CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-192

SUMMARY REVIEW

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 27, 2009

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

SUBJECT: Recommendation for approval action for iloperidone immediate release tablets for schizophrenia (for acute and maintenance treatment)

TO: File NDA 22-192
[Note: This overview should be filed with the 11-6-08 response to the agency's 7-25-08 Not Approvable letter.]

1.0 BACKGROUND

Iloperidone is an atypical antipsychotic (5HT2 and D2 receptor antagonist). It is an immediate release formulation for bid administration. This NDA seeks a claim for both the acute and maintenance treatment of schizophrenia, in a total dose range of 12 to 24 mg/day. Iloperidone was developed under IND 36,827. This NDA was first submitted 9-27-07. We issued a Not Approvable letter on 7-25-08. There were two major deficiencies that were the basis for this action, i.e., (1) lack of sufficient effectiveness data, and (2) lack of sufficient safety data in a relevant dose range. In addition to these not approvable issues, there were four other issues noted in the letter: (1) data from Dr. Gilliam's site; (2) need to repeat hepatic impairment study; (3) need for iloperidone and P-Gp interaction study; (4) need for safety update. We subsequently met with the sponsor on 9-10-08 (see meeting minutes) to discuss the Not Approvable action.

2.0 EFFICACY AND SAFETY DATA CONSIDERED IN ORIGINAL APPLICATION

2.1 Overview of Studies Pertinent to Efficacy

The NDA contained 4 short-term (4 to 6-week), double-blind, randomized, parallel group, placebo-controlled trials in adult patients with acutely exacerbated schizophrenia or schizoaffective disorder (Studies 3101, 3005, 3004, and 3000). All 4 studies involved fixed doses (or fixed dose ranges) for iloperidone, and all 4 had active controls. Three of the 4 studies included a mix of patients with schizophrenia and schizoaffective disorder.

The sponsor also presented data from 3 longer-term trials (Studies 3001, 3002 and 3003) in support of a claim for maintenance efficacy in schizophrenia. The latter 3 studies were active controlled trials, comparing iloperidone with haloperidol, and found no differences between the 2 drugs. Since we have not accepted non-inferiority studies as a reliable source of evidence for efficacy claims in schizophrenia, we did not comment further on these 3 studies in the not approvable letter.

2.2 Basis for 7-25-05 Not Approvable Action (Lack of Sufficient Effectiveness Data)

We accepted study 3101, a 4-week study comparing iloperidone 24 mg/day, ziprasidone 160 mg/day, and placebo in acutely exacerbated schizophrenic patients, as a positive study. In our 7-25-08 not approvable letter, we expressed concerns about the remaining 3 short-term studies, all in patients with a mix of schizophrenia and schizoaffective disorder. In our original review, we focused on the subsets of patients with schizophrenia in studies 3000, 3004, and 3005. Using this approach, we concluded that neither study 3000 nor study 3004 provided evidence in support of a claim for efficacy in schizophrenia, while we considered study 3005 a possibly positive study in the schizophrenic subgroup in a dose range of 12-24 mg/day. We raised 2 additional concerns, however, that we considered sufficient at that time to not consider study 3005 a second source of evidence. The first concern was the relatively consistent finding that iloperidone appeared to be inferior to other treatments, across studies 3000, 3004, and 3005. For study 3005, the iloperidone 12-16 mg/day vs risperidone 6-8 mg/day contrast favored risperidone ($p=0.005$), as did the iloperidone 20-24 mg/day vs risperidone 6-8 mg/day contrast ($p=0.093$), albeit not at the usual $p < 0.05$ level of significance. A second concern was the observation in study 3005 that the positive effect for iloperidone over placebo was coming almost entirely from the non-US sites.

2.3 Basis for 7-25-05 Not Approvable Action (Lack of Sufficient Safety Data)

We also noted in the not approvable letter our concerns about the prominent QT prolonging effect of iloperidone and the difficulty in titrating patients to an effective dose of iloperidone. We indicated that the QT signal would relegate iloperidone to essentially second line status. Based on the statistically significant superiority of risperidone 6-8 mg/day to iloperidone 12-16 mg/day ($p=0.005$) in study 3005, we considered the iloperidone 20-24 mg/day dose range the only acceptable dose range for this drug in this study. Given that the only other source of positive evidence came from an iloperidone dose of 24 mg/day in study 3101, we raised a concern that the sponsor had safety data for only 508 iloperidone patients in this dose range of 20-24 mg/day, including only 64 patients treated for at least 6 months and only 22 for at least 1 year. Thus, we indicated that, even if we were to accept the effectiveness data from studies 3101 and 3005 as sufficient, the sponsor would need at least 1000 additional patients exposed within the 20-24 mg/day dose range, including 300 for 6 months and 100 for 1 year.

2.4 Summary of Efficacy Data for Studies 3000, 3004, and 3005

The sponsor responded to our 7-25-08 not approvable letter with an initial 8-21-08 response, and with several subsequent documents, and then requested a meeting with the division. We provided preliminary comments to the sponsor in which we expressed our continued concern that the application was deficient with regard to both efficacy and safety data. We did, however, acknowledge their complaint that they were not informed until the time of the action letter that we would focus on the subgroups of patients with schizophrenia in studies 3000, 3004, and 3005. We felt, however, that our advice to them to limit enrollment to patients with schizophrenia in study 3101 should have been a clear signal that this subgroup would be our focus in analyzing the other three studies as well. Nevertheless, we indicated that we would consider the data for both approaches, i.e., the schizophrenic subgroup and all patients randomized. What follows under this heading is the summary data for studies 3000, 3004 and 3005, using both approaches and the protocol specified analyses. [Note: these tables are taken from the final meeting minutes for our 9-10-08 meeting with the sponsor.]

Study 3000

FDA analysis: Table 1 summarizes the FDA's analysis focusing on the schizophrenia sample. The primary contrast is between iloperidone 8mg and 12mg combined against placebo. The primary contrast did not separate from placebo (p=0.148), and therefore, no additional comparisons are permitted. Haloperidol is highly statistically significantly superior to placebo (p=0.005) and shows a numerical advantage over all three doses of iloperidone. Haloperidol is also numerically superior to iloperidone 8mg and 12mg combined, although this contrast just misses statistical significance (p=0.063).

Table 1. Study ILP3000ST: FDA's efficacy results: change from endpoint to baseline in PANSS total score (LOCF) in the MITT sample (excluding schizoaffective patients)

	Ilo 4 mg	Ilo 8 mg	Ilo 12 mg	Ilo 8+12mg	Hal 15mg	Placebo
Sample size	83	78	82	160	70	78
LS Means	9.2	4.8	10.1		12.9	3.5
Difference from placebo	5.7	1.4	6.7	4.0	9.4	
Unadjusted p-values	0.072	0.666	0.037	0.148	0.005	
Difference from haloperidol	-3.7	-8.1	-2.8	-5.4		-9.4
Unadjusted p-values	0.261	0.016	0.402	0.063		0.005

(Source: Vanda's Meeting Package, Table 12, Page 27 and FDA's results)

Protocol-specified primary analysis: Table 2 summarizes the protocol-specified primary analysis that includes all randomized patients. The primary contrast is between iloperidone 8mg and 12mg combined against placebo. The primary contrast did not separate from placebo (p=0.065), and therefore, no additional comparisons are permitted. Haloperidol is highly statistically significantly superior to placebo (p<0.001) and shows a numerical advantage over all three doses of iloperidone. Haloperidol is also numerically superior to iloperidone 8mg and 12mg combined, and this contrast is now statistically significant (p=0.027).

Table 2. Study ILP3000ST: sponsor's primary efficacy results: change from endpoint to baseline in PANSS total score (LOCF) in the MITT sample

	Ilo 4 mg	Ilo 8 mg	Ilo 12 mg	Ilo 8+12mg	Hal 15 mg	Placebo
Sample size	113	114	115	229	115	117
LS Means	9.0	7.8	9.9		13.9	4.6
Difference from placebo	4.4	3.2	5.2	4.2	9.3	
Unadjusted p-values	0.097	0.228	0.047	0.065	<0.001	
Difference from Haloperidol	-4.9	-6.1	-4.0	-5.1		-9.3
Unadjusted p-values	0.066	0.022	0.126	0.027		<0.001

(Source: Vanda's Meeting Package, Table 14, Page 28 and FDA's results)

Comment: Thus, either approach to defining the sample for this study yields a negative result for iloperidone. With the sponsor's preferred analysis including all randomized patients, the superiority of haloperidol over the primary iloperidone group (8 + 12 mg) is statistically significant. This study, therefore, provides no support for iloperidone but does suggest the statistically significant superiority of haloperidol over iloperidone.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.