CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200603

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	*{See Appended Electronic Signature Page}*
From	Ni A. Khin, M.D. Lead Medical Officer Division of Psychiatry Products, HFD-130 Office of Drug Evaluation I, Office of New Drugs (OND) Center for Drug Evaluation and Research (CDER)
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA#	NDA 200603
Applicant Name	Sepracor, Inc.
Date of Submission	December 30, 2010
PDUFA Goal Date	October 30, 2010
Proprietary Name / Established Name	Lurasidone hydrochloride
Dosage Forms / Strength	40, 80 and 120 mg oral tablets
Proposed Indication(s)	Schizophrenia
Recommended Action:	Approval

1. INTRODUCTION

Lurasidone hydrochloride is an atypical antipsychotic agent with high affinities to dopamine (D2) and serotonin (5-HT2) receptors as well as melanin-binding properties. The sponsor's proposed indication is for the treatment of schizophrenia based on results from 4 short-term placebo controlled studies in adults. The proposed dose range of lurasidone is 40 to (b) (4) once daily. The proposed dosing regimen is 40 to 80 mg once daily, (b) (4) given with a meal. The dosage strengths are 40, 80 and 120 mg oral tablets. Other atypical antipsychotic agents approved in the U.S. for schizophrenia include risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, asenapine and iloperidone.

The original (O-1) NDA 200603 application was submitted on 12/30/2009 by Dainippon Sumitomo Pharma America, Inc. (DSPA). Sepracor Inc., is current sponsor of this NDA as there was a merger of Sepracor and DSPA occurred in April, 2010.

The review team for this NDA submission consists of:

Material Reviewed/Consulted	**Name of discipline reviewers**
Clinical Review	Cara Alfaro, Pharm.D.
Statistical Review	George Kordzakhia, Ph.D.
Pharmacology Toxicology Review	Sonia Tabacova, Ph.D.
CMC Review	Shastri Bhamidipati, Ph.D.; Houda Mahayni, Ph.D.
Clinical Pharmacology Review	Kofi Kumi, Ph.D.; Atul Bhattaram, Ph.D.
Division of Scientific Investigations	Anthony Orencia, M.D.
OSE/DMEPA	Richard Abate, R.Ph.
Others: QT consult DRUP consult: Bone Mineral Density Results Ophthalmology DDMAC	 Hao Zhu, Ph.D., and IRT Marcea Whitaker, MD

We consulted with the QT team, Division of Cardiovascular and Renal Products (DCRP) regarding the sponsor's QT study report (D1050249) and QT prolongation language, the Division of Reproductive and Urologic Products (DRUP) regarding results from bone mineral density scans, and the Ophthalmology consult regarding the ophthalmologic examination results from the longer-term clinical trials.

We also consulted with DMEPA, Office of Surveillance and Epidemiology (OSE) on the sponsor's proposed trade name, and DDMAC, Office of Medical Policy (OMP) for their input on the proposed labeling from a promotional perspective.

2. BACKGROUND

The IND development program of lurasidone (also known as SM-13496) was initiated on 11/17/2000 under IND#61,292 by Dainippon Sumitomo Pharma America, Inc. (DSPA). The program was focused on use of lurasidone for acute treatment of schizophrenia in adults. There was an IND ownership transfer to Merck (MK-3756) during the development in September 2005. Sponsorship was transferred back to DSPA in February 2007, and Sepracor became the sponsor when these two companies merged in April of 2010.

Several guidance meetings including an end-of-phase 2 (EOP2) meeting on 9/26/2006 and a pre-NDA submission meeting on 5/22/2009 with the sponsor were held throughout the drug development program. The discussion included:

- the Division's concern about the issue of differential efficacy between clinical studies for different doses of with lurasidone, in particular, the positive finding for the 40 mg and 120 mg doses in the phase 2 study 1050006 are not replicated in the larger study D1050229
- the need to pre-specify key secondary efficacy variable in the pivotal studies and the acceptability of CGI-S as a key secondary measure
- the sponsor's safety analysis plan and our recommendation on metabolic parameters
- the format and content of NDA submission

3.0 CHEMISTRY, MANUFACTURING AND CONTROL (CMC)

The CMC reviewer (in review dated 8/27/2010) has recommended approvable from their perspective pending the sponsor's response to the issues identified in the information request letter dated 8/20/2010. The sponsor has been asked to provide additional dissolution data for different groups of lurasidone formulations and also to provide missing data elements in structured product labeling (SPL) for each strength of lurasidone tablets. Dr. Houda Mahayni, ONDQA Biopharmaceutical Reviewer, would review any changes in dissolution acceptance criteria, and if it would also require further evaluation of stability data supporting the expiration dating. An environmental assessment for which a request for categorical exclusion was made by the sponsor, and it was recommended a waiver to be granted. The CDER's Office of Compliance inspection of the manufacturing and testing facility is pending. The CMC group will be providing their comments for the drug product description and how supplied section of the labeling and also for the container packaging labels upon acceptability of the proposed trade name by the Division of Medication Error Prevention and Analysis.

4.0 NON-CLINICAL PHARMACOLOGY/TOXICOLOGY

Dr. Tabacova has provided me with a draft review of non-clinical findings, although the pharm/tox review has not been finalized yet at the time of completion of this memo. She did not identify any major concerns as the animal toxicology findings are not unexpected with this type of antipsychotic drug. I would briefly mention pre-clinical findings relevant to clinical use in this section.

In the carcinogenicity studies, there were statistically significant increases in neoplastic lesions [benign pituitary adenoma and malignant mammary tumors (carcinoma, adenoacanthoma)] in female rodents which were induced at almost all tested dose levels. Serum prolactin was elevated without dose-dependency in both males and females. Some minor hematology findings were noted: slightly lower hematocrit and higher platelet count for females at >100 mg/kg/day. Lurasidone was associated with disruption in the estrus cycle and a dose-dependent increase in mean body weight in females which was considered not to be of toxicological concern.

5.0 CLINICAL PHARMACOLOGY/BIOPPHARMACEUTICS

At the time of completion of this memo, the OCP review has not been finalized yet. In this submission, the sponsor provided results from 26 clinical pharmacology studies.

The activity of lurasidone is primarily due to the parent drug. It is believed that mechanism of antipsychotic action of lurasidone occurs through antagonism at central dopamine (D_2) and serotonin ($5HT_2$) receptors. It also displays moderate affinity at alpha-2 adrenoreceptors and 5HT1A receptors as well as melanine binding properties.

Lurasidone is absorbed after oral administration with some food effect observed. There was 3 fold increase in AUC and Cmax in the presence of food. Tmax is about 3 hrs. Steady state is reached within a week. It is noted to have 99% plasma protein binding. Elimination half life is approximately 31 hrs. There is minimal effect of age, gender, race, renal impairment or hepatic impairment status on PK measures.

Lurasidone is metabolized predominantly by Cytochrome P 3A4 isoenzymes. The drug-drug interaction studies showed a strong interaction of lurasidone with inhibitors and inducers of this enzyme. When lurasidone 10 mg dose was coadministered with ketoconazole 400 mg/day for 5 days, there was an increase of both Cmax and AUC to 7 and 9-folds, respectively. However, co-administration of lurasidone 40 mg dose with CYP inducers, rifampin 600 mg/day for 8 days, the plasma concentration of lurasidone was decreased by 6-7 folds.

A QTc exposure-response study (protocol D1050249) was conducted. This study involved 87 clinically stable patients with schizophrenia or schizoaffective disorder, who were treated with lurasidone doses of 120 mg daily, 600 mg daily, or ziprasidone 160 mg daily. Electrocardiographic assessments were obtained over an eight hour period at baseline and steady state. Lurasidone was associated with a mean increase in QTcI interval point estimate with the 90% CI corresponding to the largest upper bound of 7.5 ms at 2 hr (3.3, 11.7) and 4.6 msec at 4hr (-0.2, 9.5) for the 120 mg and 600 mg lurasidone doses, respectively, as compared to the active control, ziprasidone 160 mg with a mean QTcI increase of 16.3 ms (12.3, 20.3) at 6 hr time point. C_{max} and AUC values in the thorough QT study were 3.6-fold and 4.4-fold higher (Day 11), respectively, following administration of 600 mg lurasidone compared with the 120 mg dose. No patients treated with

lurasidone experienced QTcI increases > 60 msec from baseline, nor did any patient experience a QTcI of > 480 msec. No cases of torsade de pointes or other severe cardiac arrhythmias were observed. A metabolic inhibitor approach in this study was not used due to tolerability issues. Given lurasidone is primarily metabolized by CYP3A4 with significant increases in Cmax and AUC when coadministered with potent inhibitors (e.g. ketoconazole), (b) (4)

One of the pending items for OCP review is related to the analytical issues identified by the Division of Scientific Investigations (DSI) in clinical pharmacology inspection of the analytical site (b) (4) for Bioequivalence Protocol D1001053. Using the corrected calibration curve from (b) (4), the sponsor has been asked (email dated 9/9/10) to recalculate the PK parameters and bioequivalence assessments between the two formulations (40 mg vs. 2 x 20 mg) used in this study. Upon receipt of the sponsor's response, OCP will further evaluate the acceptability of the BE data for the 40 mg dose. OCP is also considering if the sponsor should be asked to conduct a (b) (5) a post-marketing study for investigating a 20-mg lower dosage strength formulation.

6.0 CLINICAL MICROBIOLOGY

Not applicable.

7.0 CLINICAL/STATISTICAL - EFFICACY

7.1 Overview of Studies Pertinent to Efficacy

In the NDA submission, the sponsor indicated that their efficacy analysis of schizophrenia was based on positive results from four completed 6-week, placebo-controlled clinical studies in schizophrenia: Studies D1050006, D1050196, D1050229 and D1050231. The sponsor also included their failed study (Study D1050049) as part of the NDA submission.

1) Study # D1050006: This study enrolled 149 patients (about 50/arm). It was conducted in 15 centers in the US. The sponsor claims that lurasidone was statistically superior to placebo at doses of 40 and 120 mg/day as measured by change from baseline to endpoint in BPRS derived total scores.
2) Study # D1050196: This study enrolled 180 patients (about 90/arm). It was conducted in 22 centers in the US. The sponsor claims that lurasidone 80 mg was statistically superior to placebo as measured by change from baseline to endpoint in BPRSd total scores.
3) Study # D1050229: This study enrolled 500 patients (about 125/arm). It was conducted in 48 centers in the US, Europe and Asia. The study consisted of three fixed doses of lurasidone (40, 80 and 120 mg/day) vs. placebo. The sponsor reports that lurasidone was statistically superior to placebo at 80 mg/day dose as measured by change from baseline to endpoint in PANSS total scores. The sponsor also reports that superiority of lurasidone 80 mg/day vs. placebo was demonstrated on the key secondary variable, CGI-S. However, it should be noted that the 40 and 120 mg/day doses did not separate from placebo.
4) Study #D1050231: This study enrolled 478 patients (about 120/arm). This study evaluated efficacy and safety of two fixed doses of lurasidone (40 and 120 mg/day) as compared to placebo. The study design is almost the same as Study #D1050229, except that it has an active-control arm

(olanzapine 15 mg/day). The primary endpoint is the change from baseline to endpoint in PANSS total score. The sponsor reports positive efficacy of lurasidone at both 40 and 120 mg doses as compared to placebo in this study.
5) Study #D1050049: This study enrolled approximately 350 patients (about 70/arm). The study consisted of three fixed doses of lurasidone (20, 40 and 80 mg/day), active-control (haloperidol 10 mg/day) and placebo. The sponsor reports this as a failed study because all treatment arms including haloperidol did not separate from placebo.

Our review of efficacy of lurasidone in the acute treatment of schizophrenia was focused on results of 4 short-term placebo-controlled studies which were claimed by the sponsor to be positive. The primary statistical reviewer, Dr. Kordzakhia, in his statistical review (dated 9/7/10) indicated that lurasidone doses (fixed doses of 40 mg, 80 mg and 120 mg) were observed to show statistical significance as compared to the placebo-treated group in short-term treatment of adult patients with schizophrenia. According to the clinical review (dated 9/10/10), Dr. Alfaro, the primary clinical reviewer, considered Study D1050196 (lurasidone 80 mg) and Study D1050231 (lurasidone 40 mg, lurasidone 120 mg) to be positive in support of the indication. However, she did not consider results from Study D1050006 (because of high discontinuation rate) and Study 1050229 (efficacy signal predominantly from non-US sites) in support of lurasidone's efficacy.

I would briefly describe the study design, then discuss the primary efficacy analysis results of the 4 short-term placebo-controlled efficacy studies and give my comment for each study in the subsections below. I would just summarize the results from the failed study 0049 because this failed study was not reviewed in detail. The following table (Table 1) lists the study duration, dosage use, patient population studied, primary efficacy measure and my overall assessment of study result in each of these short-term efficacy studies.

Table 1 - List of 5 short-term, double-blind, placebo-controlled studies: Study Design and Overall Result

Study	Duration	Population Studied (N)	Lurasidone Dose	Active Control (Dose)	Primary Efficacy Measure & Analysis	My Interpretation of Results (vs. Placebo) and Comments
D1050006	6 weeks	Schizophrenia, US (N=149)	2 Fixed Doses 40 mg/day 120 mg/day	None	BPRSd Total Score (LOCF)	Supportive (small sample; low completion rate)
D1050049	6 weeks	Schizophrenia, US (N=358)	3 Fixed Doses 20 mg/day 40 mg/day 80 mg/day	Haloperidol (10 mg/day)	BPRSd Total Score (LOCF)	Failed
D1050196	6 weeks	Schizophrenia, US (N=180)	1 Fixed Dose 80 mg/day	None	BPRSd (LOCF)	Positive
D1050229	6 weeks	Schizophrenia, Multiregional (N=500)	3 Fixed Doses 40 mg/day 80 mg/day 120 mg/day	None	PANSS Total Scores (MMRM)	Positive (only 80 mg dose; geographic differences: greater treatment effect in non-US)
D1050231	6 weeks	Schizophrenia, Multiregional, (N=478)	2 Fixed Doses 40 mg/day 120 mg/day	Olanzapine (15 mg/day)	PANSS Total Scores (MMRM)	Positive (greater treatment effect with olanzapine; geographic differences: greater treatment effect in Colombia)

7.2 Summary of Studies Pertinent to Efficacy Claim in Acute Treatment of Schizophrenia

7.2.1 Study D1050006

This study was a 6 week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, two fixed-dose study of lurasidone in adult patients who met the diagnosis of schizophrenia according to the DSM-IV criteria. At screening, patient had to have BPRSd total score of $\geq$ 42 (as extracted from the PANSS); a score of at least 4 on 2 or more items of the positive symptom subcluster on the PANSS; and CGI-S $\geq$ 4 for study enrollment. Following the single-blind placebo washout period of 3-7 days, eligible patients were randomized to lurasidone 40 mg/day, 120 mg/day or placebo, given once daily in the morning following breakfast during the 6-week double-blind treatment period. Patients randomized to lurasidone 40 mg/day were given this dose on Day 1. Patients randomized to lurasidone 120 mg/day were titrated to this dose over a 6-day period starting with 80 mg/day on Day 1, 80 or 120 mg on Days 2-5 and 120 mg on Day 6. Patients were hospitalized for the placebo wash-out and at least the first 2 weeks of the double-blind treatment period.

The study was conducted in 15 centers in the U.S. Among 149 subjects randomized in this study, only 51 subjects completed the study. Approximately two-thirds discontinued from the study: 70% (35/49) in the placebo, 68% (34/49) in the lurasidone 40 mg and 59% (29/47) in the lurasidone 120 mg treated-group. About 50% had dropped out by the midpoint of the study (Day 21). The common reason for discontinuation included withdrawal of consent (25%) in both the lurasidone and placebo groups and lack of efficacy (32% in the placebo, 22% in lurasidone 40 mg, and 12% for lurasidone 120 mg). Among the AE dropouts, the lurasidone-treated groups had 12% as compared to 4% in the placebo group.

Patients enrolled were between the ages of 18 and 61 years old with a mean age of 40 years. The majority (3/4) of patients were males. Fifty percent were African-American and 40 % were Caucasian in this study. Treatment groups were comparable at baseline on the demographic variables. The subtype of schizophrenia was predominantly paranoid subtype (90%) and baseline disease severity, as measured by the PANNS and CGI-S, were similar between the groups. The placebo, lurasidone 40 mg and 120 mg groups had mean baseline BPRSd total scores of 54.4, 54.6, and 52.5, respectively.

Allowable concomitant medications during the double-blind period included benzodiazepines [lorazepam ($\leq$ 8 mg/24 hours), temazepam ($\leq$30 mg/24 hours)] and zolpidem for no more than 5 consecutive days. In addition, 42.3% of patients were noted to have concomitant antipsychotics during the clinical trial. Such use was described in Dr. Alfaro's clinical review (see section 6.1). It should, however, be noted that when the sponsor used the same algorithm of concomitant medication use defined in other 3 pivotal trials, the sponsor found that n = 10 (6.7%) of patients received concomitant antipsychotics and 8 of those 10 had received the concomitant antipsychotic on the last day of receiving the double-blind study drug.

Efficacy Assessments included the PANSS, CGI-S and CGI-I. The primary endpoint was the BPRS derived from the PANSS [BPRSd] for the ITT population. The sponsor did not prespecify any key secondary variable for this study. The LOCF analysis was considered primary; the OC analysis was also used. The ANCOVA was the statistical model employed and included treatment group and pooled center as main effects and baseline BPRS scores as a covariate. The primary efficacy analysis

was based on the intent-to-treat analysis sample, that is all patients randomized who received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one evaluation on treatment. For multiplicity adjustment, pairwise comparisons (lurasidone 40 mg vs. placebo, and lurasidone 120 mg vs. placebo) were performed using a Dunnett's test at a 2-sided significance level of 0.05. Dr. Kordzakhia has confirmed the sponsor's primary efficacy results (Table 2).

Table 2 – Primary Analysis: Change from baseline to endpoint BPRSd total score in the ITT population (LOCF)

Treatment Groups (N)	Mean Baseline BPRSd total score (SD)	LS Mean Change from Baseline to Week 6 (SE)	Difference in LS mean changes between lurasidone and placebo	p-value (drug vs. placebo)
Lurasidone 40 mg (N=49)	54.6 (9.1)	-9.4 (1.6)	-5.6	0.018
Lurasidone 120 mg (N=47)	52.5 (7.6)	-11 (1.6)	-6.7	0.004
Placebo (N=49)	54.4 (8.3)	-3.8 (1.6)		

Secondary sensitivity analyses were also performed. According to the observed cases analysis (Tables 3), the lurasidone 40 and 120 mg groups did not show statistically significant treatment effect. Based on the PANSS total scores (Table 4), the lurasidone 40 mg did not also show statistical significance.

Table 3 - Change from Baseline to Endpoint in BPRSd (OC Analysis)

	Lurasidone 40 mg (n = 17)	Lurasidone 120 mg (n = 19)	Placebo (n = 17)
Baseline mean (SD)	54.2 (8.9)	52.7 (7.6)	54.7 (8.1)
LS mean (SE)	-17 (2.1)	-15 (2.1)	-9.9 (2.4)
Difference between lurasidone and placebo	-6.7 (3.1)	-4.9 (2.9)	
p-value	0.062	0.164	

Table 4 – Change from baseline to endpoint in PANSS total score (LOCF)

	Lurasidone 40 mg (n = 49)	Lurasidone 120 mg (n = 47)	Placebo (n = 49)
Baseline mean (SD)	92.2 (15.7)	90.0 (13.4)	93.9 (15.9)
LS mean (SE)	-14 (2.7)	-17 (2.7)	-6.2 (2.7)
Difference between lurasidone and placebo	-7.6 (3.67)	-11 (3.74)	
p-value	0.076	0.009	

Dr. Korzakhia conducted additional analyses of the Sponsor's data including MMRM analysis of the primary endpoint (BPRSd) and LOCF analysis of the primary endpoint by visit. The details are presented in his review. The MMRM results were found to be positive.

Table 5 - Change from Baseline to Endpoint in BPRSd (MMRM Analysis)

	Lurasidone 40 mg (n = 17)	Lurasidone 120 mg (n = 19)	Placebo (n = 17)
LS mean (SE)	-13.4 (2.1)	-13.4 (2.0)	-4.1 (2.1)
Difference between lurasidone and placebo	-9.3 (3.0)	-9.2 (2.9)	
p-value (unadjusted)	0.0025	0.0022	

In order to see if there is any possible confounding effect of concomitant antipsychotic medication use, data reanalysis was performed after excluding 10 patients. The results are still significant (p-values unadjusted): -6.8, p=0.0015 for the 40 mg vs. placebo; -6.0, p=0.0056 for 120 mg vs. placebo.

Comment:

As can be seen in clinical review, Dr. Alfaro extensively discussed her concerns for lurasidone's efficacy based on the findings in this study. She was mostly concerned about the high discontinuation rate of approximately two-third of study patients. Despite the fact that the study result remains positive in sensitivity analyses (including MMRM and LOCF by visit analysis), Dr. Alfaro continues to express her concerns about high attrition while she noted such results from additional analyses in her clinical review. We have observed in our schizophrenia database which consists of 12,585 individual patient level data from 31 multiregional clinical trials submitted in10 NDA applications between 1993 and 2005, the reported dropout rates ranged from 15% to 70%[1]. While Dr. Alfaro acknowledged that it is not unusual to have high drop-out rates in schizophrenia clinical trials, she referenced that these rates are in the range of 30-50% in drug treatment groups. The discontinuation rate for the lurasidone groups in the 3 other pivotal clinical trials (30-45%) is more consistent with the discontinuation rates generally seen in the schizophrenia trials. These patients in this study had similar severity of clinical symptoms as measured by baseline scores on PANSS or BPRSd compared to the other clinical trials. It is unclear why the discontinuation rate was so high in this clinical trial. Regardless of the reason, I would not entirely agree with Dr. Alfaro's conclusion that this study should not be considered as a pivotal study to support the efficacy of either the 40 mg/day or the 120 mg/day dose of lurasidone in the treatment of schizophrenia. As Dr. Kordzakhia noted in his statistical review, the result from this study should be interpreted with caution because of its low completion rate in this small study. In any case, this will be a matter of judgment based on the overall results from other placebo-controlled studies and prior experience with other antipsychotic drugs. The primary LOCF analysis showed statistically superiority of lurasidone 40 mg and 120 mg doses over placebo. Although the OC analysis and the analysis based on the PANSS total score change did not show the statistical significance, the results are trended to be numerically in favor of lurasidone for both the 40 mg and 120 mg dose groups as compared to placebo. The MMRM analysis showed positive outcome for both 40 and 120 mg doses. I would consider this at least as a supportive study providing efficacy for lurasidone.

7.2.2 Study D1050196

This study was a 6 week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study of lurasidone 80 mg in adult patients who met the diagnosis of schizophrenia according to the DSM-IV criteria. At screening, patient had to have BPRSd total score of $\geq$ 42 (as extracted from the PANSS); a score of at least 4 on 2 or more items of the positive symptom subcluster on the PANSS; and CGI-S $\geq$ 4 for enrollment in the study. Following the single-blind placebo washout period of 3-7 days, eligible patients were randomized to receive either lurasidone 80 mg or placebo, given once daily in the morning following breakfast during the 6-week double-blind treatment period. Patients were hospitalized during the washout period and at least for the first 4 weeks of the double-blind treatment period.

1 Chen YF, Wang SJ, Khin NA, Hung HMJ, Laughren TP. Trial Design Issues and Treatment Effect Modeling in Multi-Regional Schizophrenia Trials. Pharmaceut. Statist, 2010. e.pub ahead of print. May 21, 2010: 1-13. DOI: 10.1002/pst.439

The study was conducted in 22 centers in the U.S. Among 180 subjects randomized in this study, 99 subjects completed the study. Eighty-one discontinued from the study; 48% (43/90) in the placebo, 42% (38/90) in the lurasidone 80 mg treated-group. The common reason for discontinuation included withdrawal of consent (20% in the lurasidone and 10% in the placebo groups) and lack of efficacy (32% in the placebo, 10% in lurasidone). Among the AE dropouts, the lurasidone-treated group had 6.7% as compared to 1.1% in the placebo group.

The majority (3/4) of patients were males. Patients enrolled had a mean age of 41 years. Fifty-seven percent were African-American and 34% were Caucasian. The subtype of schizophrenia was predominantly paranoid subtype (81%). Treatment groups were comparable at baseline on the demographic variables and disease severity. The placebo and the lurasidone 80 mg groups had mean baseline BPRSd total scores of 56.1 and 55.1, respectively.

Allowable concomitant medications during the double-blind period included lorazepam, temazepam, and zolpidem. There were 10 (5.6%) patients who received concomitant antipsychotics during the clinical trial.

Efficacy assessments included the PANSS and CGI-S. The primary endpoint was the BPRS derived from the PANSS [BPRSd] for the ITT population. The sponsor did not pre-specify any key secondary variable for this study. The LOCF analysis was considered primary; the OC analysis was also used. The ANCOVA was the statistical model employed and included treatment group and pooled center as main effects and baseline BPRS scores as a covariate. The primary efficacy analysis was based on the intent-to-treat analysis sample, that is all patients randomized who received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one evaluation on treatment. For multiplicity adjustment, pairwise comparison was performed using a Dunnett's test at a 2-sided significance level of 0.05. Dr. Kordzakhia has confirmed the sponsor's primary efficacy results (Table 6). Sensitivity analyses were also performed.

Table 6 – Primary Analysis: Change from baseline to endpoint BPRSd total score in the ITT population (LOCF)

Treatment Groups (N)	Mean Baseline BPRSd total score (SD)	LS Mean Change from Baseline to Week 6 (SE)	Difference in LS mean changes between lurasidone and placebo	p-value (drug vs. placebo)
Lurasidone 80 mg (N=90)	55.1 (6.0)	–8.9 (1.3)	-4.7	0.0118
Placebo (N=90)	56.1 (6.8)	–4.2 (1.4)		

Comment:

Both Dr. Alfaro and Dr. Kordzakhia considered this study as a positive study for efficacy of lurasidone 80 mg in the acute treatment of schizophrenia.

7.2.3 Study D1050229

This study was a 6 week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study of lurasidone (40 mg/day, 80 mg/day, or 120 mg/day) in adult patients who met the diagnosis of schizophrenia according to the DSM-IV criteria using the Mini-International Neuropsychiatric Interview Plus (MINI Plus). At screening/baseline, patient had to have PANSS total score $\geq$ 80; a score of $\geq$ 4 on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content and suspiciousness; CGI-S $\geq$ 4 to be eligible

for study enrollment. Following the single-blind placebo washout period of 3-7 days, patients were randomized to lurasidone 40 mg/day, 120 mg/day or placebo, given once daily in the morning with a meal or within 30 minutes after eating during the 6-week double-blind treatment period. For patients randomized to lurasidone 40 or 80 mg/day, dosing was initiated at the full dose on Day 1. Patients randomized to lurasidone 120 mg/day were titrated to this dose over a 6-day period starting with 80 mg/day on Day 1-3 then 120 mg thereafter. Patients were hospitalized for the placebo wash-out and also for 3 weeks of the double-blind treatment period.

This study was conducted in 48 foreign and U.S. sites: France (1), India (6), Malaysia (2), Romania (5), Russia (7), Ukraine (6), and U.S. (21). A total of 500 patients were randomized in this study: 125 to lurasidone 40 mg, 123 to lurasidone 80 mg, 124 to lurasidone 120 mg and 128 to placebo. Thirty-four percent (172/500) discontinued the study: 33% (41) in the lurasidone 40 mg, 30% (37) in the lurasidone 80 mg and 31% (39) in the lurasidone 120 mg treated-groups and 43% (55) in the placebo. The common reason for discontinuation included insufficient clinical response and withdrawal of consent. Among the AE dropouts, the lurasidone-treated groups had about 7% as compared to 2% in the placebo group.

Patients enrolled were between the ages of 18 and 72 years old with a mean age of 39 years. The majority of patients were males (~70%). Approximately half of the patients were Caucasians and one-third were African-American in this study. Treatment groups were comparable at baseline on the demographic variables. The groups were also balanced with regard to geographic region: Asia (15% lurasidone groups vs. 15% placebo group), Europe (30% lurasidone groups vs. 31% placebo group) and the United States (56% lurasidone groups vs. 54% placebo). The subtype of schizophrenia was predominantly paranoid subtype (>85%) and baseline disease severity, as measured by the PANSS (mean total score 96) and CGI-S (mean score 5), were similar between the groups.

Allowable concomitant medications during the double-blind period included lorazepam, temazpam and zolpidem. About 15% of patients had taken concomitant antipsychotics during this clinical trial.

The primary efficacy variable was the PANSS total score. Secondary efficacy variables included the PANSS negative subscale, the BPRS positive symptom score, and the CGI-severity score. The prespecified key secondary endpoint was change from baseline in the CGI-S. The primary efficacy analysis was the change from baseline PANSS total score at week 6, as evaluated using a MMRM model for the ITT population under the assumption of an unstructured covariance matrix. The model included factors for pooled center, time, baseline PANSS total score, treatment, and treatment-by-time interaction. The Hommel-based tree-gatekeeping procedure was applied to p-values from the MMRM analysis to control the family-wise Type I error rate at 5% by taking into account multiple doses and multiple primary and key secondary endpoints.

Our statistical reviewer has confirmed the sponsor's primary efficacy and key secondary results. Sensitivity analyses were also performed.

Table 7 – Primary Analysis: Change from baseline to endpoint PANSS total score in the ITT population (MMRM)

Treatment Groups	Mean Baseline Total Score (SD)	LS Mean Change (SE)	Difference in mean changes (drug-placebo)	p-value (drug vs. placebo)
Lurasidone 40 mg (N=121)	96.5 (11.5)	-19.2 (1.7)	-2.1	0.59
Lurasidone 80 mg (N=118)	96.0 (10.8)	-23.4 (1.8)	-6.4	0.03
Lurasidone 120 mg (N=123)	96.0 (9.7)	-20.5 (1.8)	-3.5	0.39

Placebo (N=124)	96.8 (11.1)	-17.0 (1.8)		

The results showed lurasidone 80 mg was statistically significantly better than placebo in both the primary efficacy and the key secondary endpoints. Doses of 40 mg and 120 mg failed to demonstrate efficacy for either of the two endpoints.

Comment:

Dr. Kordzakhia considered this study as a positive study for efficacy of lurasidone 80 mg. As can be seen in Dr. Alfaro's clinical review (section 6.1), she noted statistically significantly positive efficacy results of lurasidone 80 mg/day dose according to the pre-specified primary analysis. However, she discussed her concerns for lurasidone's efficacy based on the findings from exploratory geographic subgroup analyses. Due to the discrepancies in lurasidone 80 mg effect sizes between the US and Non-US groups, Dr. Alfaro considered the overall efficacy of lurasidone in this clinical trial to be marginal. The pharmacometric reviewer, Dr. Bhattaram, also evaluated the exposure analysis and noted that the lurasidone concentrations were higher for each fixed dose group in the Non-US sites compared to the US sites for patients completing the clinical trial which may be due to differences in baseline weights (higher mean weight in US sites). As mentioned in our recent statistical treatment effect modeling paper[1], a slightly higher mean baseline PANSS total score in the non-US sites and a higher mean body weight in US sites could be some important contributing factors which might be able to explain such regional differences. Given the fact that the sole US study D1050196 showed positive efficacy for the 80 mg dose, and in other multiregional study D1050221 the treatment effect appeared to be numerically in favor of lurasidone in both US and non-US, I am less troubled about the finding of geographic differences as part of exploratory subgroup analyses in this multiregional study (also see section 7.3.1 of this memo). I would consider this study as a positive study for efficacy of lurasidone 80 mg/day in the acute treatment of schizophrenia.

7.2.4 Study 1050231

This study was a 6 week, multicenter, randomized, double-blind, placebo and active-controlled (olanzapine 15 mg/day), parallel-group, fixed-dose study of lurasidone (40 or 120 mg/day) in adult patients who met the diagnosis of schizophrenia according to the DSM-IV criteria using the MINI Plus. At screening/baseline, patient had to have PANSS total score $\geq$ 80; a score of $\geq$ 4 on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content and suspiciousness; CGI-S $\geq$ 4 to be eligible for study enrollment. Following the single-blind placebo washout period of 3-7 days, patients were randomized to lurasidone 40 mg/day, lurasidone 120 mg/day, olanzapine 15 mg/day or placebo, given once daily in the morning with a meal or within 30 minutes after eating during the 6-week double-blind treatment period. For patients randomized to lurasidone 40 or 120 mg/day, dosing was initiated at the full dose on Day 1. Patients randomized to olanzapine were started with 10 mg/day for Day 1-7 then 15 mg/day thereafter. Patients were hospitalized for the placebo wash-out and also for 3 weeks of the double-blind treatment period.

This study was conducted in 52 centers consisting 25 US and 27 foreign sites: Columbia (5), India (14), Lithuania (4), and Philippines (4). Overall, 478 patients were randomized in this study: 120 to lurasidone 40 mg, 119 to lurasidone 120 mg, 123 to olanzapine 15 mg and 116 to placebo. Thirty-eight percent (180/478) discontinued the study: 36% (43) in the lurasidone 40 mg, 45% (53) in the

lurasidone 120 mg, 32% (39) in the olanzapine 15 mg and 39% (45) in the placebo-treated groups. The common reason for discontinuation included insufficient clinical response and withdrawal of consent. Among the AE dropouts, the 120 mg lurasidone-treated groups had about 10% as compared to 5% in the placebo group.

Patients enrolled were between the ages of 18 and 68 years old with a mean age of 38 years. The majority of patients were males (78%). Approximately one-third of the patients were White, one-third were Black and 1/4 were Asian in this study. Treatment groups were comparable at baseline on the demographic variables. The treatment groups were also balanced with regard to geographic region: Asia (15%), Europe (30%) and the United States (~55%). The subtype of schizophrenia was predominantly paranoid subtype (>85%) and baseline disease severity, as measured by the PANSS (mean total score around 96) and CGI-S (mean score 5), were similar between the groups.

Allowable concomitant medications during the double-blind period included lorazepam ($\leq$ 6 mg/day), zolpidem ($\leq$ 10 mg/day), zolpidem CR ($\leq$ 12.5 mg/day) and temazepam ($\leq$ 30 mg/day). About 8% of patients had taken concomitant antipsychotics during this clinical trial.

Efficacy assessments included the PANSS and CGI-S. The primary efficacy variable was the PANSS total score. The pre-specified key secondary endpoint was change from baseline in the CGI-S. The primary efficacy analysis was the change from baseline PANSS total score at week 6, as evaluated using a MMRM model for the ITT population under the assumption of an unstructured covariance matrix. The model included factors for pooled center, time, baseline PANSS total score, treatment, and treatment-by-time interaction. The Hommel-based tree-gatekeeping procedure was applied to p-values from the MMRM analysis to control the family-wise Type I error rate at 5% by taking into account multiple doses and multiple primary and key secondary endpoints.

Our statistical reviewer has confirmed the sponsor's primary efficacy and key secondary results. Sensitivity analyses were also performed.

Table 8 – Primary Analysis: Change from baseline to endpoint PANSS total score in the ITT population (MMRM)

Treatment Groups	Mean Baseline Total Score (SD)	LS Mean Change (SE)	Difference in mean changes (drug-placebo)	p-value (drug vs. placebo)
Lurasidone 40 mg (N=118)	96.6 (10.7)	-25.7 (2.0)	-9.7	0.002
Lurasidone 120 mg (N=118)	97.9 (11.3)	-23.6 (2.1)	-7.5	0.022
Olanzapine 15 mg (N=121)	96.3 (12.2)	-28.7 (1.9)	-12.6	<0.001
Placebo (N=114)	95.8 (10.8)	-16.0 (2.1)		

The result showed both lurasidone treatment arms (40 mg and 120 mg) were statistically significantly superior to placebo in the primary efficacy and the key secondary endpoints as well. It should be noted that the active control, Olanzapine 15 mg, showed better treatment effect compared to lurasidone and placebo arms.

Comment:

Both Drs. Alfaro and Kordzakhia considered this study as a positive study for efficacy of lurasidone 40 and 120 mg in the acute treatment of schizophrenia. I agree with them.

7.2.5 Study 1050049

Study D1050049 was a 6-week, multicenter, randomized, fixed-dose, double-blind, parallel group, placebo- and active comparator trial. Patients were randomized to lurasidone 20 mg, lurasidone 40 mg, lurasidone 80 mg, haloperidol 10 mg or placebo. This study was conducted in 33 sites in the U.S.

Table 9 – Primary Analysis: Change from baseline to endpoint BPRSd total score in the ITT population (LOCF)

Treatment Groups	Mean Baseline Total Score	LS Mean Change (SE)	Difference in mean changes (drug-placebo)	p-value (drug vs. placebo)
Lurasidone 20 mg (N=71)	55.4	-5 (1.4)	5.2	0.36
Lurasidone 40 mg (N=67)	54.8	-5.2 (1.4)	5.1	0.44
Lurasidone 80 mg (N=71)	54.5	-8.0 (1.4)	-1.28	1.00
Haloperidol 10 mg (N=72)	56.1	-9.8 (1.4)	-3.7	0.75
Placebo (N=72)	56.8	-7.9 (1.4)		

Comment:

This study was a failed study, neither the active-control (haloperidol) nor lurasidone separated from placebo on the primary efficacy variable.

7.3 Comments on Other Important Efficacy Issues

7.3.1 Subgroup Analyses: Clinical Predictors of Response

Exploratory subgroup analyses were conducted to evaluate the effect of the following variables on treatment response for all 4 clinical studies:

- Gender (Male, Female)
- Race (Caucasians, Blacks, Other)

The results showed the treatment effect appeared to be numerically in favor of lurasidone as compared to placebo across subgroups in all 4 studies except for the African American racial subgroup for the 120 mg treatment arm in Study D1050229.

Additional exploratory subgroup analyses were conducted for two multi-regional studies D1050229 and D1050231 based on:

- Age (<55, ≥55 yrs)
- Geographic Regions (US vs. non-US; by region analysis)

The subgroup analysis for age (< 55, ≥ 55 years) did not indicate differential response, though the numbers of patients in the ≥ 55 years of age group were very small.

Geographic subgroup analyses

Studies D1050006 and D1050196 were conducted solely in the US. Study D1050229 was conducted in 48 sites including 21 U.S. and 27 foreign (Europe and Asia) sites: France (1), India (6), Malaysia (2), Romania (5), Russia (7), and Ukraine (6). The numbers of subjects were fairly well balanced between these geographic regions with n = 268 in US sites and n = 218 in Non-US sites. Study D1050231 was conducted in 48 sites including 25 US and 27 foreign sites: Columbia (5), India (14), Lithuania (4), and Philippines (4). Approximately 60% of patients were in US (n = 281) and 40% (n = 190) in non-US sites.

In both studies (studies D1050229 and 1050231), mean baseline PANSS total scores were slightly higher in the non-US sites. Mean baseline body weight was higher in the US patients.

As can be seen the tables which were extracted from Dr. Kordzakhia's statistical review, it appeared that the observed treatment effects were predominantly from non-US patients regardless of the dose in study D1050229. As commented by Dr. Alfaro in her clinical review, none of the lurasidone treatment groups separate from placebo for US sites in this study. The lurasidone treatment groups separate from placebo for 2 of the 3 dose groups in the Non-US sites. These differences in efficacy between US and non-US sites are based largely on the response in the lurasidone treated group as the placebo responses were quite similar between the two.

Table 10 - Study D1050229 Subgroup Analysis: PANSS Total Score LS mean Change from Baseline (MMRM)

Subgroup	Lurasidone 40 mg		Lurasidone 80 mg		Lurasidone 120 mg		Placebo	
Region	n	LS mean change	n	LS mean change	n	LS mean change	n	LS mean change
US N=281	69	-17.0 (2.4)	63	-20.1 (2.4)	69	-17.3 (2.4)	67	-18.1 (2.4)
Non-US N=190	52	-22.1 (2.6)	55	-27.1 (2.5)	54	-24.3 (2.6)	57	-16.5 (2.6)

Among the geographic regions, the sites in Europe had ~40 patients per treatment group. The treatment effect was observed mostly in the European sites. The treatment effect (lurasidone-placebo difference) was significant: -8.3 for lurasidone 40 mg, -10.6 for lurasidone 80 mg and -7.5 for lurasidone 120 mg. The sites in Asia were small with ~20 patients per treatment group. The treatment difference was -1.5 for lurasidone 40 mg, -11.1 for lurasidone 80 mg ($p = 0.081$) and -10.2 for lurasidone 120 mg. By excluding data from Russian/Ukraine from non-US sites, the 40 mg lurasidone dose did numerically worse than the placebo: +1 for lurasidone 40 mg, -10 for lurasidone 80 mg and -6.5 for lurasidone 120 mg.

In study D1050231, the treatment effect appeared to be numerically in favor of lurasidone when compared with placebo for both the US and non-US, although the observed treatment effect tends to be larger in non-US as observed in study D1050229. It should, however, be noted that the effect in both drug-treated groups and placebo group were larger in non-US than the US. In this study, the South America (Colombia sites) contributed significantly to the overall positive results in the by region subanalysis.

Table 11 - Study D1050231 Subgroup Analysis: PANSS Total Score LS Mean Change from Baseline (MMRM)

Subgroup	Lurasidone 40 mg		Lurasidone 120 mg		Olanzapine 15 mg		Placebo	
Region	n	LS mean change	n	LS mean change	n	LS mean change	n	LS mean change
US N=281	69	-20.0 (2.3)	72	-17.5 (2.4)	73	-23.0 (2.1)	67	-12.8 (2.3)
Non-US N=190	49	-32.5 (3.1)	46	-32.6 (3.5)	48	-36.2 (3.2)	47	-21.2 (3.4)

The pharmacometric reviewer, Dr. Bhattaram, conducted the PK/PD exposure analyses between the regions for studies D1050229 and 1050231. It was noted that the lurasidone concentrations were higher for each fixed dose group in the Non-US sites compared to the US sites for patients

completing the clinical trial. It was commented that the differences in concentrations between the US and Non-US sites may be due to differences in baseline weights (i.e., higher mean weight in US sites than non-US). Dr. Alfaro noted in her clinical review that, although there were differences in serum concentrations between the geographic regions, this does not fully explain the discrepancy in effect between the regions. The 40 mg dose in the non-US sites performed more robustly than the 120 mg dose in the US sites: LS mean -20.3 vs. -14.9, LS mean difference from placebo –6.5 vs. 0.2 in Study 229; and LS mean -30.7 vs. -14.2, LS mean difference from placebo -10.5 vs. -3.8 in Study 231. Dr. Alfaro opined that the CYP3A4 activity would likely be one of the possible contributing factors for this drug. However, the CYP3A4 status was not ascertained in both studies to evaluate further on this issue.

7.3.2 Dose Response Relationship

As mentioned before, there is no consistent dose-response data for this drug based on the available data from 4 short-term, efficacy studies. There was some evidence for the 120 mg dose in D1050231, but this dose was less optimal than the 40 mg dose. For D1050196 and D1050229, only 80 mg/day dose was effective. In D1050229 which involved all 3 doses, no benefit was seen for 40 and 120 mg/day dose. Overall, no additional benefit was seen in the high dose, 120 mg/day.

In terms of exposure analysis in those patients who completed the clinical trials, the pharmacometrics reviewer found a trend in changes in PANSS total scores and higher lurasidone AUC in study D1050231 but not in study D1050229 (see clinical pharmacology/pharmacometrics review). No PK data available for study D1050006 to conduct exposure analysis.

7.3.3 Size of Treatment Effect

The treatment effect sizes that were statistically significantly different from placebo seemed to be comparable to effect sizes noted in clinical trials in schizophrenia for approved antipsychotics at effective doses.

Table 12 – LS mean difference (drug-placebo difference) in change from baseline to primary efficacy endpoint total score in Fixed Dose Short-term Schizophrenia Trials

Study	Primary efficacy/method	Lurasidone 20 mg	Lurasidone 40 mg	Lurasidone 80 mg	Lurasidone 120 mg	Olanzapine 15 mg
D1050006	BPRSd (LOCF)	-	-5.6*	-	-6.7*	-
D1050196	BPRSd (LOCF)	-	-	-4.7*	-	-
D1050229	PANSS (MMRM)	-	-2.1	-6.4*	-3.5	-
D1050231	PANSS (MMRM)	-	-9.7*	-	-7.5*	-12.6*

* Statistically significant difference as compared to placebo.

7.3.4 Duration of Treatment

There were no pertinent data from adequately designed and well-controlled studies to address the long-term efficacy of lurasidone in this submission. We should ask the sponsor to conduct a maintenance study as post-marketing commitment should the division decide to approve this NDA for acute treatment in schizophrenia.

7.3.5 Secondary Efficacy Variables

Two of the pivotal trials, D1050229 and D1050231, had the CGI-S as a prespecified key secondary variable, and the results showed in favor of lurasidone as compared to placebo. There was no pre-specified key secondary variable in other two studies D1050006 and D105019; CGI-S was included as a secondary efficacy variable. Dr. Kordzakhia did not find CGI-S data at intermittent visits. Dr. Kordzakhia, however, noted in his statistical review that the finding of very small p-values for change from baseline to endpoint in CGI-S in these two studies in that any application of multiple testing procedures would still lead to a statistical significance.

(b) (4)

7.4 Conclusions Regarding Efficacy Claim in Acute Treatment of Schizophrenia

In my opinion, the sponsor has provided sufficient evidence to support the efficacy claim of lurasidone in the acute treatment of schizophrenia. Given more convincing and replicable data for the 80 mg dose, I am inclined to accept 80 mg as the target dose for now. There is some support for 40-120 mg doses. I may not object use of the 40 mg dose; perhaps, it is a matter of judgment looking at the overall results. No additional benefits seen at the high dose of 120 mg.

According to the email communication dated 9/7/10, the sponsor also completed another multi-regional (US and Colombia) placebo and active-controlled (quetiapine XR 600 mg) study (D1050233) of lurasidone doses 80 mg and 160 mg (N=488). Preliminary result indicates that the statistical superiority of both lurasidone doses. Although we have not yet had an opportunity to review this study data as the sponsor will not submit these data as an NDA amendment to the original NDA submission, knowing this preliminary finding, I am less hesitant to make my recommendation of approval of the drug based on the submitted efficacy data.

While I agree with Dr. Alfaro that we should review the sponsor's data to better establish efficacy at the lower end based on the result from their ongoing additional non-IND study D1001002 (N=460) in Asia region investigating lurasidone 40 mg and 80 mg doses as compared to the placebo and the active comparator (risperidone 4 mg/day), I do not think we need to review this study to make the efficacy determination. The Agency leadership should come into judgment on this matter.

8.0 SAFETY

8.1 General Safety Considerations

The evaluation of safety data from the lurasidone clinical development program included the sponsor's submitted safety data in the original submission (as of July 1, 2009) for 2675 subjects (323 healthy volunteers and 2352 patients with schizophrenia) who received lurasidone in Phase 1, 2 and 3 studies in single doses ranging from 0.1 – 100 mg, and repeated doses up to 120 mg/day for 6 weeks of double-blind treatment to 12 months of open-label treatment (including up to 600 mg/day for less than one week). In phase 2/3 short-term placebo-controlled studies, 1004 patients were exposed to lurasidone. The integrated safety summary was focused on a review of data for 2094 lurasidone-treated subjects in all phase 2/3 trials. A total of 488 subjects were exposed for at

least 6 months and 174 subjects were exposed for at least 12 months, covering a total of 566.9 patient-years of exposure.

Dr. Alfaro's clinical review also covered the 4 month safety update data submitted on April 28, 2010 which included deaths and SAE cases from two recently completed studies and several ongoing studies (including 3 bipolar depression studies). The cut off date for the safety update submissions was December 1, 2009. In the pooled safety datasets for Phase 2/3 trials, 503 patients had cumulative exposure $\geq$ 24 weeks and 225 patients had cumulative exposure $\geq$ 52 weeks.

8.2 Safety Findings and Issues of Particular Interest

8.2.1 Deaths, Serious Adverse Events and AE dropouts

Deaths

Among a total of 18 deaths occurred in the clinical trials, 13 were in patients receiving lurasidone and 2 deaths remain blinded to study drug. Of these 15 deaths,

- 4 were sudden deaths. In the 3 cases of sudden deaths in which patients were receiving lurasidone, deaths occurred after receiving lurasidone for 24 days (post-mortem CT showed venous bleeding in the brain stem and pericardial bleeding), 210 days (autopsy showed pulmonary embolism and myocardial infarction) and 360 days (also received haloperidol injection on the same day when the last dose of study drug was given). In the one case in which the patient received blinded study medication, the death occurred after receiving study medication for > 150 days and this case was reclassified to massive GI bleeding from a large gastro-duodenal ulcer.

  Among these 4 cases, the case of 49 yr old Asian female (D1001002-0107-0004) with normal baseline labs and ECG complaint of giddiness (and clutching her head) and noted to have skin excoriation/bleeding in upper extremities and anorexia during the study drug treatment, died on day 24. Since no autopsy was performed, no specific cause of death was identified. It is uncertain on how to interpret the post-mortem CT scan finding of brain-stem venous bleeding but one cannot rule out bleeding from pre-existing AV malformation in a middle aged person. There was insufficient information to reach any conclusion about the cause of death in this 49 yr old. In my opinion, this is one case in which the cause of death and the relationship to study drug cannot be fully evaluated.

- 7 with preexisting disease, serious medical events that are considered as relatively common background events or contributing factors or other causes not attributable to study drug: hypertensive heart disease, metastatic lung cancer, septic shock, accidental thermal burns, heroin overdose, traffic accident, and myocardial infarction (this last case remained blinded to study drug but per autopsy, cause of death was probable cardiac arrhythmia due to congenital artery anomaly/hypoplasia of right coronary artery and cardiomegaly as contributing factor). There was no obvious pattern to any of these deaths.

- 4 died as a result of completed suicide were taking lurasidone at the time of the event. There were no suicides in patients on placebo or active control. The distribution of time of treatment to occurrence of suicide ranged from 20 up to 223 days.

It appears that most if not all deaths on lurasidone occurred during the open-label treatment and did not likely seem to be causally related to treatment with lurasidone. They were mostly related to the illnesses under treatment or with other medical conditions or confounding factors. All 4 of the sudden deaths were not unexplained sudden deaths (i.e., not cardiac sudden death). This drug did not seem to exhibit QT signal based on the QT study and ECG findings in phase 2/3 studies.

In addition to the 4 completed cases of suicide, in the phase 2/3 short-term placebo-controlled trials, suicidal ideation reported as an adverse event occurred in 0.4% (4/1004) of patients receiving lurasidone and 0.2% (1/455) of patients receiving placebo. The sponsor applied the Columbia Classification Algorithm of Suicidal Assessment (C-CASA) across all clinical trials with lurasidone. For all phase 2/3 clinical trial database, suicidal ideation (0.7%, 14/2094), completed suicide (0.2%, 4/2094), suicide attempt (0.1%, 3/2094), suicide behavior (0.1%, 3/2094), self-injurious behavior (< 0.1%, 2/2094) were noted for lurasidone. Given suicide is a common event in schizophrenia trials and the lifetime risk of suicide in schizophrenia is about 10-15%, in my view, no further analyses would be necessary. The standard suicidality language for antipsychotic drug labeling as proposed would be sufficient for lurasidone.

Non-Fatal SAEs

In the phase 2/3 placebo-controlled trials, approximately 5% of patients in the lurasidone treatment groups and the placebo groups experienced serious adverse events. The most common serious adverse events were psychotic disorder/schizophrenia occurring with similar frequencies in the lurasidone (4%) and placebo (3.3%) groups.

The majority of serious adverse events were related to the illnesses under treatment or with other medical conditions or confounding factors. Most of the SAEs were exacerbation of psychotic symptoms and no further comments will be made in this review as these cases represent underlying illness being treated. In general, antipsychotic drugs lower the seizure threshold. It is not uncommon to see SAE cases of seizures/convulsions reported in the NDAs so as 4 in the lurasidone trials (see section 8.2.4 of this review memo). Given the high incidence of suicide and cardio-vascular morbidity (CAD, MI, CVA) in schizophrenia patients, these types of SAEs reported were largely the same as what we generally seen in the NDA submission of antipsychotic trials. There were events not likely attributable as study drug-related as they were relatively common medical background events (e.g., MI, CVA, uterine leiomyoma, cholecystitis, pneumonia) and other factors (e.g., overdose, accidents/injury). The relatively few serious adverse events that were possibly or probably related to treatment with lurasidone included dystonia/akathisia and increased CK.

Based on my understanding of the way Dr. Alfaro presented the cases and described her safety AE profile assessment related to data quality in her review, she seems overly cautious in interpreting these cases and the findings. Upon my review of these cases from a clinical perspective, they appear less troubling to me (see also discussion under section 11.1). Some of the events were noted to occur in open-label phase and difficult to interpret the causality. I would briefly reiterate the following cases that I consider clinically relevant and will make my points although more concern with several of the non-fatal SAE cases were elaborated by Dr. Alfaro in her clinical review and their case reports/narratives were described in depth.

- Two cases of respiratory failure were noted. One case (D1001018-0072) involved a 41 yr old who died secondary to septic shock noted on autopsy. The second case (D1001001-00484) was associated with a high blood concentration of nitrazepam and the event was highly likely to have been benzodiazepine-related respiratory depression and not related to the study medication. While I acknowledge Dr. Alfaro's concern about the concentration of nitrazepam was not reported in the narrative, this information was reported in the case report form.
- A case of angioedema leading to respiratory failure (D1050237-0027-00046) was also reported. The patient was a 50 yr old black male who was receiving a number of concomitant medications (including amlodipine for hypertension), but had been receiving these medications since 2005. On Day 2 of treatment with double-blind study medication (lurasidone 80 mg) the subject developed severe angioedema and was admitted to the hospital. The patient was intubated and treated for respiratory failure. He recovered from the event 2 days later. The sponsor reported this angioedema case as SAE and hypersensitivity was listed as part of the concomitant illness in the narrative. While I acknowledge Dr. Alfaro's concern about respiratory failure was not included in characterization of the event in the narrative; this information could be identified in the case report form. It should also be noted that the sponsor reported all of these cases as SAE. In any case, the sponsor has met the regulatory requirement by providing the required case report forms needed to conduct a proper review of the application.

The most common drug class known to be associated with angioedema is angiotensin-converting-enzyme (ACE) inhibitors (0.1-2%) and angiotensin receptor blockers (<0.1%). While there is limited numbers on calcium-channel blocker induced angioedema, a recent publication indicates amlodipine as one of the drugs reported to cause angioedema[2]. In addition, it was reported that the combined use of nicardipine, a strong CYP3A4 inhibitor, with amlodipine, a CYP3A4 substrate, may lead to a significantly increased serum concentration of amlodipine, potentially leading to an abnormal increase in kinin production, which may increase vascular permeability and vasodilation, precipitating angioedema[3]. Time on amlodipine in development of angioedema for the above mentioned case in the lurasidone trial is quite protracted; it is less likely to be considered as a sole potential cause. Within 2 days of addition of lurasidone, the manifestation of serious angioedema leading to respiratory failure, potential drug-drug interaction between these two agents via CYP3A4 should also be considered.

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with other atyptical antipsychotics such as risperidone. Both risperidone and paliperidone labels list patients with a known hypersensitivity to the product as contraindication and also denoted the fact that cases of angioedema have been observed in the clinical trials. Olanzapine and aripiprazole also list angioedema as part of the AE listing. In the sponsor's proposed lurasidone labeling, a known hypersensitivity to the product is listed as contraindication (b) (4)

[redacted]

[2] Southward J, Irvine E and Rabinovich M. Probable Amlodipine-Induced Angioedema. Ann Pharmacother 2009; 43:772-6.

[3] Nakamura K, Ariyoshi N, Iwatsubo T, et al. Inhibitory effects of nicardipine to cytochrome P450 (CYP) in human liver microsomes. Biol Pharm Bull 2005; 28:882-5.

AE Dropouts

In phase 2/3 placebo-controlled studies, the proportion of subjects discontinuing from a study due to an adverse event was 9.4% for lurasidone-treated subjects, mostly from schizophrenia/psychotic symptoms and akathisia; and 5.9% for placebo-treated subjects. In the all phase 2/3 studies, 21.4% (449/2096) of patients discontinued due to an adverse event.

8.2.2 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). The AEs that are considered common and drug-related included: sedation/somnolence (23% vs.10%), akathisia (15% vs. 3%), nausea (12% vs. 6%) and agitation (6% vs. 3%). Sedation/somnolence and akathisia showed dose-relatedness.

8.2.3 Vital Signs and ECG Changes

Lurasidone appears to have a slightly higher incidence of orthostatic hypotension of 1.3%, compared to placebo, 0.9%. There also appears to be a relationship of orthostatic hypotension and lurasidone dose; the 40 mg dose is similar to placebo, and the 80 mg and 120 mg doses are associated with greater frequency of orthostatic hypotension with 1.4% and 1.7% of patients.

In the double-blind phase 2/3 studies, no clinically significant differences in mean changes in vital signs from baseline to final visit assessment were noticed between the two treatment groups.

The proportions of patients with potentially clinically important vital sign change were slightly greater in the lurasidone groups than in the placebo group for the following vital sign parameters: High standing pulse $\geq$ 120 bpm and $\geq$ 15 bpm increase from baseline - 3.9%(27/690) in lurasidone, 2.4% (8/329) in placebo; Low sitting systolic BP $\leq$ 90 and $\geq$ 20 mmHg decrease from baseline - 2.1% (19/907) in lurasidone, 1.4% (5/360) in placebo.

During the short-term, placebo-controlled clinical trials, there were 4 patients on lurasidone reported as AE dropouts due to cardiac disorder (angina, sinus bradycardia, tachycardia, and ventricular extrasystole) as compared to 2 in the placebo group for sinus arrhythmia. No reported cases of QTcF >500msec with lurasidone, nor no patients treated with lurasidone experienced QTc increases > 60 msec from baseline. I am not aware of any possibly drug-related cases of TdP accounted for in any of the phase 2/3 clinical trials with lurasidone. No other severe cardiac arrhythmia cases were observed.

8.2.4 Seizures

In clinical trial database with lurasidone, there were a total of 4 cases reported for seizures and 3 of them were listed as part of the AE dropouts in all phase 2/3 studies. These event of convulsions occurred at 10, 16, 60 and 310 days after initiating lurasidone. In the short-term placebo-controlled studies, seizures/convulsions reported in < 0.1% (1/1004) of the lurasidone-treated patients, compared to 0.2% (1/455) placebo-treated patients.

8.2.5 Metabolic Effects

Weight Gain

In the 6 week, double-blind, placebo controlled studies, lurasidone was associated with 0.75 kg mean increase from baseline, as compared 0.26 kg increase in the placebo group. The proportion of patients with ≥ 7% increase in body weight was noted to be 5.6% in the lurasidone group and 4% in the placebo group. There did not seem to have any dose-relatedness among the lurasidone groups. The greatest weight gain was seen in the olanzapine 15 mg active control group: 4.1 kg mean increase and 34.4% outliers.

In all phase 2 and 3 studies (up to 52 weeks), the categorical weight increase of > 7% was 11.9% at week 24 (n=480), and 17.7% at week 52 (n =192).

There was only one patient listed as weight increased in the AE dropouts in all phase 2/3 studies.

Glucose Level

In the 6 week, double-blind, placebo controlled studies, lurasidone was associated with 1.4 mg/dL (N=1004) mean increase of blood glucose from baseline, as compared 0.6 mg/dL increase in the placebo group (N=455). There did not seem to have any dose-relatedness among the lurasidone groups. The greatest change was seen in the olanzapine 15 mg active control group: mean increase of 9 mg/dL (N=122).

Regarding the shift data for fasting glucose, from normal baseline to high shifts (< 100 to ≥ 126 mg/dL) occurred in 6.1% (36/593) of patients in the lurasidone group, 3.7% (10/272) of patients in the placebo group and 8.2% (7/85) of patients in the olanzapine 15 mg group. Shifts from borderline impaired to high fasting glucose (≥ 100 and < 126 to ≥ 126 mg/dL) occurred in 13.9% (25/187) of patients in the lurasidone group, 12.3% (10/81) of patients in the placebo group and 31.8% (7/22) of paitents in the olanzapine group. There were no significant differences in HbA1c shifts from normal to ≥ 6.1% between the lurasidone (7.7%; 51/659) and placebo groups (5%; 15/302).

There was only one patient listed as blood glucose increased among the AE dropouts in all phase 2/3 studies.

Lipid Profile

No mean increases were noted in the total cholesterol (fasting), LDL cholesterol (fasting) or triglycerides (fasting) for the lurasidone group. The shift changes in lipids were similar between the lurasidone and placebo groups.

8.2.6 Hyperprolactinemia

Lurasidone was associated with an increase in prolactin in the clinical trials. The mean change from normal baseline was 9 ng/ml for lurasidone groups (N=795), 0.6 ng/ml for the placebo group (N=348), 6.7 ng/ml for olanzapine 15 mg (N=96) and 17 ng/ml for the haloperidol 10 mg group (N=72).

There was a relationship to lurasidone dose, mean change from normal baseline was 4.5 ng/ml in the lurasidone 20 mg group (n=60), 5.9 ng/ml in the lurasidone 40 mg group (n=286), 9.8 ng/ml in the lurasidone 80 mg group (n=216) and 12.9 ng/ml in the lurasidone 120 mg group (n=233). Although females exhibited a more pronounced elevation, the relationship to dose was observed in both gender.

The percent of patients with elevations > 5x ULN were 3.6% for the lurasidone groups (fairly equally among the 40, 80 and 120 mg lurasidone doses) and 0.7% for the placebo group.

It was reported that two patients who received 40 and 120 mg of lurasidone (N=1004) dropped out of the study due to hyperprolactinemia in all phase 2/3 placebo-controlled trials.

Galactorrhea was observed in no patients during the phase 2/3 placebo-controlled trials, but 2 patients in all phase 2/3 database and 2 additional patients reported in study D1050237, a 12 month active controlled study with open label extension.

8.2.7 Hepatic Effects

There was no significant difference in mean change from baseline to endpoint in liver enzyme measurements between the lurasidone and placebo groups. The proportion of subjects with normal to high shifts in AST, ALT and alkaline phosphatase was 2.9%, 5.2% and 0.9%, respectively for the lurasidone group and 5.6%, 5.0% and 0.7%, respectively for the placebo group.

During the review cycle, Dr. Alfaro asked the sponsor to perform an analysis of cases meeting criteria for Hy's Law. The sponsor identified one case (0131-00007), a 27 yr old male who completed the double-blind phase of study D1050229 and then enrolled in the open-label extension phase of the study, was noted to have increases in liver enzymes (ALT = 1720 U/L, AST = 1444 U/L, total bilirubin = 7.7 mg/dL) on day 44 of lurasidone 120 mg/day open-label treatment. The patient was discontinued from the study, and his LFT returned to normal range 3 months later. It was indicated that this case was thought to be due to infectious hepatitis. Although this was not confirmed by serology, I tend to agree with the sponsor's and the investigator's assessment given that the subject was from a site in India where infectious hepatitis is highly prevalent in the region. Regarding the second case identified by Dr. Alfaro, patient was receiving the active comparator, quetiapine XR 600 mg.

8.2.8 Extrapyramidal Symptoms (EPS) and Tardive Dyskinesia (TD)

In all phase 2/3 studies, approximately 21 cases of dystonia (2 of these identified as an SAE) and 35 cases of akathisia as discontinuation due to adverse event were identified in the lurasidone treated group (N=2096). One cases of TD noted in the lurasdione group leading to discontinuation from the trial.

In phase 2/3 placebo-controlled trials, the sponsor reported that the incidence of reported EPS-related events, excluding akathisia, for lurasidone was 16.7% vs. 6.6% for placebo-treated patients; and the incidence of akathisia for lurasidone was 15% vs. 3.3% for placebo-treated patients.

As expected with atypical antipsychotics, the EPS profile of lurasidone seemed comparable to other atypical antipsychotic agents. Rates of adverse events potentially related to EPS including dystonia, dyskinesia, akathesia and Parkinosonian related events seemed higher in the lurasidone group as compared to placebo group. There was a dose-related increase for akathisia and agitation in patients treated with lurasidone compared to placebo.

In Dr. Alfaro's clinical review, the numbers were further broken down. Dystonias occurred in 3.5% of patients in the lurasidone groups, 0.7% of patients in the placebo group and 12.5% of patients in the comparator haloperidol 10 mg group. However, she noted that the rates of dystonia are higher if other dystonia-related preferred terms are included such as oculogyric crisis, oromandibular dystonia and torticollis. Similarly, parkinsonian adverse events occurred in 4.9% of patients in the lurasidone groups, 0.4% of patients in the placebo group. In the haloperidol 10 mg group, 18% experienced extrapyramidal disorder.

Examining the dose-relatedness of adverse events in the phase 2/3 short-term placebo-controlled trials, there appeared to be an increase in frequency with increasing dose for akathisia: i.e., 5.6% (4/71) in the 20 mg, 11.4% (41/360) in the 40 mg, 14.9% (42/282) in the 80 mg and up to 22% (64/291) in the 120 mg groups. Though there was not a clear dose-relationship to dystonia related or parkinsonian-related adverse events, however, most of the preferred terms related to this adverse event were highest (about 10-15%) in the lurasidone 120 mg group.

For the pooled data from placebo-controlled phase 2/3 studies, there was no significant difference between lurasidone and placebo in terms of the mean changes from baseline to endpoint in the EPS rating scale scores such as the Barnes Akathisia Scale (BAS) and the Simpson-Angus Scale (SAS). Regarding the abnormal shift change from baseline to end points, a greater percentage of change was seen in lurasidone groups as compared to placebo. As expected, the greatest change was observed with haloperidol (Table 13).

Table 13 - Shift change from baseline to endpoint in BAS and SAS

	Lurasidone 20 mg (N = 71)	Lurasidone 40 mg (N = 360)	Lurasidone 80 mg (N = 282)	Lurasidone 120 mg (N = 291)	All Lurasidone (N=1004)	Placebo (N=455)	Haldol 10 mg (N=72)	Olanzapine 15 mg (N=122)
BAS: Worsened	11.3%	13%	16.2%	20.7%	16%	7.6%	33.3%	9%
SAS: Normal Abnormal	4.2%	4%	4%	8.4%	5.3%	2.5%	11.1%	4.9%

While I acknowledge Dr. Alfaro's statement in her clinical review that "determining the frequency of parkinsonian-related adverse events was difficult since there was potential splitting for preferred terms tremor, cogwheel rigidity, bradykinesia, drooling, etc.", it should be noted that there has not been a single consistent way among various sponsors in putting all these AE terms together in calculating the EPS-related adverse reaction rates. Additionally, Dr. Alfaro speculated that there were some issues with coding and identification of parkinsonian-related adverse events which may have led to underreporting of these adverse events (see discussion in section 11.1 regarding this issue). In conjunction with the angioedema case, it was apparent to me that she was concerned about some particular AE terms such as swollen face, eyelid swelling, swollen tongue, thick tongue, lip swelling, edema, etc. I would request the sponsor to look for any relevant clinical information in the case reports of these patients who were involved in phase 2/3 placebo-controlled studies in order

to further clarify or to determine which of these events were either EPS-related events or hypersensitivity reaction.

8.2.9 Neuroleptic Malignant Syndrome (NMS) and Increased CPK

In all phase 2/3 clinical trials, there were two identified cases of NMS. Two other cases diagnosed with rhabdomyolysis were discontinued due to this adverse event. Upon review of limited clinical data available, Dr. Alfaro noted in her review that these cases showed predominantly CPK increase without associated clinical symptoms consistent with rhabdomyolysis.

Increased blood CPK was listed as part of the reasons for adverse event discontinuation for 4 patients in lurasidone groups and 2 in the placebo group. In the 2% incidence table, 1.6% (16/1004) in lurasidone groups and 1.3% (6/455) in placebo were listed to have increased CPK.

The sponsor's proposed labeling includes the class NMS language, including the statement that NMS has been reported in association with administration of antipsychotic drugs, including this drug. This proposal seems acceptable to me.

8.3 Conclusion Regarding Safety Data

Although the sponsor reported the case of severe angioedema as a SAE, Dr. Alfaro was disturbed by the fact that the event leading to respiratory depression was only identified upon her review of CRF (not part of the narrative). Using this and another case of a patient in quetiapine group meeting criteria for Hy's law were found during her review from data tabulation that were not identified by the sponsor, she is making an overarching conclusion that her safety concerns are related to data quality and recommended that all CRF data be re-reviewed and all the clinical data be recompiled into an ISS. I do not concur with her recommendation (see comments under section 11.1). Furthermore, I disagree with Dr. Alfaro that the ISS should be recompiled to include the two recently completed Phase 3 clinical trials, D1001002 and D1050233. In my opinion, data from these two short-term efficacy studies would not be necessary to make the overall safety determination of this drug.

There were no substantial different findings regarding death, serious adverse events (SAEs), discontinuation due to AE, or common adverse events (AEs) that would materially change what was found during the reviews of schizophrenia trials for atypical antipsychotic agents. Based on available data, the overall AE profile for lurasidone is quite similar to that observed for other approved atypical antipsychotic products. Significant safety signals that emerged in the available lurasidone clinical trial databases include EPS with a dose-dependent increase in akathisia, nausea, somnolence/sedation and agitation. Dose-dependent increase in prolactin level was also noted. Some modest weight gain was observed with this drug. We have asked the sponsor to conduct a more comprehensive look for clinically relevant information in the CRFs of patients with the reported adverse event terms of swollen face, eyelid swelling, swollen tongue, thick tongue, lip swelling, edema, etc., to further clarify and to determine which of these AEs were hypersensitivity or EPS-related adverse events, and recalculate the rates, as needed. We have also asked the sponsor to combine certain related AE terms and revise the 2% incidence table. All of these safety findings, in my view, can be adequately described in the labeling.

9.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

During the filing meeting, the review team discussed and determined not to take it to the PDAC given this drug is another atypical psychotic agent with D2/5HT-2 antagonist property and did not seem to have any particular efficacy or safety concern as compared to the profiles of other approved products in the same category.

10.0 PEDIATRICS

In the original NDA submission, the sponsor requested for pediatric waiver (b) (4) and deferral (b) (4) They did not include the pediatric plan with their deferral request. We, therefore, asked them to do so. The Division received the updated request and the proposed plan on September 14, 2010. In accordance with the Division's policy regarding pediatric studies in schizophrenia, the request for waiver has been updated for lurasidone in the 0-12 yr old population as studies are highly impractical due to the low incidence of schizophrenia in this age range, and the deferral request in the 13 to 17 yrs old adolescent population. The deferred adolescent studies would be considered post-marketing studies. In the proposed pediatric plan, the sponsor has designed to first conduct a pediatric PK study (scheduled to start in April 2012) to obtain PK data that will be used to provide information pertinent to the dosing of lurasidone in adolescents with schizophrenia (scheduled to start in April 2013). The sponsor proposed to submit the clinical study reports by October 30, 2015. The pediatric plan, the proposed pediatric deferral and waiver requests will be taken to PeRC review which is scheduled for October 13, 2010.

11.0 OTHER RELEVANT REGULATORY ISSUES

11.1 DSI Clinical Site Inspections & Comments on Data Quality Issues Raised by Dr. Alfaro

Routine DSI data audit inspections were conducted for two domestic clinical investigator sites: Dr. Tram Tran-Johnson (site #15 in Study 10500006 and site #37 in Study 1050231) in San Diego, California, and Robert Riesenberg, M.D. (site # 14 in Study 10500006, site #17 in Study 1050229 and 1050231). These sites were chosen to be inspected due to their high numbers of subject enrollment. Two additional international sites were chosen for inspection: Laura Giraldo Ospina, M.D. (site #464) and Rodrigo Cordoba, M.D. (site #465) both in Bogota, Colombia, due to their significant contribution to the overall efficacy signal in Study D1050231. Geographic analyses showed significant results favoring lurasidone over placebo consistently in Colombia, and not other regions (e.g., U.S. or India). Current sponsor, Sepracor Inc., was also inspected. Except for some minor record keeping deficiencies by the sponsor, DSI clinical inspection summary report (dated 8/9/2010) did not indicate data integrity issues in any of these inspected sites.

I was not aware of Dr. Alfaro's efficacy and safety concerns were also related to data quality as identified in her review until she brought the issues up towards the later part of the review cycle. Dr. Alfaro repetitively noted in her review about lack of detail information in case narratives and the sponsor needs to do more to evaluate this data quality concern. A few examples that she mentioned in her review were her identification of respiratory depression in the SAE report of angioedema, the Hy's law case of patient on quetiapine XR 600 mg and the normal range of amylase and lipase concentrations in a case of pancreatitis. As required, the sponsor has provided the case report forms and data tabulations needed to conduct a proper review of the application.

Indeed, Dr. Alfaro wrote in her review that she identified these items in the CRF or from the JMP tabulations. It would have been very helpful to the clinical reviewer if the narratives written by the sponsors were complete and comprised of relevant clinical information in detail as Dr. Alfaro expected. However, in my view, they are not required to do so.

Regarding the issue on missing data, the sponsor on their own discovered and amended the laboratory data from 27 patients in the study report for D1050006. The sponsor indicated that no other safety data were missing from these 27 patients. Although laboratory data from these patients were not part of the integrated safety summary in the original submission, these data did not seem to affect the overall results.

In terms of patient disposition issues, Dr. Alfaro was troubled by re-categorizing reason for discontinuation from withdrawal of consent to adverse events in a few patients during her case reviews. It is not uncommon to re-categorize to capture AE dropouts as long as the listing of withdrawal of consent was routinely included as part of the reasons for discontinuation in all NDA submissions. She also commented as potential adverse event coding issues indicating the sponsor to further characterize seriousness of adverse event even after SAE report was made. Given an example of SAE coded as fall, she indicated that the sponsor should be asked to recode adverse events (of note, denial of suicidal thoughts and auditory hallucination in this case). Based on available information, I do not believe recoding would be able to contribute significant change in characterization of seriousness of such AE.

Her remarks also included data collection and CRF design issues such as CRFs did not include a space where the clinical presentation of the event could be described or the timing of the concomitant medications in relation to when efficacy assessments were made. Another remark was the lab report on prolactin concentration were included as part of the hard copies of CRF, as for some earlier studies, the sponsor did not use electronic CRF. At this stage, there is not much the sponsor could do to address such concern.

I note in Dr. Alfaro's clinical review (section 7.1.2) stating that "The JMP file for adverse events was reviewed with an emphasis on the verbatim to preferred term coding. In general, it appeared that most verbatim terms were appropriately coded to preferred terms." She then identified isolated instances from the case narratives and AE reports and raised her worry about the issues of AE coding and under reporting of adverse events in other sections in her clinical safety review. A number of adverse events of her concerns occurred in the clinical trials program were those related to further differentiating hypersensitivity reactions and EPS (see also sections 8.2.1 and 8.2.8 of this memo). Given DSI clinical sites and sponsor inspections did not identify under reporting of AE as part of the inspectional deficiencies nor identify any data integrity issues, in my opinion, it is unnecessary to ask the sponsor to conduct 100% audit. Instead, we should ask the sponsor to conduct a more comprehensive look for relevant clinical information in the CRFs of the patients with the reported adverse event terms such as swollen face, eyelid swelling, swollen tongue, thick tongue, lip swelling, edema, etc., in order to further clarify and determine which of these AEs were hypersensivity or EPS-related adverse events, and recalculate the rates as necessary.

11.2 Other Outstanding Regulatory Issues/Foreign Regulatory Action

Lurasidone is not marketed in any country in the world. I am not aware of any exclusivity or patent issues of concern, or other regulatory matters for this drug. No financial disclosure issue was identified.

11.3 World Literature

The sponsor reported that they conducted a comprehensive literature review (as of 3/6/2009 and 8/26/2009) utilizing Biosis, Medline, EMBASE and ToxFile pertaining to the pharmacology and safety of lurasidone. The sponsor stated that their literature review identified no findings that would adversely affect their conclusions regarding the safety of lurasidone.

11.4 Other Discipline Consults

11.4.1 Bone Density Scans

There were 16 AE cases related to bone fractures (some associated with falls) reported out of 2096 lurasidone patients in all phase 2/3 clinical trials. It included a 62 yr old male and a 57 yr old female, both cases with no prior history of osteoporosis, reported spinal compression fracture occurred at Day 25 and 275 of lurasidone treatment, respectively.

The Division of Reproductive and Urologic Products was consulted to evaluate DEXA scan data, as well as any other clinical data related to risk for bone fractures, from study D1050237. Study D1050237 was a 12 month double-blind study comparing lurasidone (40-120 mg/day, flexible dose) and risperidone (2-6 mg/day, flexible dose) which included DEXA scans and laboratory assessments for bone turnovers. According to the consultative report dated 9/22/2010, due to the limited 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. However, it appears that the effect of lurasidone on BMD at the lumbar spine and hip over 12 months is similar to risperidone.

11.4.2 QT consult

(b) (4)

11.4.3 Ophthalmology consult

Given the melanin binding property of the drug, ophthalmologic assessments such as slit lamp examinations, fundoscopic assessments and visual acuity assessments were included in part of the protocols. The sponsor did not report any clinically significant findings. The Division of Anti-

Infective and Ophthalmology Products was consulted in looking at the ophthalmologic examination results from the longer-term clinical trial D1050237. Final consultative report is still pending.

12.0 LABELING

In terms of the proprietary name request, the Sponsor's proposed trade names for the product, (b) (4), in the original submission were found to be unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA). On 9/3/10, we received the sponsor's request for review of two names (b) (4) t or Latuda), and currently, they are under review by DMEPA. Once one of these names is deemed acceptable, CMC will then provide their comments on the container packaging labels.

Should the Division decide to approve this drug based on available data in the NDA submission, all disciplines will be providing the labeling comments and some modifications to the sponsor's proposed labeling in a separate document and will further negotiate the label changes with the sponsor.

13.0 RECOMMENDATION/RISK BENEFIT ASSESSMENT

In my view, the sponsor has submitted data supportive of a conclusion that lurasidone is effective and acceptably safe in the acute treatment of schizophrenia. There was sufficient efficacy data from short-term placebo-controlled studies to support the claim for lurasidone in the treatment of schizophrenia at 80 mg dose. Available study data suggests that some efficacy of lurasidone 40 mg dose for acute treatment of schizophrenia. No additional benefit was observed in the 120 mg dose. Dose-dependent increases in akathisia and prolactin levels were noted. The safety profile of lurasidone observed in the clinical trials seems quite similar to other approved atypical antipsychotic agents.

Considering schizophrenia is a severe and highly debilitating mental illness, it is believed that the benefit of having lurasidone as an additional option available to schizophrenia patients, justifies the risk of potential adverse events identified in the development program thus far. I do not concur with Dr. Alfaro's recommendation that the Division issue a complete response letter and ask the sponsor to recompile and submit additional data from two recently completed controlled studies to support their intended claim. Based on the submitted data, the efficacy and safety profile of lurasidone in short-term treatment of schizophrenia can be adequately described in the labeling.

Based on the available data in the submission, it is recommended that this NDA be granted an approval status. Final approval is contingent on satisfactory response by the sponsor to the agency's requests (including their CRF audits on hypersensitivity vs. EPS-related events, the agreement to conduct a maintenance study in adults and additional PK and efficacy/safety studies in pediatric population as post-marketing studies) and mutual agreement on labeling as well as the conclusions of CMC, clinical pharmacology and pharmacology/toxicology reviews. Addendum to this CDTL review memo will be generated if my recommendation changes upon review of any of these pending issues.

Cc: HFD-130/Laughren/Mathis/Alfaro/Sohn

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/s/

NI A KHIN
09/29/2010