (1.1, 9.2)  | 22                         | 12.2 | 2.3 | (8.4, 15.9)  |

The largest upper bounds of the 2-sided 90% CI for the mean QTcI change from baseline in lurasidone 120 mg and lurasidone 600 mg are 11.7 ms and 9.5 ms respectively.

We also evaluated the gender difference of the QTc interval for the study drug. The analysis results are listed in Table 11 and

Table 12. It appears that the findings based on the gender are very different. However, the results may not be reliable because of the small sample sizes in each group.

**Table 11: Analysis Results of  $\Delta$ QTcI for the Male Subgroup**

| Time (hr) | $\Delta$ QTcI: Lurasidone 120 |      |     |             | $\Delta$ QTcI: Lurasidone 600 |      |     |             | $\Delta$ QTcI: Ziprasidone |      |     |             |
|-----------|-------------------------------|------|-----|-------------|-------------------------------|------|-----|-------------|----------------------------|------|-----|-------------|
|           | N                             | Mean | SD  | 90% CI      | N                             | Mean | SD  | 90% CI      | N                          | Mean | SD  | 90% CI      |
| 1         | 18                            | -0.1 | 2.9 | (-4.9, 4.7) | 15                            | 0.6  | 3.1 | (-4.7, 5.8) | 18                         | 9.3  | 2.9 | (4.5, 14.1) |
| 2         | 18                            | 4.7  | 2.5 | (0.5, 8.9)  | 16                            | 1.5  | 2.7 | (-2.9, 6.0) | 18                         | 9.4  | 2.5 | (5.2, 13.7) |
| 4         | 18                            | 2.6  | 2.8 | (-2.0, 7.3) | 15                            | 4.3  | 3.1 | (-0.9, 9.4) | 17                         | 9.9  | 2.9 | (5.1, 14.7) |
| 6         | 18                            | 0.4  | 2.8 | (-4.3, 5.1) | 15                            | 3.0  | 3.1 | (-2.2, 8.1) | 17                         | 13.5 | 2.9 | (8.7, 18.3) |
| 8         | 16                            | 0.0  | 2.6 | (-4.4, 4.4) | 15                            | 1.5  | 2.7 | (-3.1, 6.0) | 16                         | 8.6  | 2.6 | (4.2, 13.0) |

**Table 12: Analysis Results of  $\Delta$ QTcI for the Female Subgroup**

| Time (hr) | $\Delta$ QTcI: Lurasidone 120 |      |     |              | $\Delta$ QTcI: Lurasidone 600 |      |     |               | $\Delta$ QTcI: Ziprasidone |      |     |              |
|-----------|-------------------------------|------|-----|--------------|-------------------------------|------|-----|---------------|----------------------------|------|-----|--------------|
|           | N                             | Mean | SD  | 90% CI       | N                             | Mean | SD  | 90% CI        | N                          | Mean | SD  | 90% CI       |
| 1         | 5                             | -3.7 | 6.2 | (-14.7, 7.3) | 4                             | 4.7  | 6.9 | (-7.6, 17.1)  | 6                          | 13.8 | 5.7 | (3.7, 24.0)  |
| 2         | 5                             | 8.9  | 7.3 | (-4.0, 21.9) | 4                             | 0.9  | 8.2 | (-13.7, 15.4) | 6                          | 18.4 | 6.6 | (6.5, 30.2)  |
| 4         | 5                             | 6.5  | 6.5 | (-5.1, 18.0) | 4                             | -2.4 | 7.4 | (-15.5, 10.8) | 6                          | 22.7 | 5.9 | (12.1, 33.2) |
| 6         | 5                             | 0.3  | 4.2 | (-7.3, 7.9)  | 4                             | -0.8 | 4.7 | (-9.3, 7.7)   | 6                          | 17.5 | 3.9 | (10.5, 24.5) |
| 8         | 5                             | -1.1 | 4.9 | (-9.7, 7.6)  | 4                             | 10.4 | 5.4 | (0.7, 20.1)   | 6                          | 15.1 | 4.5 | (7.1, 23.1)  |

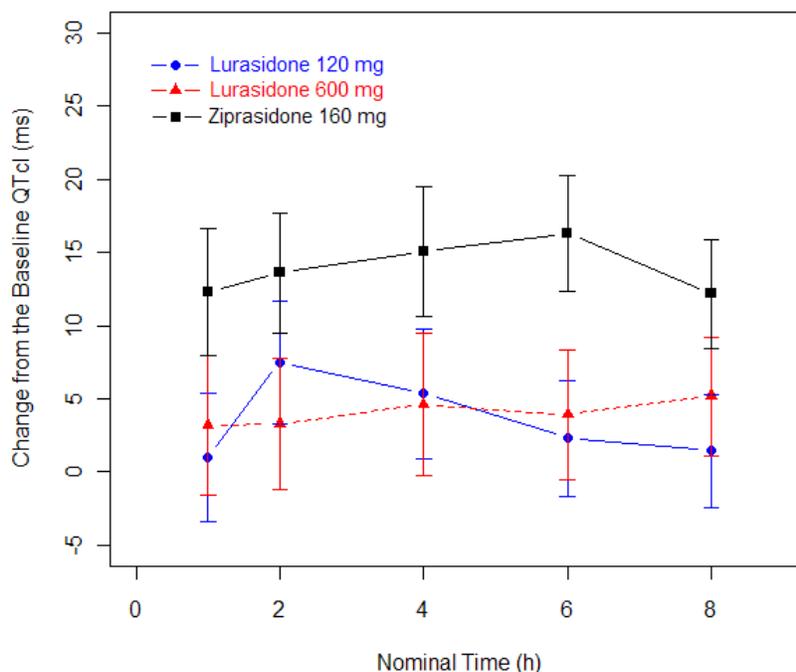
### 5.2.1.2 Assay Sensitivity Analysis

The sponsor used ziprasidone (80 mg titrated to 160 mg) as the positive control, instead of commonly used moxifloxacin. The largest lower bound of 90% CI in ziprasidone is 12.3 ms (the corresponding mean effect is 16.3 ms).

### 5.2.1.3 Graph of $\Delta$ QTcI Over Time

The following figure displays the time profile of  $\Delta$ QTcI for different treatment groups.

**Figure 3: Mean and 90% CI  $\Delta$ QTcI Timecourse**



*Reviewer's comments:*

*This trial is not a typical TQT study. Because of the absence of the placebo arm, we cannot perform the standard double delta analysis for the QTc interval. Also, instead of using a positive control with a well established PK profile, like moxifloxacin, the sponsor used ziprasidone as the positive control. However, the sponsor did not provide any PK information for ziprasidone. Thus, it is hard to draw any assay sensitivity conclusions.*

#### 5.2.1.4 Categorical Analysis

Table 13 lists the number of subjects as well as the number of observations whose QTcI values are  $\leq 450$  ms, between 450 ms and 480 ms, as measured on Day 11. No subject's QTcI was above 480 ms. There was a single subject (ID = 042) with QTcI greater than 450 ms, see Table 15.

**Table 13: Categorical Analysis for QTcI**

| Treatment Group | Total N |        | Value $\leq 450$ ms | Value $> 450$ ms<br>Value $\leq 480$ ms |
|-----------------|---------|--------|---------------------|---|
|                 | # Subj. | # Obs. | # Obs. (%)          | # Obs. (%)                              |
| Baseline        | 67      | 325    | 323                 | 2                                       |
| Lurasidone 120  | 23      | 113    | 113                 | 0                                       |
| Lurasidone 600  | 20      | 96     | 96                  | 0                                       |
| Ziprasidone 160 | 24      | 116    | 114                 | 2                                       |

Table 14 lists the categorical analysis results for  $\Delta$ QTcI. No subject's change from baseline was above 60 ms. Subjects with  $\Delta$ QTcI greater than 30 ms are summarized in Table 15.

**Table 14: Categorical Analysis of  $\Delta$ QTcI**

| Treatment Group | Total N |        | Value $\leq$ 30 ms | 30 ms<Value $\leq$ 60 ms |
|-----------------|---------|--------|--------------------|--------------------------|
|                 | # Subj. | # Obs. | # Obs.             | # Obs.                   |
| Lurasidone 120  | 23      | 113    | 113                | 0                        |
| Lurasidone 600  | 20      | 96     | 96                 | 0                        |
| Ziprasidone 160 | 24      | 116    | 109                | 7                        |

**Table 15: Outliers' Summary ( $\Delta$ QTcI > 30)**

| Subject ID | Treatment   | Time | Corresponding QTcI baseline | $\Delta$ QTcI |
|------------|-------------|------|-----------------------------|---------------|
| 042        | Ziprasidone | 1    | 412                         | 35            |
| 042        | Ziprasidone | 2    | 409                         | 54            |
| 042        | Ziprasidone | 4    | 408                         | 57            |
| 042        | Ziprasidone | 8    | 410                         | 33            |
| 020        | Ziprasidone | 6    | 365                         | 44            |
| 023        | Ziprasidone | 1    | 387                         | 36            |
| 123        | Ziprasidone | 8    | 372                         | 32            |

### 5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval, as measured on Day 11. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper bounds of 90% CI for the PR mean differences of lurasidone 120 mg, lurasidone 600, and ziprasidone are 9.5 ms, 7.8 ms, and 6.5 ms, respectively.

**Table 16: Analysis Results of  $\Delta$ PR for Lurasidone and Ziprasidone**

| Time (hr) | $\Delta$ PR: Lurasidone 120 |      |     |             | $\Delta$ PR: Lurasidone 600 |      |     |             | $\Delta$ PR: Ziprasidone |      |     |             |
|-----------|-----------------------------|------|-----|-------------|-----------------------------|------|-----|-------------|--------------------------|------|-----|-------------|
|           | N                           | Mean | SD  | 90% CI      | N                           | Mean | SD  | 90% CI      | N                        | Mean | SD  | 90% CI      |
| 1         | 23                          | 1.5  | 2.6 | (-2.8, 5.8) | 19                          | 3.1  | 2.8 | (-1.6, 7.8) | 18                       | -0.5 | 2.5 | (-4.7, 3.7) |
| 2         | 23                          | 6.0  | 2.1 | (2.5, 9.5)  | 20                          | 1.1  | 2.2 | (-2.6, 4.8) | 18                       | 1.8  | 2.0 | (-1.6, 5.2) |
| 4         | 23                          | 3.0  | 2.5 | (-1.2, 7.2) | 19                          | -0.2 | 2.8 | (-4.8, 4.4) | 17                       | 1.9  | 2.5 | (-2.3, 6.1) |
| 6         | 23                          | 0.9  | 2.2 | (-2.7, 4.6) | 19                          | 0.1  | 2.4 | (-3.9, 4.0) | 17                       | 2.9  | 2.2 | (-0.7, 6.5) |
| 8         | 21                          | 3.7  | 2.3 | (-0.2, 7.5) | 19                          | 2.5  | 2.4 | (-1.6, 6.5) | 16                       | 0.0  | 2.3 | (-3.8, 3.7) |

The outlier analysis results for PR are presented in Table 17.

**Table 17: Outliers' Summary (PR ≥ 200 ms)**

| Subject ID | Treatment      | Time | Corresponding PR baseline | PR  |
|------------|----------------|------|---------------------------|-----|
| 134        | Lurasidone 600 | 1    | 183                       | 201 |
| 054        | Lurasidone 120 | 6    | 192                       | 200 |
| 120        | Ziprasidone    | 2    | 205                       | 210 |
| 120        | Ziprasidone    | 4    | 197                       | 207 |
| 120        | Ziprasidone    | 6    | 215                       | 212 |

### 5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval, as measured on Day 11. The point estimates and the 90% confidence intervals are presented in Table 18. The largest upper bound of 90% CI for the QRS mean in lurasidone 120, lurasidone 600, and ziprasidone are 1.5 ms, 0.2, and 1.2 ms, respectively.

**Table 18: Analysis Results of ΔQRS for Lurasidone and Ziprasidone**

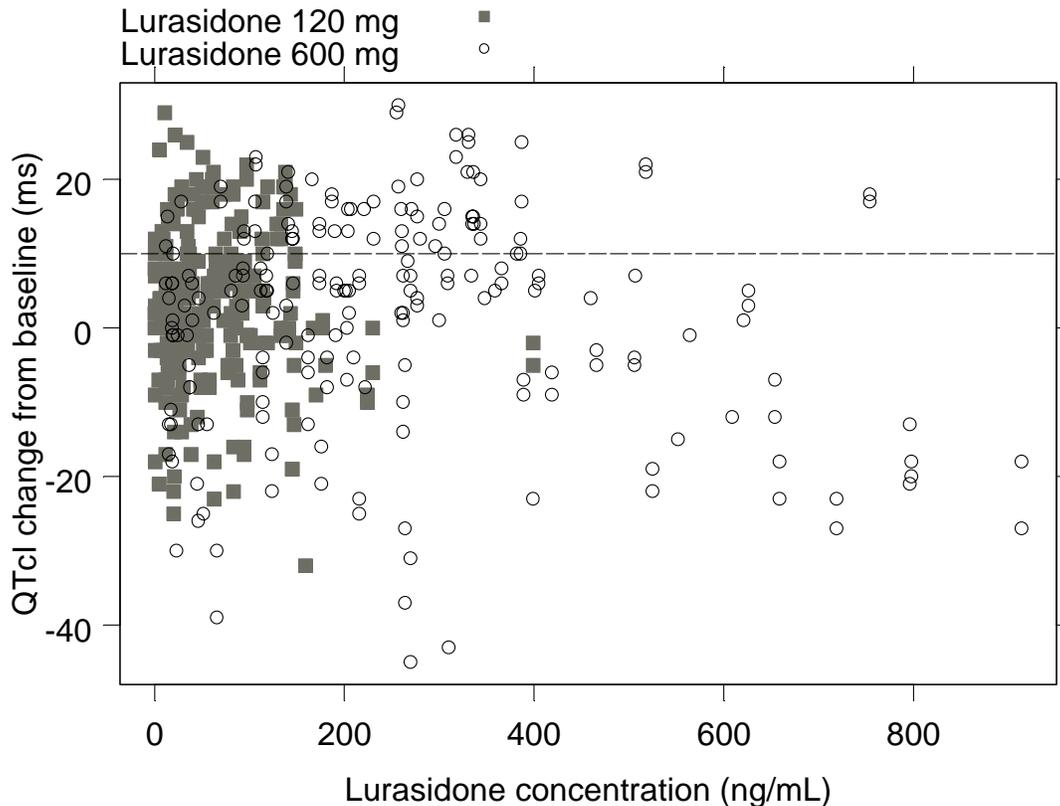
| Time (hr) | ΔQRS: Lurasidone 120 |      |     |             | ΔQRS: Lurasidone 600 |      |     |              | ΔQRS: Ziprasidone |      |     |             |
|-----------|----------------------|------|-----|-------------|----------------------|------|-----|--------------|-------------------|------|-----|-------------|
|           | N                    | Mean | SD  | 90% CI      | N                    | Mean | SD  | 90% CI       | N                 | Mean | SD  | 90% CI      |
| 1         | 23                   | -0.8 | 1.0 | (-2.4, 0.8) | 19                   | -1.6 | 1.1 | (-3.3, 0.2)  | 18                | -0.5 | 0.9 | (-2.1, 1.0) |
| 2         | 23                   | -0.3 | 1.0 | (-1.9, 1.3) | 20                   | -3.3 | 1.0 | (-5.0, -1.6) | 18                | -0.9 | 0.9 | (-2.5, 0.6) |
| 4         | 23                   | -0.1 | 1.0 | (-1.7, 1.5) | 19                   | -1.9 | 1.1 | (-3.6, -0.1) | 17                | -1.3 | 0.9 | (-2.9, 0.2) |
| 6         | 23                   | -1.3 | 0.9 | (-2.7, 0.2) | 19                   | -3.2 | 0.9 | (-4.7, -1.6) | 17                | -0.2 | 0.8 | (-1.6, 1.2) |
| 8         | 21                   | -0.4 | 1.0 | (-2.1, 1.3) | 19                   | -2.2 | 1.1 | (-4.0, -0.5) | 16                | -0.5 | 1.0 | (-2.2, 1.1) |

There were no subjects with QRS higher than 110 ms.

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔQTcI and lurasidone concentrations is visualized in Figure 4 with no evident exposure-response relationship.

**Figure 4:  $\Delta$  QTcI vs. Lurasidone concentration**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

### 5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 78% of the ECGs were annotated in the primary lead V2, with less than 1.5% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

### 5.4.3 PR and QRS Interval

Three subjects had a PR >200 ms, one of them with an increase over baseline > 25% (3 h post-dose). However, none of them had a PR >215 ms.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

| Highlights of Clinical Pharmacology  |   |             |   |
|--|---|-------------|---|
| Therapeutic dose   | Starting dose: 40 mg or 80 mg/day.<br>The maximum clinical dose regimen: 120 mg/day   |             |   |
| Maximum tolerated dose   | 400 mg/day in schizophrenic subjects  |             |   |
| Principal adverse events:<br>Non-Schizophrenic Subjects                              | <p>Data presented for non-schizophrenic subjects for clinical pharmacology studies are only included in the PINON study group presented in the Integrated Summary of Safety (ISS). The maximum dose tested was 100 mg/day.</p> <p>The PINON studies were clinical pharmacology studies of lurasidone conducted in both healthy Japanese and Caucasian subjects, as well as subjects with hepatic or renal impairment.</p> <p>The most common treatment emergent adverse events (TEAEs) (&gt;10% of subjects in the “all lurasidone” group) for lurasidone-treated subjects in the PINON group were:</p> <ul style="list-style-type: none"> <li>• somnolence (20.7%) and</li> <li>• blood prolactin increased (20.1%).</li> </ul> <p>The incidence of TEAEs occurring in <math>\geq 3\%</math> of the PINON grouping by treatment group is presented in <a href="#">Table 11</a> of the ISS.</p> |             |   |
| Principal adverse events:<br>Dose Limiting Adverse Events for Schizophrenic Subjects | <p>The dose limiting adverse events have been extracted from data presented in the ISS.</p> <ul style="list-style-type: none"> <li>• Studies <a href="#">D1050160</a> and <a href="#">D1050217</a> were the multiple dose clinical pharmacology studies conducted to determine the maximum tolerated dose (MTD) of lurasidone in schizophrenic patients.</li> <li>• The number and percentage of MTD subjects with TEAEs leading to dose adjustment or discontinuation for both of these studies is represented in <a href="#">Post Hoc Table 6.1.2.2-1</a>.</li> </ul>   |             |   |
| Maximum dose tested  | <table border="1"> <tr> <td>Single Dose</td> <td> <p><u>Healthy male subjects:</u><br/>100 mg</p> <p><u>Patients with schizophrenia:</u><br/>520 mg</p> </td> </tr> </table>  | Single Dose | <p><u>Healthy male subjects:</u><br/>100 mg</p> <p><u>Patients with schizophrenia:</u><br/>520 mg</p> |
| Single Dose  | <p><u>Healthy male subjects:</u><br/>100 mg</p> <p><u>Patients with schizophrenia:</u><br/>520 mg</p>   |             |   |

|   |   |   |
|---|---|---|
|   | Multiple Dose   | <p><u>Healthy male subjects:</u><br/>80 mg/day or 40 mg twice per day (BID) for 6 days</p> <p><u>Patients with schizophrenia:</u><br/>520 mg/day (non-titrated) for 6 days;</p> <p><b>Titration 1:</b><br/>Titrate to a total daily dose of 600 mg/day (administered as 200 mg x 2 day, 400 mg x 2 days, 520 mg x 2 days, and 600 mg x 2 days)</p> <p><b>Titration 2:</b><br/>Titrate to a total daily dose of 600 mg QD (administered as 120 mg x 1 day, 200 mg x 1 day, 400 mg x 2 days, 520 mg x 2 days, and 600 mg x 5 days).</p>                             |
| Exposures Achieved at Maximum Tested Dose   | Single Dose   | <p><u>Healthy male subjects:</u><br/>100 mg<br/><math>C_{max} = 105</math> (37%) ng/mL<br/><math>AUC_{(0-\infty)} = 421</math> (40%) ng*h/mL</p> <p><u>Patients with schizophrenia:</u><br/>520 mg<br/><math>C_{max} = 259.3</math> (66%) ng/mL<br/><math>AUC_{(0-\infty)} = 1014.2</math> (78%) ng*h/mL</p>  |
|   | Multiple Dose   | <p><u>Healthy male subjects:</u><br/>40 mg BID<br/><math>C_{max} = 60</math> (30%) ng/mL<br/><math>AUC_{(0-\tau)} = 230</math> (32%) ng*h/mL</p> <p><u>Patients with schizophrenia:</u><br/>520 mg QD<br/><math>C_{max} = 417</math> (32%) ng/mL<br/><math>AUC_{(0-24h)} = 2467</math> (22%) ng*h/mL</p> <p>600 mg (titration 1)<br/><math>C_{max} = 749</math> (36%) ng/mL<br/><math>AUC_{(0-24h)} = 6765</math> (24%) ng*h/mL</p> <p>600 mg QD (titration 2)<br/><math>C_{max} = 516</math> (37%) ng/mL<br/><math>AUC_{(0-24h)} = 3420</math> (30%) ng*h/mL</p> |
| Range of linear PK (Based on modeling data) | $C_{max}$ : 10 to 160 mg<br>$AUC_{(0-\tau)}$ : 10 to 600 mg                   |   |
| Accumulation at steady state                | 1.80-fold (23%) based on the mean $AUC_{0-24}$ ratio of 120 mg/day for 5 days |   |

| Metabolites                          | <p>Exo-hydroxylated lurasidone (ID-14283, minor), and endo-hydroxylated lurasidone (ID-14326, minor) (each as a mixture of positions 5- and 6-substitution products) displayed anti-D2 dopaminergic and anti-5-HT2 actions similar to those of lurasidone, and failed to induce catalepsy.</p> <p>The cleaved product, ID-11614 (minor), showed moderate (about 25 times weaker than lurasidone) affinity for the rat 5-HT2A receptor, but its general CNS pharmacological actions (inhibition of spontaneous activity, potentiation of hexobarbital anesthesia, muscle relaxation, etc., in mice) are very weak.</p> <p>Other metabolites had low or no affinity for D2 or 5-HT2A receptors. The 5-exo-hydroxylated and 6-exo-hydroxylated lurasidone species also showed binding affinities for dopamine D2, 5-HT2A and 5-HT7 receptors similar to the lurasidone parent compound.</p> <p>Affinities to Human Receptors of Lurasidone Metabolites</p> <table border="1" data-bbox="607 674 1356 1079"> <thead> <tr> <th rowspan="2">Drugs</th> <th colspan="5">Binding affinity (K<sub>i</sub>, nmol/L)</th> </tr> <tr> <th>D2 Receptor</th> <th>5-HT1A Receptor</th> <th>5-HT2A Receptor</th> <th>5-HT7 Receptor</th> <th>α2C Receptor</th> </tr> </thead> <tbody> <tr> <td>Lurasidone</td> <td>0.994</td> <td>6.38</td> <td>0.357</td> <td>2.10</td> <td>16.2</td> </tr> <tr> <td>ID-14283</td> <td>1.21</td> <td>8.36</td> <td>0.375</td> <td>2.06</td> <td>36.5</td> </tr> <tr> <td>ID-14326</td> <td>1.62</td> <td>2.00</td> <td>0.337</td> <td>2.16</td> <td>8.31</td> </tr> <tr> <td>(<i>R,R</i>)-ID-20219<sup>b</sup></td> <td>&gt;1000<sup>a</sup></td> <td>&gt;1000<sup>a</sup></td> <td>&gt;1000<sup>a</sup></td> <td>&gt;1000<sup>a</sup></td> <td>&gt;1000<sup>a</sup></td> </tr> <tr> <td>(<i>R,R</i>)-ID-20220<sup>b</sup></td> <td>&gt;1000<sup>a</sup></td> <td>&gt;1000<sup>a</sup></td> <td>&gt;1000<sup>a</sup></td> <td>&gt;1000<sup>a</sup></td> <td>&gt;1000<sup>a</sup></td> </tr> </tbody> </table> <p>a IC<sub>50</sub> value<br/>b (<i>R,R</i>) shows the absolute configuration of substituent at cyclohexane ring.</p> |  | Drugs              | Binding affinity (K <sub>i</sub> , nmol/L) |                    |  |  |  | D2 Receptor | 5-HT1A Receptor | 5-HT2A Receptor | 5-HT7 Receptor | α2C Receptor | Lurasidone | 0.994 | 6.38 | 0.357 | 2.10 | 16.2 | ID-14283 | 1.21 | 8.36 | 0.375 | 2.06 | 36.5 | ID-14326 | 1.62 | 2.00 | 0.337 | 2.16 | 8.31 | ( <i>R,R</i> )-ID-20219 <sup>b</sup> | >1000 <sup>a</sup> | ( <i>R,R</i> )-ID-20220 <sup>b</sup> | >1000 <sup>a</sup> |
|--------------------------------------|---|--|--------------------|--|--------------------|--|--|--|-------------|-----------------|-----------------|----------------|--------------|------------|-------|------|-------|------|------|----------|------|------|-------|------|------|----------|------|------|-------|------|------|--------------------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Drugs                                | Binding affinity (K <sub>i</sub> , nmol/L)  |  |                    |  |                    |  |  |  |             |                 |                 |                |              |            |       |      |       |      |      |          |      |      |       |      |      |          |      |      |       |      |      |                                      |                    |                    |                    |                    |                    |                                      |                    |                    |                    |                    |                    |
|                                      | D2 Receptor   | 5-HT1A Receptor  | 5-HT2A Receptor    | 5-HT7 Receptor                             | α2C Receptor       |  |  |  |             |                 |                 |                |              |            |       |      |       |      |      |          |      |      |       |      |      |          |      |      |       |      |      |                                      |                    |                    |                    |                    |                    |                                      |                    |                    |                    |                    |                    |
| Lurasidone                           | 0.994   | 6.38   | 0.357              | 2.10                                       | 16.2               |  |  |  |             |                 |                 |                |              |            |       |      |       |      |      |          |      |      |       |      |      |          |      |      |       |      |      |                                      |                    |                    |                    |                    |                    |                                      |                    |                    |                    |                    |                    |
| ID-14283                             | 1.21  | 8.36   | 0.375              | 2.06                                       | 36.5               |  |  |  |             |                 |                 |                |              |            |       |      |       |      |      |          |      |      |       |      |      |          |      |      |       |      |      |                                      |                    |                    |                    |                    |                    |                                      |                    |                    |                    |                    |                    |
| ID-14326                             | 1.62  | 2.00   | 0.337              | 2.16                                       | 8.31               |  |  |  |             |                 |                 |                |              |            |       |      |       |      |      |          |      |      |       |      |      |          |      |      |       |      |      |                                      |                    |                    |                    |                    |                    |                                      |                    |                    |                    |                    |                    |
| ( <i>R,R</i> )-ID-20219 <sup>b</sup> | >1000 <sup>a</sup>  | >1000 <sup>a</sup>   | >1000 <sup>a</sup> | >1000 <sup>a</sup>                         | >1000 <sup>a</sup> |  |  |  |             |                 |                 |                |              |            |       |      |       |      |      |          |      |      |       |      |      |          |      |      |       |      |      |                                      |                    |                    |                    |                    |                    |                                      |                    |                    |                    |                    |                    |
| ( <i>R,R</i> )-ID-20220 <sup>b</sup> | >1000 <sup>a</sup>  | >1000 <sup>a</sup>   | >1000 <sup>a</sup> | >1000 <sup>a</sup>                         | >1000 <sup>a</sup> |  |  |  |             |                 |                 |                |              |            |       |      |       |      |      |          |      |      |       |      |      |          |      |      |       |      |      |                                      |                    |                    |                    |                    |                    |                                      |                    |                    |                    |                    |                    |
| Absorption                           | Absolute/Relative Bioavailability   | <p>Relative bioavailability was estimated up to 19.1% (6%).</p> <p><b>Tmax</b></p> <p><b><u>Median (range) for parent</u></b></p> <p><b>Single dose</b></p> <p><u>Healthy male subjects:</u><br/>1.0 h (1.0 - 2.0) - 1.5 h (1.0 - 1.5)</p> <p><u>Patients with schizophrenia:</u><br/>1.3 h (1.0 - 2.0) - 3.0 h (2.0 - 6.0)</p> <p><b>Multiple doses</b></p> <p><u>Healthy male subjects:</u><br/>1.5 h (1.0 - 1.5)</p> <p><u>Patients with schizophrenia:</u><br/>1.0 h (1.0 - 2.0) - 4.0 h (3.0 - 6.0)</p> |                    |  |                    |  |  |  |             |                 |                 |                |              |            |       |      |       |      |      |          |      |      |       |      |      |          |      |      |       |      |      |                                      |                    |                    |                    |                    |                    |                                      |                    |                    |                    |                    |                    |

|              |                           |  |
|--------------|---------------------------|--|
|              |                           | <p><b><u>Median (range) for metabolites</u></b></p> <p><b>Multiple doses</b></p> <p><u>Healthy male subjects:</u><br/>ID-14283: 2.0 h (1.5 - 4.0)<br/>ID-14326: 4.0 h (1.5 - 4.0)</p> <p><u>Patients with schizophrenia:</u><br/>ID-14283: 1.5 h (1.0 - 4.0) - 4.0 h (3.0 - 6.0)<br/>ID-14326: 2.0 h (1.5 - 2.0) - 4.0 h (3.0 - 8.0)<br/>ID-20219: 2.5 h (1.0 - 6.0)<br/>ID-20220: 3.0 h (1.5 - 6.0)</p> |
| Distribution | Vd/F or Vd                | <p><b><u>Vd/F</u></b></p> <p><b>Single dose</b></p> <p><u>Healthy male subjects:</u><br/>4937 L<sup>a</sup> (49%) - 8583 L (46%)</p> <p><u>Patients with schizophrenia:</u><br/>9082 L (48%) - 13822 L<sup>b</sup> (50%)</p> <p><b>Multiple doses</b></p> <p><u>Healthy male subjects:</u><br/>9247 L (37%)</p> <p><u>Patients with schizophrenia:</u><br/>3220 L (46%) - 4410 L (57%)</p>               |
|              | % bound                   | >99% (32%) binding to HSA and human $\alpha$ 1-AGP   |
| Elimination  | Route                     | <p><b><u>Primary route; percent dose eliminated</u></b><br/>Total radioactivity: Feces: 67% to 80%</p> <p><b><u>Other routes; percent dose eliminated</u></b><br/>Total reactivity: Urine: 9% to 19%</p>   |
|              | Terminal t <sub>1/2</sub> | <p><b><u>Mean (%CV) for parent</u></b></p> <p><b>Single dose</b></p> <p><u>Healthy male subjects:</u><br/>12.2 h (13%) to 18.3 h (7%)</p> <p><u>Patients with schizophrenia:</u><br/>28.8 h (46%) to 37.4 h (35%)</p> <p><b>Multiple doses</b></p> <p><u>Healthy male subjects:</u><br/>35.6 h (13%)</p> <p><u>Patients with schizophrenia:</u><br/>9.1 h (5%) to 14.7 h (18%)</p>                       |

|                   |            |   |
|-------------------|------------|---|
|                   |            | <p><b>Mean (%CV) for metabolites</b></p> <p><b>Single dose</b></p> <p><u>Healthy male subjects:</u><br/>ID-14283: 7.5 h (20%) to 10.0 h (21%)<br/>ID-14326: 3.0 h (21%) to 8.7 h (28%)</p> <p><u>Patients with schizophrenia:</u><br/>ID-14283: 18.0 h (45%) to 21.5 h (29%)<br/>ID-14326: 8.1 h (58%) to 17.0 h (40%)</p> <p><b>Multiple doses</b></p> <p><u>Healthy male subjects:</u><br/>ID-14283: 33.1 h (23%)<br/>ID-14326: 12.4 h (19%)</p> <p><u>Patients with schizophrenia:</u><br/>ID-14283: 7.5 h (12%) to 10.0 h (-)<br/>ID-14326: 8.6 h (15%) to 11.1 h (-)</p> |
|                   | CL/F or CL | <p><b>CL/F</b></p> <p><b>Single dose</b></p> <p><u>Healthy male subjects:</u><br/>237 L/h (16%) - 353 L/h (39%)<sup>c</sup></p> <p><u>Patients with schizophrenia:</u><br/>205 L/h (43%) - 298 L/h (37%)</p> <p><b>Multiple doses</b></p> <p><u>Healthy male subjects:</u><br/>190 L/h (35%)</p> <p><u>Patients with schizophrenia:</u><br/>175 L/h (34%) - 244 L/h (32%)</p>   |
| Intrinsic Factors | Age        | No age effect   |
|                   | Sex        | Female to Male<br>C <sub>max</sub> : 1.07-fold increase<br>AUC: 1.18-fold increase  |
|                   | Race       | Asian to Non-Asian<br>C <sub>max</sub> : 1.05-fold increase<br>AUC: 1.53-fold increase  |

|                   |                            |  |
|-------------------|----------------------------|--|
|                   | Hepatic & Renal Impairment | <p><b><u>Hepatic</u></b></p> <p>Mild: <math>C_{max}</math> 1.3-fold increase<br/> <math>AUC_{(0-\infty)}</math> 1.3-fold increase</p> <p>Moderate: <math>C_{max}</math> 1.2-fold increase<br/> <math>AUC_{(0-\infty)}</math> 1.8-fold increase</p> <p>Severe: <math>C_{max}</math> 1.3-fold increase<br/> <math>AUC_{(0-last)}</math> 3.0-fold increase</p> <p><b><u>Renal</u></b></p> <p>Mild: <math>C_{max}</math> 1.4-fold increase<br/> <math>AUC_{(0-\infty)}</math> 1.5-fold increase</p> <p>Moderate: <math>C_{max}</math> 1.9-fold increase<br/> <math>AUC_{(0-\infty)}</math> 1.9-fold increase</p> <p>Severe: <math>C_{max}</math> 1.5-fold increase<br/> <math>AUC_{(0-\infty)}</math> 2.0-fold increase</p>  |
| Extrinsic Factors | Drug interactions          | <p><b><u>Other Drugs to Affect Lurasidone</u></b></p> <p><b>Ketoconazole</b><br/> Lurasidone: <math>C_{max}</math> 6.9-fold increase<br/> <math>AUC_{(0-last)}</math> 9.0-fold increase</p> <p><b>Diltiazem</b><br/> Lurasidone: <math>C_{max}</math> 2.1-fold increase<br/> <math>AUC_{(0-\infty)}</math> 2.2-fold increase</p> <p><b>Rifampin</b><br/> Lurasidone: <math>C_{max}</math> 6.8-fold decrease<br/> <math>AUC_{(0-last)}</math> 6.0-fold decrease</p> <p><b>Lithium</b><br/> Lurasidone: <math>C_{max}</math> equivalent (1.1-fold decrease)<br/> <math>AUC_{(0-12h)}</math> equivalent<br/> (1.1-fold increase)</p> <p><b><u>Potential for Lurasidone to Affect Other Drugs</u></b></p> <p><b>Digoxin</b><br/> <math>C_{max}</math> equivalent (1.09-fold increase)<br/> <math>AUC_{(0-last)}</math> equivalent (1.10-fold increase)</p> <p><b>Oral Contraceptive (Ortho Tri-Cyclin)</b><br/> Ethinyl estradiol <math>C_{max}</math> equivalent (1.02-fold decrease)<br/> <math>AUC_{(0-24h)}</math> equivalent (1.03-fold increase)</p> <p>Norelgestromin <math>C_{max}</math> equivalent (1.08-fold increase)<br/> <math>AUC_{(0-24h)}</math> equivalent (1.1-fold increase)</p> |



**Table 5: Study Design and Schedule of Assessments (Continued)**

|   |
|---|
| <p>Notes: HIV = human immunodeficiency virus; <math>\beta</math>-hCG = beta human chorionic gonadotropin; CRU = clinical research unit; bid = twice daily; ECG = electrocardiogram.</p> <p><sup>a</sup>Prestudy was performed approximately 4 weeks prior to study start. Poststudy was performed approximately 14 days following the last dose of study drug. If the poststudy visit occurred earlier than 14 days, a subsequent visit or telephone follow-up were conducted to determine whether any adverse events occurred within the full 14 days after the subject's last dose of study medication.</p> <p><sup>b</sup>Existing antipsychotic medication was tapered over 3 days while in an inpatient setting; all subjects were then required to receive no antipsychotic treatment (a washout period) for 7 days (this could be inpatient or outpatient at the discretion of the investigator).</p> <p><sup>c</sup>Height was collected prestudy only; weight was collected at prestudy, taper/washout period, and poststudy.<sup>d</sup> For women of childbearing potential only, results had to be confirmed negative prior to drug administration.</p> <p><sup>e</sup>Subjects may have been released from the CRU following completion of all study-related procedures.</p> <p><sup>f</sup>Supine blood pressure, pulse rate, respiratory rate, and oral temperature taken at prestudy and poststudy. Blood pressure and pulse rate taken once daily during Taper/Washout Period, Treatment Period, and Restabilization Period.</p> <p><sup>g</sup>Safety ECGs were performed and reviewed by the investigator on Day 0 (baseline) prior to time zero, on Days 1 through 11 prior to the AM dose, and on Day 12 prior to time zero.</p> <p><sup>h</sup>Safety ECGs were also performed and reviewed by the investigator on Day 1 and Day 2 at 1.5 and 6 hours post AM dose.</p> <p><sup>i</sup>ECGs were extracted by (b) (4) laboratory at predose, 1, 2, 4, 6, and 8 hours after time zero at baseline (Day 0) and following the AM dose (Day 11). Subjects were awakened and maintained in a supine position and prohibited from drinking any liquids 10 minutes prior to and 5 minutes following each ECG timepoint. Subsequently, ECGs were re-extracted by eResearch Technology at the following timepoints: 1, 2, 3, 4, 5, 6, 7 and 8 hours at baseline (Day 0) and following the AM dose on Day 11.</p> <p><sup>j</sup>Trough samples were taken for lurasidone on Days 2 through 11 prior to the AM dose.</p> <p><sup>k</sup>Blood samples were taken for lurasidone assay and ziprasidone (for archive) on Day 11 at the following timepoints: 1, 2, 3, 4, 6, 8, and 24 hours following the AM dose.</p> <p><sup>l</sup>Laboratory safety analyses were performed after approximately an 8 hour fast.</p> <p><sup>m</sup>Performed prior to reinstating antipsychotic medication(s).</p> <p>* At the discretion of the investigator</p> |
|---|

| Application Type/Number | Submission Type/Number | Submitter Name                                 | Product Name   |
|-------------------------|------------------------|--|----------------|
| NDA-200603              | ORIG-1                 | DAINIPPON<br>SUMITOMO<br>PHARMA AMERICA<br>INC | Lurasidone HCl |

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/s/

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HAO ZHU  
07/02/2010

KEVIN M KRUDYS  
07/06/2010

ANDREJUS PARFIONOVAS  
07/07/2010

JOANNE ZHANG  
07/14/2010

MONICA L FISZMAN  
07/14/2010

NORMAN L STOCKBRIDGE  
07/14/2010

**Executive CAC**

**Date of Meeting: July 13, 2010**

Committee: David Jacobson-Kram, Ph.D., OND-IO, Chair  
Abigail Jacobs, Ph.D., OND-IO, Member  
Paul Brown, Ph.D., OND IO, Member  
Wendy Schmidt, Ph.D., DAIOP, Alternate Member  
Aisar Atrakchi, Ph.D., DPP, Supervisor  
Sonia Tabacova, Ph.D., DPP, Presenting Reviewer

Author of Draft: Sonia Tabacova

The following information reflects a brief summary of the Committee discussion and its recommendations.

**NDA # 200603**

**Drug Name: Lurasidone HCl** (b) (4)

**Sponsor:** Dainippon Sumitomo Pharma America, Inc., Fort Lee, New Jersey

**Mouse Carcinogenicity Study**

**Neoplastic findings:** Oral administration of Lurasidone HCl in 0.5% methylcellulose to Crl:CD-1®(ICR)BR mice (60/sex/dose) at doses of 0, 0, 30, 100, 300, and 1200/650 mg/kg/day in males for 104 weeks [HD reduced as of Day 410 due to excessive (>20%) weight loss] and at 0, 0, 30, 100, 300, and 650 mg/kg/d in females for 98 weeks (shorter dosing duration in females due to excessive mortality) did not produce neoplastic lesions in the males. In the females, however, statistically significant increases in neoplastic lesions [benign pituitary pars distalis adenoma and malignant mammary tumors (carcinoma, adenoacanthoma)] were induced at all tested dose levels, with highly significant positive trends vs. pooled control groups (see table below). In particular, the

**Selected Neoplasms in Mice (All Female)\***

|                                | Veh |    | Low | Mid- |    | Trend | vs vs  | High   | Med-Hi | Medium | Low    |
|--------------------------------|-----|----|-----|------|----|-------|--------|--------|--------|--------|--------|
|                                | 1   | 2  |     | Med  | Hi |       |        |        |        |        |        |
| N                              | 60  | 60 | 60  | 60   | 60 | 60    |        |        |        |        |        |
| ADRENAL, MEDULLA               |     |    |     |      |    |       |        |        |        |        |        |
| B-PHEOCHROMOCYTOMA             | 0   | 0  | 0   | 0    | 3  | 0     | 0.3776 | .      | 0.0261 | .      | .      |
| HARDERIAN GLAND                |     |    |     |      |    |       |        |        |        |        |        |
| Adenoma/Carcinoma              | 5   | 3  | 7   | 3    | 5  | 8     | 0.0354 | 0.0489 | 0.3406 | 0.5383 | 0.1383 |
| MAMMARY, FEMALE                |     |    |     |      |    |       |        |        |        |        |        |
| Adenoma/Carc./-sarcoma/-canth. | 2   | 1  | 13  | 19   | 26 | 20    | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| M-ADENOACANTHOMA               | 1   | 0  | 7   | 6    | 7  | 5     | 0.1028 | 0.0080 | 0.0011 | 0.0061 | 0.0014 |
| M-CARCINOMA                    | 2   | 1  | 7   | 12   | 18 | 13    | 0.0011 | 0.0000 | 0.0000 | 0.0002 | 0.0113 |
| M-CARCINOSARCOMA               | 0   | 0  | 0   | 1    | 2  | 2     | 0.0259 | 0.0800 | 0.0898 | 0.3333 | .      |
| OVARY                          |     |    |     |      |    |       |        |        |        |        |        |
| Cystad./Gran./Thecal/Tubul.    | 1   | 0  | 2   | 4    | 1  | 2     | 0.2543 | 0.1961 | 0.5073 | 0.0446 | 0.2307 |
| PANCREAS                       |     |    |     |      |    |       |        |        |        |        |        |
| B-ISLET CELL ADENOMA           | 0   | 0  | 0   | 1    | 3  | 1     | 0.1546 | 0.2857 | 0.0261 | 0.3333 | .      |
| PITUITARY                      |     |    |     |      |    |       |        |        |        |        |        |
| B-ADENOMA, PARS DISTALIS       | 3   | 4  | 11  | 17   | 27 | 29    | 0.0000 | 0.0000 | 0.0000 | 0.0001 | 0.0068 |

\* FDA statistical analysis (statistical reviewer: Steve Thomson)

tests of overall trend and pairwise comparison between the highest dose group and pooled control in mammary carcinoma in females were statistically significant, as were the tests of pooled tumors (adenomas, carcinomas, carcinosarcomas, and adenoacanthomas) for trend and pairwise comparisons. Similarly the tests of overall trend and pairwise comparison between the highest dose group and control in pituitary pars distalis adenoma in females were highly statistically significant. The pairwise comparisons of mammary carcinoma in the mid-high dose and middle dose groups to control were statistically significant, while for the low dose group the difference was close to adjusted statistical significance ( $p \approx 0.01$ ). The pairwise comparisons for these groups were also statistically significant for mammary adenoacanthoma. Similarly the pairwise comparisons of the mid-high dose, middle, and low dose groups to the pooled controls for pituitary pars distalis adenoma were statistically significant. In pooled mammary tumors all these comparisons were also statistically significant.

Some other neoplasms were increased in single dose groups without dose-dependence. Thus, the pooled cancers of the ovary were statistically significantly higher in the middle dose group vs. pooled vehicle; and adrenal pheochromocytoma and islet cell adenoma of the pancreas were statistically significant in the mid-high dose group vs. pooled vehicle, but not in the highest dose group. No other tests achieved statistical significance.

**Non-neoplastic findings:** Dose-related significant increases in mortality occurred in females at 300 or 650 mg/kg/day. Findings in the female reproductive system indicated a disruption in the estrus cycle, which, along with the marked elevation of serum prolactin and the increased incidence of tumors in the pituitary and mammary gland, is likely related to the dopamine type 2-receptor antagonistic properties of the drug. The percentages of females with evidence of estrus cycling showed that lurasidone affected the estrus cycle at dose levels of 100 mg/kg/day and higher. This was supported by histopathology findings in the female reproductive system indicative of estrus cycle disruption, i.e., ovarian, uterine, cervical and vaginal atrophy. Serum prolactin (measured during Week 52) was markedly and significantly elevated at all dose levels in comparison to control, and prolactin levels in females were 2 to 4 times higher than those in males in all dose groups.

Plasma exposure to lurasidone increased with dose, less than dose-proportionally, in both males and females. Females had higher systemic exposure values ( $C_{max}$  and  $AUC_{0-24hr}$ ) than males across all collection time points. Values for  $AUC_{0-24hr}$  were higher after multiple dosing in females, but not in males.

**NOEL for neoplasia:**

Males: 1200/650 mg/kg/day.

Females: NOEL was not reached for pituitary adenoma and mammary malignant neoplasia (carcinoma, adenoacanthoma) (below the LD of 30 mg/kg/day).

**Rat Carcinogenicity Study**

Oral (gavage) administration of lurasidone in 0.5% methylcellulose to CrI:CD(SD)@IGS BR rats (65/sex/dose) for 104 weeks at doses of 0, 0, 3, 12, 50/36 mg/kg/day (HD reduced to 36 mg/kg of body weight/day beginning on Days 404 and 403 for males and

females, respectively) resulted in the following **neoplastic findings**:

**Males:** Skin fibroma/fibrosarcoma was significantly increased over the pooled vehicle control only at mid-dose, but not at high dose (see table on the next page) No other significant effects, either in terms of positive trend or significant increase over the controls, were noted.

**Females:** Increased incidence of mammary carcinomas was found at mid- and high-dose; the test of trend was statistically significant, as was the test comparing the HD and MD to the pooled vehicle; at the mid-dose, the incidence of mammary adenomas was also significantly increased over pooled controls, but there was no increase in this tumor incidence at the high dose. The incidence of other mammary tumors was similar for control and treated females. No other tests of trend or comparisons between the high dose and controls achieved the multiplicity adjusted significance levels.

**Selected Neoplasms in Rats\***

|                            | Incidence |     |     |     |      | Significance Levels |             |               |            |
|----------------------------|-----------|-----|-----|-----|------|---------------------|-------------|---------------|------------|
|                            | Veh       | Veh | Low | Med | High | Trend               | High vs Veh | Medium vs Veh | Low vs Veh |
| N                          | 1         | 2   | 65  | 65  | 65   |                     |             |               |            |
| Male Rats                  |           |     |     |     |      |                     |             |               |            |
| HEMATO NEOPLASIA           |           |     |     |     |      |                     |             |               |            |
| M-LYMPHOMA                 | 0         | 1   | 4   | 1   | 2    | 0.4121              | 0.3047      | 0.5432        | 0.0396     |
| MAMMARY, MALE              |           |     |     |     |      |                     |             |               |            |
| Adenoma/Carc./Fibro.       | 0         | 1   | 1   | 4   | 1    | 0.5059              | 0.6019      | 0.0372        | 0.5284     |
| SKIN                       |           |     |     |     |      |                     |             |               |            |
| Fibroma/Fibrosarcoma       | 2         | 0   | 2   | 7   | 1    | 0.6429              | 0.2982      | 0.0064        | 0.3789     |
| M-FIBROSARCOMA             | 1         | 0   | 2   | 5   | 0    | 0.8026              | 0.3630      | 0.0156        | 0.2364     |
| Female Rats                |           |     |     |     |      |                     |             |               |            |
| MAMMARY, FEMALE            |           |     |     |     |      |                     |             |               |            |
| Adenoma/Carc./Fibro./mixed | 38        | 38  | 41  | 50  | 42   | 0.1771              | 0.1966      | 0.0121        | 0.3523     |
| B-ADENOMA                  | 11        | 5   | 10  | 20  | 12   | 0.2538              | 0.2477      | 0.0044        | 0.4292     |
| M-CARCINOMA                | 19        | 14  | 21  | 30  | 32   | 0.0008              | 0.0009      | 0.0027        | 0.2483     |
| THYROID                    |           |     |     |     |      |                     |             |               |            |
| Adenoma/Carc. C cell       | 4         | 4   | 2   | 4   | 8    | 0.0398              | 0.1423      | 0.3807        | 0.7363     |

\* FDA statistical analysis (statistical reviewer: Steve Thomson)

**Non-neoplastic findings:**

No increase in mortality in either gender. Body weight reduction: in females at MD and HD and in males at all doses; due to excessive reduction in mean body weight (>20% for both genders) at the initial HD of 50 mg/kg/day, it was reduced to 36 mg/kg/day beginning on Days 404 and 403 for M and F, respectively. Female estrus cycle disruption occurred at all dose levels in a dose-dependent manner, supported by microscopic findings of increased incidence of absence of corpora lutea in the ovary and increased vaginal cornification at the terminal sacrifice of females at all dose levels. In males, increased incidence of milk secretion was observed at all dose groups. Serum prolactin was elevated dose-dependently vs. controls in the males at all dose levels (reaching a plateau between MD and HD); in the females, prolactin was increased at LD and MD but not at HD. Plasma exposure to lurasidone increased greater-than-dose-proportionally; Cmax and AUC0-24hr values were higher in F than in M across all collection time points..

In summary, lurasidone resulted in increased incidence of mammary carcinomas in female rats at MD and HD, and increased incidence of milk secretion in males at all dose groups. The incidence of all other neoplastic lesions in either gender was not elevated at any of the tested dose levels.

**NOEL for neoplasia:**

Females: mammary carcinoma: 3 mg/kg/day;

Males: 50/36 mg/kg/day

**Executive CAC Recommendations and Conclusions:**

Rat:

The Committee agreed that the study was adequate, noting prior Exec CAC concurrence with the protocol.

The Committee concluded that the mammary carcinomas in mid and high dose female rats were drug related.

Mouse:

The Committee agreed that the study was adequate, noting prior Exec CAC concurrence with the protocol.

The Committee concluded that the mammary carcinomas and adenoacanthomas and benign pituitary pars distalis adenomas were drug related in females only, at all dose groups.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

cc:\

/Division File, DPP  
Aisar Atrakchi/Team leader, DPP  
Sonia Tabacova/Reviewer, DPP  
Ann Sohn/CSO/PM, DPP  
/ASeifried, OND-IO

| Application Type/Number | Submission Type/Number | Submitter Name                                 | Product Name   |
|-------------------------|------------------------|--|----------------|
| NDA-200603              | ORIG-1                 | DAINIPPON<br>SUMITOMO<br>PHARMA AMERICA<br>INC | Lurasidone HCl |

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ADELE S SEIFRIED  
07/15/2010

DAVID JACOBSON KRAM  
07/15/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 1, 2010

To: Thomas Laughren, MD, Director  
Division of Psychiatry Products

Through: Melina Griffis RPh, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Richard Abate, RPh, MS, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Lurasidone HCl Tablets 40 mg, 80 mg and 120 mg

Application  
Type/Number: NDA 200603

Applicant: Dainippon Sumitomo Pharma Co. Ltd.

OSE RCM #: 2010-64

## **1 INTRODUCTION**

This review provides comments from the Division of Medication Error Prevention and Analysis regarding potential medication error issues identified with the proposed container labels and carton labeling for Lurasidone HCL tablets (NDA 200603) submitted by Dainippon Sumitomo Pharma on December 30, 2009. DMEPA found the proposed proprietary name for this product, (b) (4) included on the labels and labeling, unacceptable. We notified Dainippon Sumitomo Pharma in a letter, April 21, 2010 of this finding. We provide recommendations in Section 3.2 with regards to the proposed product labels and labeling.

## **2 MATERIAL REVIEWED**

Using Failure Mode and Effects Analysis,<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the product labels and labeling submitted December 30, 2009 to identify vulnerabilities that may lead to medication errors. In addition, we requested the draft hospital unit-dose blister labels which the Applicant submitted June 11, 2010. See Appendices for samples of the draft container labels and carton labeling.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

Our Label and Labeling Risk Assessment indicates that the presentation of information on the label and labeling introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval, and thus we provide recommendations in the following sections that aim at reducing the risk of medication errors.

### **3.1 COMMENTS TO THE DIVISION**

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to Dainippon Sumitomo Pharma with regard to this review. If you have further questions or need clarifications, please contact Sandra Griffith, project manager, at 301-796-2445.

We request the recommendation in Section 3.2 be communicated to the Applicant prior to the approval of this NDA.

### **3.2 COMMENTS TO THE APPLICANT**

#### **A. General Comments**

The proprietary name, (b) (4), was found unacceptable. Thus, we request you provide draft labels that reflect your new proprietary name or revise the draft labels to reflect the established name.

#### **B. Carton Labeling, Container labels and Professional Sample Blistercards (All strengths and quantities)**

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1. Revise the presentation of the established name on the container labels, carton labeling and blistercard so that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).
2. Relocate the strength presentation to appear directly below the established name and above the bar graphic on the principle display panel.
3. Relocate the “each tablet contains” statement to appear below the bar graphic or on the side panel. See below.

(b) (4)

C. Carton Labeling for professional samples (10 x 7 tablet blistercards)

The proprietary and established names appear on the portion of the carton that is intended to be removed upon opening. Revise the presentation of the proprietary and established names in conjunction with the strength to provide this information on the carton before and after the carton is opened.

D. Professional sample Blistercards (7 tablets)

Relocate the “each tablet contains” statement to the inside center panel of the blistercard, panel containing the tablets. Inclusion of this statement on the inside center panel provides the patient with the amount of lurasidone HCl each tablet contains on the panel holding the tablets.

E. Hospital Unit-Dose Blister Labels (10 tablets)

1. Revise the strength presentation to provide additional methods to differentiate the strengths (e.g. color, shapes, or outlining).
2. Increase the prominence of the strength presentation to improve identification.
3. Relocate the dosage form, tablet, to appear below the established name.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

| Application Type/Number | Submission Type/Number | Submitter Name                                 | Product Name   |
|-------------------------|------------------------|--|----------------|
| NDA-200603              | ORIG-1                 | DAINIPPON<br>SUMITOMO<br>PHARMA AMERICA<br>INC | Lurasidone HCl |

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RICHARD A ABATE  
07/01/2010

MELINA N GRIFFIS  
07/01/2010

DENISE P TOYER  
07/01/2010

CAROL A HOLQUIST  
07/01/2010

# DSI CONSULT: Request for Clinical Inspections

**Date:** {See Appended Electronic Signature}

**To:** Leslie Ball, M.D., Director  
Tejashri Purohit-Sheth, MD, Branch Chief, GCP2  
Anthony Orenca, MD, Medical Officer  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Thomas Laughren, M.D., Director  
Division of Psychiatry Products/HFD-130

**From:** Ann Sohn, Regulatory Health Project Manager/DPP/HFD-130

**Subject:** Request for Clinical Site Inspections

## **I. General Information**

Application#: NDA-200603 O-1

Sponsor/Sponsor contact information (to include phone/email):

Dainippon Sumitomo Pharma America, Inc.

One Bridge Plaza, Suite 510

Fort Lee, NJ 07024

Phone: 201-228-8333

Fax: 201-592-5939

Contact: Bridget Walton, Associate Director, Regulatory Affairs

Email: bwalton@dsp-a.com

Drug: Lurasidone (b) (4)

NME: Yes

Standard or Priority: Standard

Study Population < 18 years of age: No

Pediatric exclusivity: No

PDUFA: October 30, 2010

Action Goal Date: September 4, 2010

Inspection Summary Goal Date: August 2, 2010

## **II. Background Information**

Lurasidone (b) (4) is a new molecular entity studied for the treatment of schizophrenia in adults. The Sponsor has submitted clinical data from four pivotal trials to support this indication.

### **III. Protocol/Site Identification**

Protocol D1050006 was a randomized, placebo-controlled, double-blind, multicenter 6 week trial evaluating the efficacy and safety of two doses of lurasidone (40 mg/day or 120 mg/day) compared to placebo. Subjects were enrolled at 15 sites in the United States.

Protocol D1050196 was a randomized, placebo-controlled, double-blind, multicenter 6 week trial evaluating the efficacy and safety of lurasidone (80 mg/day) compared to placebo. Subjects were enrolled at 22 sites in the United States.

Protocol D1050229 was a randomized, placebo-controlled, double-blind, multicenter 6 week trial evaluating the efficacy and safety of three doses of lurasidone (40 mg/day, 80 mg/day, 120 mg/day) compared to placebo. Subjects were enrolled at sites in the US, India, Russia, Ukraine, Romania, France and Malaysia.

Protocol D1050231 was a randomized, placebo-controlled, double-blind, multicenter 6 week trial evaluating the efficacy and safety of two doses of lurasidone (40 mg/day and 120 mg/day) compared to placebo. Subjects were enrolled at sites in the US, India, Lithuania, Philippines, and Colombia.

The study reports and the clinical investigator site information can be found in EDR.

EDR link: <\\CDSESUB1\EVSPROD\NDA200603\200603.ENX>

| <b>Site # (Name,Address, Phone number, email, fax#)</b> | <b>Protocol #</b> | <b>Number of Subjects</b> | <b>Indication</b>          |
|---|-------------------|---------------------------|----------------------------|
| Site #14<br>Robert Riesenberg<br>Atlanta, GA; USA       | D1050006          | 27                        | Treatment of Schizophrenia |
| Site # 17<br>Robert Riesenberg<br>Atlanta, GA; USA      | D1050231          | 10                        | Treatment of Schizophrenia |
| Site #17<br>Robert Riesenberg<br>Atlanta, GA; USA       | D1050229          | 15                        | Treatment of Schizophrenia |
| Site # 15<br>Tram K Tran-Johnson<br>San Diego, CA; USA  | D1050006          | 29                        | Treatment of Schizophrenia |
| Site #37<br>Tram K Tran-Johnson<br>San Diego, CA; USA   | D1050231          | 16                        | Treatment of Schizophrenia |
| Site #465<br>Rodrigo Cordoba<br>Bogotá Colombia         | D1050231          | 14                        | Treatment of Schizophrenia |

| <b>Site # (Name,Address, Phone number, email, fax#)</b> | <b>Protocol #</b> | <b>Number of Subjects</b> | <b>Indication</b>          |
|---|-------------------|---------------------------|----------------------------|
| Site #464<br>Laura Giraldo<br>Bogotá Colombia           | D1050231          | 12                        | Treatment of Schizophrenia |

#### **IV. Site Selection/Rationale**

##### **Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

The sites in the United States were chosen for several reasons. In study D1050006, though there were 15 sites that enrolled subjects, sites 14 and 15 randomized nearly 40% of the total number of subjects. Additionally, investigators Drs. Riesenbergs and Tran-Johnson enrolled subjects in 3 or 4 of the pivotal schizophrenia trials for this drug. It is important to ascertain whether any duplicate enrollment occurred across these trials (e.g. did any of the same patients enroll in more than one pivotal trial at each site?).

##### **International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify)

The sites in Colombia were chosen primarily due to their significant contribution to the overall efficacy signal in this multicenter trial. Though study D1050231 enrolled subjects in the US, India, Lithuania, Philippines and Colombia; the geographic region analyses showed significant results favoring the Sponsor drug over placebo consistently in the Colombia region (Latin America) and not the other regions.

Should you require any additional information, please contact Ann Sohn at Ph: 301-796-2232 or Dr. Cara Alfaro at Ph: 301-796- 1033.

Page 4-Request for Clinical Inspections

Concurrence: (as needed)

\_\_\_\_\_ Cara Alfaro, Pharm.D., Clinical Analyst  
\_\_\_\_\_ Ni Khin, MD, Medical Team Leader  
\_\_\_\_\_ Thomas Laughren, MD, Director, Division Director (for  
foreign inspection requests only)

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-200603

-----  
ORIG-1

-----  
DAINIPPON  
SUMITOMO  
PHARMA AMERICA  
INC

-----  
Lurasidone HCl

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
-----

ANN J SOHN  
02/25/2010

THOMAS P LAUGHREN  
02/25/2010

**RPM FILING REVIEW**  
(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)**

| <b>Application Information</b>   |  |                          |
|--|--|--------------------------|
| NDA # 200603<br>BLA#   | NDA Supplement #:S-<br>BLA STN #   | Efficacy Supplement Type |
| Proprietary Name: (b) (4)<br>Established/Proper Name: lurasidone hydrochloride, SM-13496<br>Dosage Form: tablets<br>Strengths: 40mg, 80mg, 120mg   |  |                          |
| Applicant: Dainippon Sumitomo Pharma America, Inc.<br>Agent for Applicant (if applicable): Bridget Walton, MS, RAC   |  |                          |
| Date of Application: December 30, 2009<br>Date of Receipt: December 30, 2009<br>Date clock started after UN:   |  |                          |
| PDUFA Goal Date: October 30, 2010  | Action Goal Date (if different):   |                          |
| Filing Date: February 28, 2010   | Date of Filing Meeting: February 23, 2010  |                          |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1  |  |                          |
| Proposed indication(s)/Proposed change(s): acute treatment of adults with schizophrenia  |  |                          |
| Type of Original NDA:<br>AND (if applicable)<br>Type of NDA Supplement:  | <input checked="" type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)<br><input type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2)  |                          |
| <b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:<br/> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a><br/>           and refer to Appendix A for further information.</i></b> |  |                          |
| Review Classification:   | <input checked="" type="checkbox"/> Standard<br><input type="checkbox"/> Priority<br><br><input type="checkbox"/> Tropical Disease Priority Review Voucher submitted   |                          |
| <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b><br><br><b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>   |  |                          |
| Resubmission after withdrawal? <input type="checkbox"/>  | Resubmission after refuse to file? <input type="checkbox"/>  |                          |
| Part 3 Combination Product? <input type="checkbox"/><br><b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>  | <input type="checkbox"/> Drug/Biologic<br><input type="checkbox"/> Drug/Device<br><input type="checkbox"/> Biologic/Device   |                          |
| <input type="checkbox"/> Fast Track<br><input type="checkbox"/> Rolling Review<br><input type="checkbox"/> Orphan Designation<br><br><input type="checkbox"/> Rx-to-OTC switch, Full<br><input type="checkbox"/> Rx-to-OTC switch, Partial<br><input type="checkbox"/> Direct-to-OTC<br><br>Other:                             | <input type="checkbox"/> PMC response<br><input type="checkbox"/> PMR response:<br><input type="checkbox"/> FDAAA [505(o)]<br><input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]<br><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)<br><input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) |                          |

| Collaborative Review Division (if OTC product):  |   |    |    |         |
|--|---|----|----|---------|
| List referenced IND Number(s): 61292   |   |    |    |         |
| Goal Dates/Names/Classification Properties   | YES   | NO | NA | Comment |
| PDUFA and Action Goal dates correct in tracking system?<br><br><i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>  | X   |    |    |         |
| Are the proprietary, established/proper, and applicant names correct in tracking system?<br><br><i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i> | X   |    |    |         |
| Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system?<br><br><i>If not, ask the document room staff to make the appropriate entries.</i>  | X   |    |    |         |
| Application Integrity Policy   | YES   | NO | NA | Comment |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>                       |   | X  |    |         |
| <b>If yes</b> , explain in comment column.   |   |    |    |         |
| <b>If affected by AIP</b> , has OC/DMPQ been notified of the submission? <b>If yes</b> , date notified:  |   |    |    |         |
| User Fees  | YES   | NO | NA | Comment |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature?  | X   |    |    |         |
| <u>User Fee Status</u><br><br><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>  | Payment for this application:<br><br><input checked="" type="checkbox"/> Paid<br><input type="checkbox"/> Exempt (orphan, government)<br><input type="checkbox"/> Waived (e.g., small business, public health)<br><input type="checkbox"/> Not required |    |    |         |
| <br><br><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>                                    | Payment of other user fees:<br><br><input checked="" type="checkbox"/> Not in arrears<br><input type="checkbox"/> In arrears  |    |    |         |
| <i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>                                      |   |    |    |         |

| <b>505(b)(2)<br/>(NDAs/NDA Efficacy Supplements only)</b>  | <b>YES</b>      | <b>NO</b>        | <b>NA</b>              | <b>Comment</b>         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|--|-----------------|------------------|------------------------|------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?   |                 |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).   |                 |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?<br><br><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>   |                 |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b><br><a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a><br><br><b>If yes, please list below:</b>   |                 |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>   | Application No. | Drug Name        | Exclusivity Code       | Exclusivity Expiration |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Application No.  | Drug Name       | Exclusivity Code | Exclusivity Expiration |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |                 |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |                 |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |                 |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i> |                 |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>Exclusivity</b>   | <b>YES</b>      | <b>NO</b>        | <b>NA</b>              | <b>Comment</b>         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at:</b><br><a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>   |                 | X                |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?<br><br><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>   |                 |                  |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)<br><br><b>If yes, # years requested:</b><br><br><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>  |                 | X                |                        |                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

|  |  |   |  |  |
|--|--|---|--|--|
| Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDA</i> s only)?  |  | X |  |  |
| <b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?<br><br><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i> |  |   |  |  |

| Format and Content  |   |           |           |                |
|---|---|-----------|-----------|----------------|
| <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>   | <input type="checkbox"/> All paper (except for COL)<br><input checked="" type="checkbox"/> All electronic<br><input type="checkbox"/> Mixed (paper/electronic)<br><br><input checked="" type="checkbox"/> CTD<br><input type="checkbox"/> Non-CTD<br><input type="checkbox"/> Mixed (CTD/non-CTD) |           |           |                |
| <b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?  |   |           |           |                |
| <b>Overall Format/Content</b>   | <b>YES</b>  | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| <b>If electronic submission</b> , does it follow the eCTD guidance <sup>1</sup> ?<br><b>If not</b> , explain (e.g., waiver granted).  | X   |           |           |                |
| <b>Index:</b> Does the submission contain an accurate comprehensive index?  | X   |           |           |                |
| Is the submission complete as required under 21 CFR 314.50 ( <i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 ( <i>BLA</i> s/ <i>BLA</i> efficacy supplements) including:<br><br><input checked="" type="checkbox"/> legible<br><input checked="" type="checkbox"/> English (or translated into English)<br><input checked="" type="checkbox"/> pagination<br><input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)<br><br><b>If no</b> , explain. | X   |           |           |                |
| <b>Controlled substance/Product with abuse potential:</b><br>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?<br><br><i>If yes, date consult sent to the Controlled Substance Staff:</i>   |   | X         |           |                |
| <b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?<br><br><b>If yes</b> , BLA #   |   |           |           |                |

| <b>Forms and Certifications</b>   |            |           |           |                |
|---|------------|-----------|-----------|----------------|
| <p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> |            |           |           |                |
| <b>Application Form</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is form FDA 356h included with authorized signature?  | X          |           |           |                |
| <i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i>   |            |           |           |                |
| Are all establishments and their registration numbers listed on the form/attached to the form?  |            |           |           |                |
| <b>Patent Information<br/>(NDAs/NDA efficacy supplements only)</b>  | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is patent information submitted on form FDA 3542a?  | X          |           |           |                |
| <b>Financial Disclosure</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?   | X          |           |           |                |
| <i>Forms must be signed by the APPLICANT, not an Agent.</i>   |            |           |           |                |
| <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>   |            |           |           |                |
| <b>Clinical Trials Database</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is form FDA 3674 included with authorized signature?  | X          |           |           |                |
| <b>Debarment Certification</b>  | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is a correctly worded Debarment Certification included with authorized signature? ( <i>Certification is not required for supplements if submitted in the original application</i> )   | X          |           |           |                |
| <i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i>  |            |           |           |                |
| <i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>  |            |           |           |                |

| <b>Field Copy Certification<br/>(NDAs/NDA efficacy supplements only)</b>  | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
|---|------------|-----------|-----------|----------------|
| <p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p> | X          |           |           |                |

| <b>Pediatrics</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
|---|------------|-----------|-----------|----------------|
| <p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> | X          |           |           |                |
| <p><b>If the application triggers PREA</b>, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>   |            | X         |           |                |
| <p><b>If studies or full waiver not included</b>, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>   | X          |           |           | (b) (4)        |
| <p><b>If a request for full waiver/partial waiver/deferral is included</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>  | X          |           |           |                |
| <p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>  |            |           |           |                |

| <b>Proprietary Name</b>  | <b>YES</b>   | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
|--|--|-----------|-----------|----------------|
| Is a proposed proprietary name submitted?<br><br><i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>  | X  |           |           |                |
| <b>Prescription Labeling</b>   | <input type="checkbox"/> <b>Not applicable</b>   |           |           |                |
| Check all types of labeling submitted.   | <input checked="" type="checkbox"/> Package Insert (PI)<br><input type="checkbox"/> Patient Package Insert (PPI)<br><input type="checkbox"/> Instructions for Use (IFU)<br><input type="checkbox"/> Medication Guide (MedGuide)<br><input checked="" type="checkbox"/> Carton labels<br><input checked="" type="checkbox"/> Immediate container labels<br><input type="checkbox"/> Diluent<br><input type="checkbox"/> Other (specify) |           |           |                |
|  | <b>YES</b>   | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is Electronic Content of Labeling (COL) submitted in SPL format?<br><br><i>If no, request in 74-day letter.</i>  | X  |           |           |                |
| Is the PI submitted in PLR format?   | X  |           |           |                |
| <b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?<br><br><i>If no waiver or deferral, request PLR format in 74-day letter.</i> |  |           |           |                |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?   | X  |           |           |                |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK?<br>(send WORD version if available)   |  |           | X         |                |
| REMS consulted to OSE/DRISK?   |  |           | X         |                |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?  | X  |           |           |                |
| <b>OTC Labeling</b>  | <input type="checkbox"/> <b>Not Applicable</b>   |           |           |                |
| Check all types of labeling submitted.   | <input type="checkbox"/> Outer carton label<br><input type="checkbox"/> Immediate container label<br><input type="checkbox"/> Blister card<br><input type="checkbox"/> Blister backing label<br><input type="checkbox"/> Consumer Information Leaflet (CIL)<br><input type="checkbox"/> Physician sample<br><input type="checkbox"/> Consumer sample<br><input type="checkbox"/> Other (specify)                                       |           |           |                |
|  | <b>YES</b>   | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Is electronic content of labeling (COL) submitted?<br><br><i>If no, request in 74-day letter.</i>  |  |           |           |                |

|   |            |           |           |                |
|---|------------|-----------|-----------|----------------|
| Are annotated specifications submitted for all stock keeping units (SKUs)?<br><i>If no, request in 74-day letter.</i>   |            |           |           |                |
| If representative labeling is submitted, are all represented SKUs defined?<br><i>If no, request in 74-day letter.</i>   |            |           |           |                |
| All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?   |            |           |           |                |
| <b>Consults</b>   | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)<br><i>If yes, specify consult(s) and date(s) sent:</i> | X          |           |           | QT Consult     |

| <b>Meeting Minutes/SPAs</b>  | <b>YES</b> | <b>NO</b> | <b>NA</b> | <b>Comment</b> |
|--|------------|-----------|-----------|----------------|
| End-of Phase 2 meeting(s)?<br><b>Date(s):</b> September 26, 2006<br><i>If yes, distribute minutes before filing meeting</i>  | X          |           |           |                |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br><b>Date(s):</b> May 22, 2009<br><i>If yes, distribute minutes before filing meeting</i>                                  | X          |           |           |                |
| Any Special Protocol Assessments (SPAs)?<br><b>Date(s):</b> 6-4-03, 6-4-07, 12-18-07<br><i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | X          |           |           |                |

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** February 23, 2010

**BLA/NDA/Supp #:** 200603

**PROPRIETARY NAME:** (b) (4)

**ESTABLISHED/PROPER NAME:** lurasidone hydrochloride

**DOSAGE FORM/STRENGTH:** 40mg, 80mg, 120mg tablets

**APPLICANT:** Dainippon Sumitomo Pharma America, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** treatment of acute schizophrenia

**BACKGROUND:** NME

**REVIEW TEAM:**

| Discipline/Organization                                     | Names     |               | Present at filing meeting? (Y or N) |
|---|-----------|---------------|-------------------------------------|
| Regulatory Project Management                               | RPM:      | Ann Sohn      | Y                                   |
|   | CPMS/TL:  | Keith Kiedrow | Y                                   |
| Cross-Discipline Team Leader (CDTL)                         |           |               |                                     |
| Clinical  | Reviewer: | Cara Alfaro   | Y                                   |
|   | TL:       | Ni Khin       | Y                                   |
| Social Scientist Review ( <i>for OTC products</i> )         | Reviewer: |               |                                     |
|   | TL:       |               |                                     |
| OTC Labeling Review ( <i>for OTC products</i> )             | Reviewer: |               |                                     |
|   | TL:       |               |                                     |
| Clinical Microbiology ( <i>for antimicrobial products</i> ) | Reviewer: |               |                                     |
|   | TL:       |               |                                     |

|   |           |                                  |   |
|---|-----------|----------------------------------|---|
| Clinical Pharmacology   | Reviewer: | Kofi Kumi                        | Y |
|   | TL:       | Ray Baweja                       | Y |
| Biostatistics   | Reviewer: | George Kordzakhia                | Y |
|   | TL:       | Peiling Yang                     | Y |
| Nonclinical<br>(Pharmacology/Toxicology)  | Reviewer: | Sonia Tabacova                   | Y |
|   | TL:       | Aisar Atrakchi/ Barry<br>Rosloff | Y |
| Statistics (carcinogenicity)  | Reviewer: |                                  |   |
|   | TL:       |                                  |   |
| Immunogenicity (assay/assay<br>validation) ( <i>for BLAs/BLA efficacy<br/>supplements</i> ) | Reviewer: |                                  |   |
|   | TL:       |                                  |   |
| Product Quality (CMC)   | Reviewer: | Shastri Bhamidipati              | Y |
|   | TL:       | Tom Oliver                       | Y |
| Quality Microbiology ( <i>for sterile<br/>products</i> )                                    | Reviewer: |                                  |   |
|   | TL:       |                                  |   |
| CMC Labeling Review ( <i>for BLAs/BLA<br/>supplements</i> )                                 | Reviewer: |                                  |   |
|   | TL:       |                                  |   |
| Facility Review/Inspection  | Reviewer: |                                  |   |
|   | TL:       |                                  |   |
| OSE/DMEPA (proprietary name)  | Reviewer: | Rick Abate                       | Y |
|   | TL:       | Melina Griffis/ Todd<br>Bridges  | N |
| OSE/DRISK (REMS)  | Reviewer: |                                  |   |
|   | TL:       |                                  |   |
| Bioresearch Monitoring (DSI)  | Reviewer: | Anthony Orenca                   | Y |
|   | TL:       |                                  |   |

|                 |                            |        |
|-----------------|----------------------------|--------|
| Other reviewers | Atul Bhattaram<br>Li Zhang | Y<br>Y |
| Other attendees |                            |        |

**FILING MEETING DISCUSSION:**

|   |   |
|---|---|
| <b>GENERAL</b>  |   |
| <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>   | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO                     |
| <ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> none</p>  | <input type="checkbox"/> Not Applicable   |
| <b>CLINICAL</b>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE        |
| <b>Comments:</b>  | <input checked="" type="checkbox"/> Review issues for 74-day letter   |
| <ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul> | <input type="checkbox"/> YES<br>Date if known:<br><input type="checkbox"/> NO<br><input checked="" type="checkbox"/> To be determined |
|   | Reason:   |

|   |  |
|---|--|
| <ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p> | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter            |
| <p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>  | <input type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter |
| <p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter |
| <p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter            |
| <p><b>PRODUCT QUALITY (CMC)</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter |

|                  |  |
|------------------|--|
| <b>Comments:</b> |  |
|------------------|--|

|  |   |
|--|---|
| <p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p> | <p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES<br/><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p> |
| <p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>   | <p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p>  |
| <p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>   | <p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES<br/><input type="checkbox"/> NO</p>  |
| <p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>  | <p><input type="checkbox"/> Not Applicable<br/><input type="checkbox"/> FILE<br/><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>  |
| <p><b><u>CMC Labeling Review (BLAs/BLA supplements only)</u></b></p> <p><b>Comments:</b></p>   | <p><input type="checkbox"/> Review issues for 74-day letter</p>   |

| <b>REGULATORY PROJECT MANAGEMENT</b>  |  |
|---|--|
| <b>Signatory Authority:</b> Office Director, Robert Temple, MD              |  |
| <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (optional): |  |
| <b>Comments:</b>  |  |
| <b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>                                  |  |
| <input type="checkbox"/>  | The application is unsuitable for filing. Explain why:   |
| <input checked="" type="checkbox"/>   | The application, on its face, appears to be suitable for filing.<br><br><u>Review Issues:</u><br><br><input type="checkbox"/> No review issues have been identified for the 74-day letter.<br><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):<br><br><u>Review Classification:</u><br><br><input checked="" type="checkbox"/> Standard Review<br><br><input type="checkbox"/> Priority Review |
| <b>ACTIONS ITEMS</b>  |  |
| <input checked="" type="checkbox"/>   | Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.   |
| <input type="checkbox"/>  | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).   |
| <input type="checkbox"/>  | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.  |
| <input type="checkbox"/>  | BLA/BLA supplements: If filed, send 60-day filing letter   |
| <input type="checkbox"/>  | If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>   |
| <input type="checkbox"/>  | Send review issues/no review issues by day 74  |
| <input type="checkbox"/>  | Other  |

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-200603

-----  
ORIG-1

-----  
DAINIPPON  
SUMITOMO  
PHARMA AMERICA  
INC

-----  
Lurasidone HCl

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANN J SOHN  
02/24/2010