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APPLICATION NUMBER:

22-192

OFFICE DIRECTOR MEMO

Office Director's Memo to File

Date: May 6, 2009

From: Robert Temple, MD
Director, ODE-I

To: Memo to File, NDA 22-192

Subject: Approval of iloperidone (FANAPT, NDA 22-192) for acute treatment of schizophrenia. Sponsor Vanda

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I. Background

Iloperidone is an atypical antipsychotic submitted for use in acute and maintenance treatment of schizophrenia. A not approvable letter was issued on 7/25/08 based on the applicant's failure to have submitted two adequate and well-controlled studies showing effectiveness and a strong tendency toward substantial inferiority to the comparator drugs used in the trials. Dr. Laughren's July 11, 2008 review and my July 21, 2008 review detailed the reasons. Both of us agreed that study 3101, a 4 week 3-arm comparison of iloperidone 24 mg (12 mg bid), ziprasidone 160 mg and placebo, the only study sponsored by the applicant, Vanda, clearly showed an effect on the PANSS (the PANSS and the BPRS are standard measures of severity of schizophrenia, regularly used in clinical trials) that was significantly greater than placebo and approximately equal to the effect of ziprasidone. That mostly domestic study had 50% African-American participants.

For various reasons we were not able to conclude that there was a second supportive study, although several of them were "close" and their flaws were at least debatable. Drs. Khin (team leader) and Dinh (biostats) considered study 3005, a 6 week comparison of iloperidone 12-16 mg, and iloperidone 20-24 mg, risperidone 6-8 mg, and placebo also positive, but Dr. Laughren and I had reservations about it related to the sequence of analyses (their planned primary endpoint analysis of the whole population (both schizo-affective and schizophrenic patients) given 12-16 mg failed ($p = 0.09$), so that the positive finding for the whole group at 20-24 mg ($p= 0.01$) could not be reached. Actually our own analysis of the population of interest (just the schizophrenic patients), attained nominal significance at 0.03 (12-16 mg) and 0.005 (20-24 mg). Two problems kept us from accepting it. First, the effect size was almost

significantly less than risperidone (p = 0.09 for 20-24; p = 0.005 for 12-16 mg). Substantially smaller effectiveness of an anti-schizophrenic drug was considered a safety problem. Second, all of the favorable effect was in the outside-US sites, a troubling finding.

Two other placebo-controlled studies showed either no effect in the schizophrenic population (study 3004, with a high dose of iloperidone 10-16 mg) or a borderline effect (study 3000, with doses up to 12 mg/day). Actually the 12 mg dose in study 3000 was nominally significant and reasonably large, but the effect of the combined 8 + 12 mg groups, which was the primary endpoint, was NS, so the analysis of the 12 mg dose could, technically, not be reached. Certainly, however, study 3000 provides some support for effectiveness of even a low dose (12 mg), particularly given our "priors" based on studies 3101 and 3005. It was also noted that haloperidol was nearly significantly superior to even the high dose. Also noted as supportive were 3 positive control (vs haloperidol maintenance) studies. Without a placebo these cannot be considered definitive but they suggest activity as maintenance (randomized withdrawal) studies of drug vs placebo almost never fail, suggesting that any substantial inferiority would have been detected.

Our NA letter also identified insufficient evidence of safety, specifically concern about the size of the safety database, as only the 24 mg dose seemed likely to be effective and exposure to that dose was only about 500 patients. Chemistry issues were resolved at the time of the letter and the letter asked for a repeat hepatic impairment study and a P-GP intervention study. There were no other outstanding issues. For discussion of other issues and further details on trials, see Dr. Ni Khin's team leader review of June 26, 2008 and Dr. Laughren's July 11, 2008 review.

2 Effectiveness revisited

In his memo of March 27, 2009 Dr. Laughren describes his reconsideration of the 4 placebo-controlled studies. As noted, study 3101 is clearly positive. Following discussions with Vanda we considered all patients (schizophrenic and schizo-affective) in study 3000, a study comparing iloperidone 4, 8, and 12 mg, haloperidol 15 mg and placebo. The study plan required that the 8+12 mg combined groups analysis must be done first and succeed, in order to go in to any other analyses. The analyses of either the schizophrenic or total population are in fact NS for the combined iloperidone groups. As noted, however, the 12 mg dose is nominally significant for both the total and schizophrenic population, although still quite inferior to haloperidol. Dr. Laughren still considers this a negative study providing no support, because of the failed primary endpoint (pooled 8 and 12 mg doses), but although this is statistically correct, and I certainly would not consider the study one that meets criteria for a supportive adequate well-controlled study, I would describe the study as providing some support for effectiveness. Iloperidone continues to look much less effective than haloperidol.

Study 3004, with a high dose of 10-16 mg, using the planned analysis of all patients, schizophrenic and schizo-affective, was positive but the result was driven by a huge effect in the roughly 20 (out of 150) patients per group who were schizo-affective, with almost no effect in the larger schizophrenic group. That is not the population of interest and the result is strange. Study 3004 remains a negative study in our view. The sponsor argues that the distinction between schizophrenic and schizo-affective is difficult and that treatment is the same anyway, but it seems unreasonable to ignore a diagnostic distinction built into the study, clearly made in DSM-IV, and that was so influential on the results. I note also that for study 3005, the sponsor is comfortable with excluding the schizo-affective subgroup, focusing on the schizophrenics (i.e., the opposite of what is argued for 3004).

Dr. Laughren now considers 3005 a second supportive study. He was persuaded that the lack of effect in the US subgroup was "one of those outcomes that happen in subsets" and noted that the risperidone group also did poorly in the US. He notes that there were other data supporting effectiveness in the US, notably study 3101.

Dr. Laughren also considers, in his memo, the apparent consistent disadvantage of iloperidone compared to haloperidol and risperidone (but not ziprasidone). Like iloperidone, ziprasidone is an alpha blocker that must be slowly titrated, giving, as Dr. Laughren describes in his March 27, 2009 memo, a one week or greater delay in reaching an effective dose. Haloperidol and risperidone, in contrast, reach full doses more rapidly.

The sponsor argued that slower titration led to greater dropout rates for lack of effectiveness (vs haloperidol or risperidone). In study 3005 rates were 23% for iloperidone in both groups vs 8% for risperidone LOCF analysis, because there is considerable improvement over time in the placebo groups, disadvantages the treatment with greater dropout rates. Examination of patients treated > 2 weeks in study 3005 showed little iloperidone-risperidone difference, but that, of course, is a comparison enriched for early responders, a possible biased analysis. Of perhaps greater interest, our own MMRM analysis, which better handles dropouts than LOCF, showed a highly significant effect in both dose groups in study 3005, still somewhat inferior to risperidone, however. Dr. Laughren concludes, and I agree, that it is not clear that iloperidone is inferior to available therapy, although the need for titration is plainly a disadvantage, one shared by ziprasidone and quetiapine.

3. Safety

No new safety data have emerged, but iloperidone has 2 major problems: First, it prolongs the QT substantially, > 15 msec and somewhat more if its metabolism by CYP 450 2D6 or 3A4 is interfered with. It also works less rapidly because of the need to titrate slowly. Labeling will reflect this; Indications and Usage will point out the need to consider, in choosing iloperidone, its QT prolonging properties (worse than many

alternatives) and delayed response compared to alternatives, i.e., a "sort of" second line claim, much like ziprasidone.

Iloperidone has side effects expected of an alpha blocker (tachycardia, dizziness, and hypotension), all dose-related, as well as dose-related weight gain, a class effect. It had a low rate of extrapyramidal symptoms (akathisia, bradykinesia, dyskinesia, distonia and Parkinsonism) all at rates indistinguishable from placebo. Tremor may have been slightly increased at the high dose (3.1% vs 1.9% on placebo). At the high dose, it had the usual increases, compared to placebo, in total cholesterol and triglycerides. Labeling will bear the class warning language on

1. Risk of death and stroke in elderly patients with dementia
2. Neuroleptic malignant syndrome
3. [redacted] DM b(4)
4. Weight gain (a 7% gain was seen in 4%, 12%, and 18% in patients given placebo, iloperidone 10-16 mg/day and iloperidone 20-24 mg/day. Mean weight increase vs placebo was about 2 kg.
5. Leukopenia, neutropenia, agranulocytosis
6. Hyperprolactinemia
7. Disruption of body temperature regulation
8. Dysphagia and possible aspiration
9. Suicide
10. Possible cognitive and motor impairment (somnolence 12% vs 5% on placebo)

Iloperidone labeling also will bear warning language about

1. Orthostatic hypotension and syncope (0.4% vs 0.2% on placebo)
2. Priapism (4 cases)

4. Conclusion

Iloperidone should be approved with appropriate labeling, as partly described above. The sponsor has committed to the conduct of a long-term effectiveness (maintenance)

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