

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200603

SUMMARY REVIEW

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

DATE: October 27, 2010

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for lurasidone tablets as a treatment for schizophrenia.

TO: File NDA 200603
[Note: This overview should be filed with the 12-30-09 original submission of this NDA.]

1.0 BACKGROUND

Lurasidone is an atypical antipsychotic (a D2 and 5HT2 antagonist) that has been studied for the treatment of schizophrenia. There are multiple other drugs in this same class already approved for the treatment of schizophrenia. This application is based on data from 4 short-term trials. The proposed dose range is 40 to 120 mg/day, to be given on a qd basis, with food. The studies in support of this application were conducted under IND 61292. An EOP2 meeting was held with the sponsor on 9-26-2006 and a preNDA meeting on 5-22-2009.

The primary clinical reviewer for this application was Dr. Cara Alfaro and the primary statistical reviewers was Dr. George Kordzakhia. A secondary review of this application was conducted by Dr. Ni Khin.

2.0 CHEMISTRY

The CMC review was conducted by Drs. Shastri Bhamidipati. Dr. Bhamidipati recommended, in an 8-27-10 review, that the application was approvable, once the sponsor had provided additional dissolution data and addressed several labeling issues. Dr. Richard Lostritto has written a 10-26-10 supervisory memo indicating that all remaining issues have now been resolved, including the facilities inspection, and has recommended an approval action. The only remaining CMC issues at the time of writing this memo are: (1) a pending DMEPA review of final carton and container labels, and (2) the submission by the sponsor of final dissolution specifications.

3.0 PHARMACOLOGY

The pharm/tox review was conducted by Sonia Tabacova, Ph.D. and a supervisory overview was provided by Aisar Atrakchi, Ph.D. All pharm/tox questions and issues have been resolved, including agreement on the pharm/tox sections of final labeling. The pharm/tox group does not have any concerns that would preclude a final approval action for this application.

4.0 BIOPHARMACEUTICS

The OCP review was conducted by Drs. Kofi Kumi and Atul Bhattaram.

The elimination half-life of lurasidone 40 mg is approximately 18 hours, but there is slight non-linearity of clearance, with half-lives of the 80 and 120 mg doses being slightly increased, i.e., 22 hours for 80 mg and 31 hours for 120 mg. Steady state is reached within 7 days. C_{max} is at about 3 hours. There is a very large food effect with lurasidone, with about a 3-fold increase in C_{max} with food, and a 2.2 fold increase in AUC. Lurasidone was given with food in the clinical studies, and labeling also recommends dosing with food. Lurasidone is cleared primarily by CYP3A4. Ketoconazole, a potent 3A4 inhibitor, increases the C_{max} of lurasidone by about 7-fold, and is therefore not recommended for concomitant administration. Rifampin, a potent 3A4 inducer, decreases lurasidone C_{max} by about 7-fold, and so is also not recommended for concomitant administration. 40 mg is the maximum recommended dose for patients with renal or hepatic impairment.

Two bioequivalence studies were conducted, one single dose and one multiple dose, and both showed bioequivalence between the CTM and the TBM formulations. There were data integrity issues for the single dose study, and consequently, we cannot rely solely on that study. Although the multiple dose study was not inspected, we have confidence in the site where this study was conducted, based on recent inspections. In any case, slight differences in bioequivalence would be of little clinical consequence, and furthermore, only the TBM formulation would be available.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on four multicenter, randomized, double-blind, parallel group, placebo-controlled, short-term (6-week) trials of lurasidone in adult patients with acute exacerbations of schizophrenia. These studies, all fixed-dose, covered a dose range of 40 to 120 mg/day. Two of these were exclusively US studies (D1050006 and D1050196), and two involved both US and nonUS sites (D1050229 and D1050231). There was a fifth study (D1050049) that failed to distinguish either lurasidone (at any of 3 doses: 20, 40, or 80 mg/day) or haloperidol (10 mg/day) from placebo (i.e., a “failed” study), and was not further reviewed.

-D1050006: This multicenter (15 sites) US study (006) compared lurasidone doses of 40 and 120 mg/day vs placebo (1:1:1). There were about 50 patients per group. There were very

substantial dropouts in this study (70% for placebo, 68% for 40 mg and 59% for 120 mg). Placebo had the highest % dropouts for lack of efficacy (32% for placebo, compared to 22% for 40 mg and 12% for 120 mg), and lowest for AEs. The primary endpoint was change from baseline to endpoint on BPRS total score. The primary analysis was LOCF for the ITT population. CGI-S was a secondary endpoint, but not specified as a key secondary. Dunnett's test was used for multiplicity adjustment. LS mean changes from baseline for BPRS to endpoint were: -3.8 (pbo), -9.4 (40 mg; p=0.018), and -11.0 (120 mg; p=0.004). Both dose groups were numerically superior to placebo beginning at day 3 and at every subsequent visit. Thus, even before the substantial dropouts, drug was clearly superior to placebo. An MMRM analysis also favored both doses vs placebo, but not an OC analysis (not a surprise, given the very substantial dropouts; however, both doses were strongly favored numerically, and the superiority for the 40 mg dose almost achieved statistical significance—p=0.062). Analyses of CGI-S also strongly favored both doses vs placebo.

The biometrics group considers this a positive study in favor of lurasidone, however, Dr. Alfaro does not (she considers it un-interpretable). Her primary concern is the very substantial dropout rate (66% overall). She is also concerned about the relative small size of the study (50 patients per group). On face, the trial was similar in design to other trials in this program. Dr. Alfaro does note, however, that the use of concomitant benzodiazepine use in this trial was less compared to that observed in other trials in the program, both in terms of percentage of patients getting concomitant benzodiazepines (about 25% for this trial compared to about 60% in other trials) and dose.

Comment: Although it's true that the dropout rate is unusually high for this study compared to other schizophrenia trials, I don't think this fact by itself is determinative of an un-interpretable study. The dropouts are at least in the direction one might expect (highest overall in placebo patients, and highest for lack of efficacy in placebo patients). In addition, other analyses support the LOCF findings (MMRM, and OC, at least numerically), and drug is favored over placebo for every time point, beginning at day 3. The CGI-S results also strongly favor drug over placebo. So, although I am somewhat troubled by the high dropouts, I still consider this a positive study in support of both 40 and 120 mg lurasidone doses.

-D1050196: This multicenter (22 sites) US study (196) compared a single lurasidone dose of 80 mg/day vs placebo (1:1). There were about 90 patients per group. Dropouts in this study were 48% for placebo and 42% for lurasidone. Placebo had the highest % dropouts for lack of efficacy (32% for placebo and 10% for 80 mg), and lowest for AEs. The primary endpoint was change from baseline to endpoint on BPRS total score. The primary analysis was LOCF for the ITT population. CGI-S was a secondary endpoint, but not specified as a key secondary. LS mean changes from baseline for BPRS to endpoint were: -4.2 (pbo) and -8.9 (80 mg; p=0.0118). An MMRM analysis also favored lurasidone over placebo, as did an OC analysis. Analyses of CGI-S also strongly favored lurasidone over placebo.

The biometrics group considers this a positive study in favor of lurasidone, as does Dr. Alfaro. I do as well.

-D1050229: This multicenter US and nonUS study (about 50% in each region) compared lurasidone doses of 40, 80, and 120 mg/day vs placebo (1:1:1:1). There were about 125 patients per group. Dropouts were relatively modest in this study, i.e., about 30% in each of the 3 drug groups and 43% for placebo. Placebo had the highest % dropouts for lack of efficacy (25% for placebo, and 16%, 6%, and 15% for each of the 40, 80, and 120 mg groups, respectively), and lowest for AEs. The primary endpoint was change from baseline to endpoint on PANSS total score. The primary analysis was MMRM for the ITT population. CGI-S was designated as a key secondary endpoint. The Hommel-based tree gating procedure was used for multiplicity adjustment. For this analysis, results are presented as the placebo-adjusted LS mean change from baseline, and were as follows: lurasidone 40 mg (-2.1; p=0.591); lurasidone 80 mg (-6.4; p=0.011); lurasidone 120 mg (-3.5; p=0.391). An LOCF analysis confirmed this result. An analysis of CGI-S also favored the 80 mg dose vs placebo, but not the 40 and 120 mg doses.

Subgroup analyses based on US vs nonUS sites (roughly 50:50 distribution) showed that the positive results for the 80 mg dose were coming predominantly from the nonUS sites (the drug placebo differences for the 80 mg group were -2 for the US sites vs -11 for the nonUS sites; placebo change was roughly the same for both US and nonUS sites, however, the drug effect was much reduced in the US compared to nonUS). One additional finding from this geographic analysis was that the data for the 2 other dose groups from the nonUS sites was also much more supportive of a drug effect. The results for the nonUS sites, presented as the placebo-adjusted LS mean change from baseline, were as follows: lurasidone 40 mg (-6.5; p=0.061); lurasidone 80 mg (-10.8; p=0.002); lurasidone 120 mg (-8.6; p=0.031). In other words, this separate nonUS analysis provides additional statistical support for the 120 mg dose, and at least is very close to statistical significance for the 40 mg dose, even with the much reduced power. Oddly, the data for the US sites actually show numerical superiority for placebo over drug, and this explains why the pooled results are not significant for all doses overall. The placebo responses were similar in US and nonUS sites, and the difference was a less robust drug response in US sites compared to nonUS sites. An additional finding of interest is that an analysis by the pharmacometrics reviewer revealed higher lurasidone plasma concentrations in the nonUS sites compared to US sites, and although this may contribute to the unusual differences, it certainly cannot explain them.

The biometrics group considers this a positive study in favor of lurasidone, however, Dr. Alfaro does not. Her primary concern is the lack of positive findings for the 40 and 120 mg groups for the study population overall, and the geographic differences that suggest all the positive results even are coming from the nonUS sites.

Comment: There is clearly a difference in findings from the US and nonUS sites, and this is troubling. However, in my mind, this discrepancy is partly mitigated by the fact that we have positive finding from 2 other entirely US studies (006 and 196) and also a mixed US/nonUS study that actually is predominantly (60%) US (231). In fact, if one focuses on the results from the regions in this trial that show efficacy, the findings are reasonably consistent across doses (40, 80, and 120 mg), providing, in my view, additional support for the drug overall.

-D1050231: This multicenter US and nonUS study (about 60% US and 40% nonUS) compared lurasidone doses of 40 and 120 mg/day vs olanzapine (15 mg/day) and placebo (1:1:1:1). There

were about 120 patients per group. Dropouts ranged from 32% to 45% for active drug and were 39% for placebo. As with the other studies, dropouts for lack of efficacy were highest for the placebo group. The primary endpoint was change from baseline to endpoint on PANSS total score. The primary analysis was MMRM for the ITT population. CGI-S was designated as a key secondary endpoint. The Hommel-based tree gating procedure was used for multiplicity adjustment. For this analysis, results are presented as the placebo-adjusted LS mean change from baseline, and were as follows: lurasidone 40 mg (-9.7; p=0.002); lurasidone 120 mg (-7.5; p=0.022); olanzapine 15 mg (-12.6; p<0.001). An LOCF analysis confirmed this result for lurasidone 40 mg, but just missed on 120 mg. An analysis of CGI-S also favored both lurasidone doses and the olanzapine arm vs placebo. For this study, there was reasonable consistency between the US and nonUS sites, and again, lower lurasidone plasma concentrations in US patients compared to nonUS patients may have partly explained the differences.

The biometrics group considers this a positive study in favor of lurasidone, as does Dr. Alfaro. I do as well.

-Subgroup Analyses: Subgroup analyses for these 4 studies based on gender and race generally showed consistency in the results across these subgroups.

Following is a summary of the efficacy results for these 4 studies on the primary endpoints:

Summary of Efficacy Results on Primary Endpoints				
Study Number	Treatment Difference from Placebo in Change from Baseline			
	Luras 40 mg	Luras 80 mg	Luras 120 mg	Olanz 15 mg
006 (BPRS)	-5.6*	---	-6.7**	---
196 (BPRS)	---	-4.7*	---	---
229 (PANSS)	-2.1^{ns}	-6.4*	-3.5^{ns}	---
231 (PANSS)	-9.7*	---	-7.5*	-12.6***

* <0.05
 ** <0.01
 *** <0.001

DSI inspected 4 clinical sites, and found the data generated for this program to be acceptable.

-Efficacy Conclusions: I agree with Drs. Kordzakhia and Khin that the sponsor has demonstrated efficacy for lurasidone in schizophrenia across the 3 dose groups (40, 80, and 120 mg/day), with replication at all 3 doses. Dr. Alfaro feels the efficacy data are not sufficient to support an approval action because, in her view, there is not replication for each of these 3 doses. In particular, she finds study 006 (40 and 120 mg) and study 229 (80 mg) inadequate sources of support. Dr. Alfaro’s recommendation seems to be driven in part by her knowledge that the sponsor is close to completing 2 additional 6-week efficacy trials. Study D1050002 has compared lurasidone 40 and 80 mg/day with risperidone 4 mg/day and placebo (Southeast Asia;

about 115 per group). Study D1050233 has compared lurasidone 80 and 160 mg/day with quetiapine 600 mg/day and placebo (US & Columbia; about 120 per group). [Note: Preliminary data from these studies are suggestive of a positive outcome for both trials.]

Regarding Dr. Alfaro's dissenting view, I agree that there are troubling aspects of both studies (006 and 229). I do not agree, however, that these problems are sufficient to invalidate what I consider positive results overall. In addition, I don't think we can reasonably withhold our judgment on these data based on our knowledge that more data are soon to arrive.

There is a suggestion from study 229 of a possible advantage of the 80 mg dose over the 40 mg dose, however, no suggestion from the three studies including the 120 mg dose of any advantage of this dose over lower doses. So if approved, lurasidone labeling would have to note that the 120 mg dose does not appear to enhance efficacy, and in fact, there is no compelling case for including the 120 mg dose. In addition, I agree with Dr. Alfaro that the sponsor needs to explore lower doses for efficacy. The sponsor has not conducted a maintenance study in schizophrenia, but they have committed to conducting such a study. In addition, they have committed to conducting a pediatric schizophrenia study and a study evaluating lower lurasidone doses in schizophrenia.

5.2 Safety Data

Safety Database: The safety assessment is based on data from over 2600 human subjects exposed to lurasidone in phases 1-3, including over 2300 schizophrenic patients and over 359 normal volunteers. In the phase 2-3 studies, almost 500 patients were exposed for > 6 months, and 225 for > 1 year. Although doses up to 600 mg/day were evaluated in phase 1 studies, the dose range examined in phase 3 trials was 40 to 120 mg/day. [Note: SAEs were included from the 2 ongoing phase 3 studies: D1001002 and D1050233.]

Deaths: There were 18 deaths in the development program, all in phase 2-3 trials. Thirteen occurred in lurasidone patients. Three of the 13 lurasidone deaths were classified as "sudden deaths", however, 2 had alternative explanations. The third case was a patient exposed to lurasidone for 24 days and was found on a postmortem CT scan to have "venous bleeding in the brainstem and pericardial bleeding". The 13 lurasidone deaths were as follows: 4 suicides, heroin overdose, lung cancer, auto accident, septic shock, hypertensive heart disease, accidental burns, GI bleed, death in agitated 59 y/o male schizophrenic being controlled with parenteral haloperidol, and the one unexplained brainstem bleed.

Comment: There was no pattern associated with the lurasidone cases and no reason to conclude that there was any relationship to lurasidone exposure.

SAEs: Overall, SAEs occurred at roughly the same frequency in lurasidone and placebo patients (about 5%, mostly exacerbation of underlying illness). There were 3 instances of respiratory failure in lurasidone patients. Two had alternative explanations, and the third, a case of angioedema, occurred on day 2 of treatment, and had no obvious alternative explanation.

-There were 4 cases of seizures in lurasidone patients.

-There was apparently one case of NMS.

Discontinuations for AEs: 21 cases of dystonia led to discontinuation, or were classified as SAEs.

Common AE Profile: AEs occurring at an incidence of 5% and at least twice placebo included: agitation, akathisia, nausea, sedation, and somnolence. Although EPS were coded under specific events rather than under the broad category, it is clear that lurasidone has a signal for EPS, however, not as prominent as for haloperidol. Dose-relatedness for AEs was clearest for akathisia, sedation and somnolence. Dr. Alfaro notes the case of angioedema, and in that context, also mentions other reports of “swelling face, eyelid swelling, swollen tongue, lip swelling, peripheral edema and edema” in the overall database. She raises a question of whether or not these might represent instances of hypersensitivity reaction. [Note: We subsequently requested that the sponsor specifically explore the hypersensitivity question by examining all possible cases, and they have done this. So all AEs that could even possibly be considered to represent hypersensitivity were aggregated (there were 63 such AEs), and compared across drug and placebo groups. Other than the case of angioedema, none of these cases rose to the level of being considered an SAE. The proportions of such events classified as “severe” were similar for drug and placebo, as were the proportions leading to discontinuation, and the proportions overall. Thus, except for the case of angioedema that might have been related to lurasidone, there was no signal for drug-induced hypersensitivity.]

Laboratory Data: The only clearly drug-related laboratory parameter was prolactin, and this was dose-related as well. However, the prolactin signal was weaker for lurasidone than for the control drug haloperidol.

-There was no signal for transaminase elevation with lurasidone in the controlled trials database, however, the sponsor did find one Hy’s law case in a lurasidone patient that they attributed to infectious hepatitis, based on clinical presentation and the high prevalence in the region (Tirupati, India).

-There were essentially no signals for glucose elevation or lipid changes with lurasidone.

-Two instances of “rhabdomyolysis” listed in AE tables were simply elevations of CK without any symptoms, and thus, would not qualify as rhabdomyolysis.

Weight Changes: There was only a weak signal for weight increase with lurasidone (mean increase of 0.75 kg, compared to 0.26 for placebo and 4.1 kg for olanzapine).

Vital Signs: There was a weak signal for orthostatic changes associated with lurasidone treatment, however, apparently there were no reports of syncope.

ECGs: There was a very modest QTc increase for lurasidone (7.5 ms for 120 mg and 4.6 ms for 600 mg), but less than that seen for ziprasidone (16.3 ms for 160 mg), the control drug used in the thorough QT study. There were no QTc outliers for lurasidone. The sponsor had proposed

(b) (4)
section of labeling. However, given the lack of a signal for clinically relevant QTc prolongation for this drug, we decided to describe this lack of a signal in the adverse reactions section, without any requirement for caution in this regard.

Special Assessments:

-Bone Density Data: Given the prominent prolactin signal for lurasidone, we identified possible effects on bone metabolism as a potential concern for this drug. The sponsor included DEXA scans as part of study D1050237, a 12 month comparison of lurasidone and risperidone. A review of the available data from this study was provided by the Division of Reproductive and Urologic Products. However, 12-month data were available for only 12 patients. Thus, it was not possible to reach any conclusions based on these data.

-Ophthalmological Findings: Given the melanin binding properties of lurasidone, slit lamp exams, fundoscopic exams, and acuity assessments were included in certain longer-term studies. The Division of Anti-Infective and Ophthalmological Products was consulted to review data from long-term trial D1050237. The ophthalmological data for this study were quite limited, but did not reveal any signal of a worse effect for lurasidone compared to risperidone.

Quality of Sponsor's Characterization of Safety Data: Dr. Alfaro has expressed concern about the quality of the sponsor's evaluation of the safety data for this program. This concern seems to be based on several findings:

(1) The sponsor discovered and reported, during the course of the review, that they had failed to include laboratory data for 27 patients in the CSR for study D1050006. They promptly submitted revised tables for that study.

(2) The sponsor was unable to provide information on the precise timing of patients receiving concomitant benzodiazepines, in relation to efficacy assessments. Dr. Alfaro felt this was unacceptable, since, according to the protocol, patients were not supposed to have had efficacy assessments within 8 hours of benzodiazepine administration.

(3) Dr. Alfaro felt that many of the narratives were poorly written. She cites 2 examples. The first is the case of angioedema. Dr. Alfaro felt that the narrative should have included the more detailed information that she found in the CRF (the case was listed as an SAE, and so, a CRF was easily available for Dr. Alfaro's review). A second example is one of the 2 apparent Hy's laws cases (the case of probable infectious hepatitis), for which Dr. Alfaro discovered that the narrative had incorrect ALT and AST values (she found the correct values in the JMP file). Overall, she felt that the narratives for this program were not as complete as they should have been.

(4) She does not agree with some of the coding of some of the verbatim terms into preferred terms.

(5) She noted some obvious errors in reported lab values.

(6) She was dismayed by the large proportion of discontinuations coded as "withdrawal of consent".

(7) She noted the failure to identify a possible Hy's law case in a patient taking another drug, quetiapine, and another patient listed as having possible pancreatitis (but not really, based on the information provided).

-Based on this assessment, Dr. Alfaro has asked for what is essentially a re-creation of the ISS, i.e., she apparently would like the sponsor to essentially start over and completely redo their safety analysis.

Comment: Creating an ISS is a very substantial undertaking, and it is inevitable that there will be some errors, omissions, inadequately described cases, etc. I'm not making excuses for the sponsor, because I do think there are examples here of some degree of sloppiness. However, some of Dr. Alfaro's arguments seem quite weak to me. I am not as troubled as she is by examples 1 and 2. For 1, the sponsor did promptly report the error themselves, when they discovered it. For 2, this kind of information would be very difficult to capture, even if the protocol seemingly required it. For 3 (narrative summaries), it appears that Dr. Alfaro did have relatively easy access to the information she sought, even though it was not in the actual narrative. As an agency, we don't give good advice on what our expectation is for a narrative summary, so I'm a little uncomfortable coming down too hard on sponsors when we, as agency, don't really tell them what we expect. Regarding 4, coding is ultimately a judgment, and unless she wants to do the coding herself, I don't think there is justification for complaining too much about the coding for certain events. The sponsor did include the case in question as an SAE, so Dr. Alfaro had full access to all relevant data, even if she didn't agree with the coding. I'm also not that troubled by 5, 6 and 7. Regarding 6, we also don't do a good job of advising sponsors on how to classify dropouts.

-We asked for additional work on the concern about possible hypersensitivity issue (see above), but I disagree with her recommendation that the sponsor re-review all the CRFs for this program and essentially re-create the ISS. I see no basis for making such a requirement.

Conclusions Regarding Safety: Lurasidone has an adverse event profile similar to that seen for other atypical antipsychotics, in particular, to the other "-dones", risperidone and paliperidone. I think the sponsor has adequately characterized this profile, and I agree with Dr. Khin that this adverse event profile can be characterized in labeling.

6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

Given that lurasidone is one more atypical antipsychotic with a very similar efficacy and adverse effects profile to others in the class, and there were no other review issues that were considered to justify taking this to an AC. Therefore, we did not to take this NDA to the PDAC.

7.0 LABELING AND APPROVAL LETTER

7.1 Labeling

We made a number of modifications to the sponsor's proposed labeling. We have now reached agreement with the sponsor on final labeling.

7.2 AP Letter

The AP letter includes our agreed upon final labeling.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has submitted sufficient data to support the conclusion that lurasidone is effective and acceptably safe for the treatment of schizophrenia. We have now reached agreement on final labeling, and we will forward an approval package to the Office.

cc:

Orig NDA 200603

ODE-I/R Temple

HFD-130/TLaughren/MMathis/NKhin/CAlfaro/ASohn

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/s/

THOMAS P LAUGHREN
10/27/2010