CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200603

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	200603
Applicant Name	Sunovion Inc.
Date of Submission	December 30, 2009
PDUFA Goal Date	October 30, 2010
Proprietary Name / **Established (USAN) Name**	Lurasidone hydrochloride/Latuda
Dosage Forms / Strength	40, 80 and 120 mg oral tablets
Proposed Indication(s)	1. Schizophrenia
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Cara Alfaro, PharmD
Statistical Review	George Korzakhia, PhD
Pharmacology Toxicology Review	Sonia Tabacova, PhD
CMC Review/OBP Review	Shastri Bhamidipati, PhD; Houda Mahayni, PhD
Microbiology Review	
Clinical Pharmacology Review	Kofi Kumi, PhD; Atul Bhattaram, PhD
DDMAC	
DSI	Anthony Orencia, MD
CDTL Review	Ni Khin, MD
OSE/DEpi	Richard Abate, RPh
OSE/DMEPA	
OSE/DRISK	
Other – Div Dir Review Dep Dir for Safety Review	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

I. Introduction

Lurasidone HCl (Latuda) is an atypical antipsychotic (D2 and 5HTZ antagonist), a drug class with many members that differ among themselves in effectiveness (clozapine appears more effective; olanzapine in the NIMH CATIE study appeared to have fewer drop-outs than other drugs for lack of effectiveness but more for poor tolerability) and adverse effects (olanzapine causes more weight gain and metabolic disturbances than others; ziprasidone causes more QT prolongation than the other marketed products). There remains uncertainty as to whether they differ with respect to other class problems, notably the rate of tardive dyskinesia and extrapyramidal effects. Aside from the CATIE study, there are few data comparing these drugs in studies of adequate size. Only clozapine has been shown to be effective in patients failing to respond to other drugs.

In general, many of the atypical drugs' adverse effects are dose-related, so that good dose-response information is valuable. As it is difficult to obtain, however, often requiring quite large studies, dose-response data often leave something to be desired. A contrary example is risperidone, where two randomized, parallel studies, each with several doses, showed clearly that doses above 4-6 mg had no added effect but increased adverse effects considerably.

Lurasidone has reasonable, but not fully complete D/R data and we have concluded from these data that the applicant's proposed high dose of 120 mg should not be approved, as it does not provide added benefit but increases adverse effects. The 120 mg tablet strength will also not be approved. We are asking for a post-marketing commitment to evaluate a dose < 40 mg/day, and to conduct a long-term maintenance study. Lurasidone has established effectiveness (see below for further discussion) and has a relatively benign safety profile at the 40-80 mg approved daily dose.

Lurasidone's labeling will include the Warnings and Precautions shared by all members of the class: risk of cerebrovascular events in demented older patients given atypicals, neuroleptic malignant syndrome, tardive dyskinesia, adverse metabolic effects, hyperprolactinemia, agranulocytosis, orthostatic hypotension and syncope, cognitive and motor impairment, suicide attempts, seizures, impairment of body temperature regulation, and dysphagia.

As Dr. Laughren's memo explains, CMC issues, DSI issues, pharm/tox issues, and biopharmaceutics issues are resolved. Lurasidone has an elimination half life of about 18 hours with a 40 mg dose (somewhat longer with 80 mg), reaches steady state at about 7 days (a little more than the expected 4 half lives), and has absorption substantially increased (AUC about doubled) by food. It was taken with food in trials and labeling recommends taking it with food. Interestingly, exposure was reasonably constant over meals with 350-1000 calories and was independent of meal fat content. Lurasidone is metabolized by CYP 3A4 (Ketoconazole increases AUC by 700%, so that it is reassuring that doses up to 160 mg have been tolerated and that a dose of 600 mg did not prolong the QT interval more than the 120 mg dose); labeling will warn about concomitant use with strong 3A4 inhibitors (ketoconazole) and 3A4 inducers like rifampin.

II. Effectiveness

Effectiveness is discussed by Drs. Laughren, Khin, Alfaro, and Kordzakhia. There were 5 six-week placebo-controlled studies, all but one of them randomized fixed dose-dose response studies (one used only a single dose), examining daily doses of 20-120 mg. One of the five, a US study (study 049), showed no effect at any dose, but also showed no effect of an active control, haloperidol; that is, the study lacked assay sensitivity.

Differences from Placebo, change from baseline 6 week placebo-controlled trials (doses 40, 80, 120 and controls).

Study	N (location)	40 mg	80 mg	120 mg	Active	Primary method	Other Positive
006	149 (US)	-5.6 (<0.018)	_____	-6.7 (<0.004)	_____	BPRS LOCF	PANSS, 120
049	358 [also 20 mg] (US)	NS	NS	_____	Haloper 10 NS	BPRS LOCFS	BPRS, MMPM 40, 120
196	180 (US)	_____	-4.7 (0.05)	_____	_____	PANSS Total MMRM	
229	500 (multi-reg)	-2.1 (NS)	-6.4 (0.05)	-3.5 (NS)	_____	PANSS Total MMRM	
231	478 (multi-reg)	-9.7 (0.005)	____	-7.5 (0.05)	Olanz 15 mg -12.6 (<0.001)		

It can be seen that there are two statistically significant results reported for each dose, but little evidence of a dose response, except perhaps in study 229 (80 mg > 40 mg), but even in that study the 120 mg dose did not support it. There are, in any case, 6 nominally significant findings vs placebo and 4 comparisons that failed to show an effect, two of those, however, in a study in which haloperidol also failed to show an effect. We know that effective anti-psychotic drugs are not effective in every study and these results are not unusual for a modestly effective drug.

There is not full agreement on the persuasiveness of the evidence, especially in studies 006 and 229.

1. Study 006

A major concern was a very high drop out rate by 6 weeks in this US study (70% placebo, 68% 40 mg, 59% 120 mg) with 32% of plbo leaving because of lack of effectiveness, vs 22% for 40 mg and 12% for 120 mg. I have long felt that anti-psychotic and anti-depressant trials, with large drop-out rates after 3-4 weeks, should use 3-week values as the primary endpoint, then use later measures as “sensitivity” analyses. As Dr. Laughren notes, some effect was seen from day 3 on, even before the heavy drop outs. Dr. Alfaro gives (p 37) BPRS values over time (still with LOCF analysis). There is little effect in the first week, but by day 14 essentially all of the effect is seen, at a time when about 60-80% of patients are still in the trial. I find the trial supportive of effectiveness.

2. Study 229

Study 229 was a multi-regional study in which only the 80 mg dose showed effectiveness. This was true for the planned MMRM analysis of the PANSS total as well as an LOCF analysis; CGI results were similar. Moreover, looking at the 80 mg group, the roughly half of the population that was US had almost no effect (-2), while the non-US sites had a large effect (-11). Interestingly, the non-US sites also showed effects for the 40 and 120 mg arms. The US sites, in general, showed results on lurasidone that were numerically worse than placebo for the 40 and 120 mg doses.

It has been noted by Drs Khin and Laughren that blood levels were higher in ex-US patients, perhaps because of body weight differences, but given the small, if any, D/R over a 3-fold range, this cannot account for the differences.

There is no doubt that if this study were the only US data, we would have major doubts about approval. As Dr. Laughren notes, however, we have 2 wholly US positive studies (006, 196) and study 231 that is 60% US, with closer results within and outside the US (although still smaller in the US). All in all, I find the 229 data weak in supporting domestic effectiveness, reasonably strong in providing evidence of drug effect; overall, the database supports effectiveness.

III. Safety

I have little to add to Dr. Laughren's, Khin's, and Alfaro's analyses. Deaths (13) on lurasidone include 4 SDs, 7 patients with pre-existing diseases, and 4 suicides. None seems attributable to the drug. A single case of angioedema occurring promptly (day 2 of treatment) does not seem explained by concomitant therapy, none of which was new. This is noted in labeling (contraindications) and will clearly bear watching post-marketing. The applicant has agreed to submit cases or angioedema as 15 day "Alert Reports."

The controlled trials showed little evidence of the metabolic effects of atypical anti-psychotics (no glucose or lipid changes, minimal weight gain (+ 0.75 kg, vs 0.26 kg for placebo, and 4.1 kg for olanzapine). There was a borderline increase in QT (about 6 msec, but there was no placebo group in these ill patients, and the upper bound was barely 10 msec). There was no greater effect with a 600 mg dose (7.5 x the maximum dose), reassuring given he potential for increased blood levels with concomitant use of a 3A4 inhibitor. The increase was for less than the ziprasidone control (16 msec). Lurasidone causes the expected hyperprolactinemia, but not very marked.

Dr. Laughren discusses a number of concerns raised by Dr. Alfaro about how the ISS was put together. I share Dr. Laughren's view that this effort is within the usual range, but it may suggest some repairs needed more generally, specifically what is expected in a narrative. Like Dr. Alfaro I am bothered by labeling dropouts as "withdrew consent," a wholly uninformative description and a possible way to miss "adverse drop-outs," because the true reason for drop-out may not be ascertained. When that happens we get no CRF or narrative to consider. Once the case is identified as an adverse drop-out I am less worried about the quality of the narrative because we do get narratives of adverse drop outs we also get the CRFs (submitted for deaths and adverse drop outs) and I have always expected deaths and drop-outs of interest to lead to review of the CRF. That is, we should not depend on the narrative alone.

Lurasidone causes dose-related somnolence and the expected EPS events, notably akathisia, dystonia, and Parkinsonism. The main reasons given for discontinuation were akathisia and psychosis (presumably therapeutic failure).

V. Conclusions

Lurasidone appears to have effects typical of the class, not at the upper end of effectiveness (clozapine, olanzapine) but with modest metabolic effects.

I have signed the approval letter which, among other things, asks for further dose finding (20 mg) and a study of maintenance therapy.

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

/s/

APRILE BLOUNT
10/28/2010

ROBERT TEMPLE
10/28/2010