CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-192

SUMMARY REVIEW

MEMORANDUM
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.

Study 3004

FDA analysis:
Table 3 summarizes an analysis excluding schizoaffective patients. A sequential testing approach was employed. First, a comparison was carried out between the 10-16 mg/d group and the placebo group. Subsequently, iloperidone 4-8 mg/d was tested against placebo. The results suggest that both iloperidone groups did not separate from placebo. The results also suggest that risperidone was highly significant against placebo (p=0.001). A comparison between the two iloperidone dose groups against risperidone suggests that risperidone was superior to both iloperidone dose groups (p-value = 0.006 against iloperidone 4-8 mg/d and p-value = 0.021 against iloperidone 10-16 mg/d).

Table 3. Study ILP3004ST: FDA's efficacy results: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 4-8 mg	Ilo 10-16 mg	Risp 4-8 mg	Placebo
Sample size	115	121	110	116
LS Means	5.8	6.5	10.3	4.9
Difference from placebo	0.9	1.7	5.5	
Unadjusted p-values	0.581	0.306	0.001	
Difference from risperidone	-4.5	-3.8		-5.5
Unadjusted p-values	0.006	0.021		0.001

(Source: Vanda's Meeting Package, Table 9, Page 23)

Protocol-specified analysis: Table 4 summarizes the protocol-specified analysis that includes all patients (schizophrenia and schizoaffective). Again, a sequential testing approach was employed. The comparison carried out between the 10-16 mg/d group and the placebo group was statistically significant (p-value = 0.001) in favor of iloperidone 10-16 mg/d. Subsequently, iloperidone 4-8 mg/d was tested against placebo and was statistically significant (p-value = 0.012). A comparison between the two iloperidone dose groups against risperidone suggests that risperidone was superior to both iloperidone dose groups (p-value = 0.007 against iloperidone 4-8 mg/d and p-value = 0.034 against iloperidone 10-16 mg/d).

Table 4. Study ILP3004ST: sponsor's primary efficacy results: change from endpoint to baseline in BPRS total score (LOCF) in the MITT sample

	Ilo 4-8 mg	Ilo 10-16 mg	Risp 4-8 mg	Placebo
Sample size	143	149	146	152
LS Means	6.2	7.2	10.3	2.5
Difference from placebo	3.8	4.7	7.8	
Unadjusted p-values	0.012	0.001	<0.001	
Difference from risperidone	-4.0	-3.1		-7.8
Unadjusted p-values	0.007	0.034		<0.001

(Source: Reproduced from ILP3004st-legacy Report; Table 9.1-2, page 543 and FDA's results)

Comment: Although the all-patients analysis yields a positive result vs placebo for both iloperidone dose groups, both analyses suggest clear inferiority of iloperidone at these doses to a standard dose range for risperidone. Thus, either approach to defining the sample for this study yields a result that favors a standard control agent over iloperidone.

Study 3005

FDA analysis: Table 5 summarizes an analysis excluding the schizoaffective patients. For this study, a sequential testing procedure was employed. Iloperidone 12-16 mg/d was tested first at a 0.05 level. If this test was significant, then the iloperidone 20-24 mg/d would be tested. Both iloperidone dose groups were statistically significantly superior to placebo. The results also suggest that risperidone was numerically, if not statistically, superior to iloperidone at the 20-24 mg/day group (p=0.093), and both numerically and statistically significantly superior to iloperidone at the 12-16 mg/day dose (p=0.005).

Table 5. Study ILP3005ST: FDA's efficacy results: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Sample size	178	111	119	113
LS Means *	7.4	8.8	11.4	4.3
Difference from placebo	3.1	4.5	7.1	
Unadjusted p-values	0.033	0.005	<0.001	
Difference from risperidone	-4.0	-2.7		-7.1
Unadjusted p-values	0.005	0.093		<0.001

(Source: Vanda's Meeting Package, Table 5, page 18 and FDA's results)

Protocol-specified analysis: Table 6 summarizes the protocol-specified primary analysis including both schizophrenia and schizoaffective patients. Iloperidone 12-16 mg/day did not separate from placebo (p-value = 0.09). Consequently, iloperidone 20-24 mg/d cannot be considered. We concluded this was a negative study based on the primary analysis. Risperidone appears to be superior to both iloperidone 12-16 mg/d and 20-24 mg/d (p-values < 0.001 and 0.034, respectively).

Table 6. Study ILP3005ST: sponsor's primary efficacy results: change from endpoint to baseline in BPRS total score (LOCF) in the MITT sample

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Sample size	230	141	148	152
LS Means*	7.1	8.6	11.5	5.0
Difference from placebo	2.1	3.5	6.5	
Unadjusted p-values	0.090	0.010	<0.001	
Difference from risperidone	-4.4	-3.0		-6.5
Unadjusted p-values	<0.001	0.034		<0.001

(Source: Reproduced from ILP3005st-legacy Report; Table 9.1-2, page 586 and FDA's results)

Comment: For this study, the all-patients analysis yields a negative result for the 12-16 mg/day group, and, therefore, the 20-24 mg/day group cannot be considered. Furthermore, this is yet another demonstration of the apparent inferiority of iloperidone at these doses to a standard dose range for risperidone. Thus, once again, either approach to defining the sample for this study yields a result that appears to favor a standard control agent over iloperidone.

In summary:

- For study 3000, whether the analysis focuses on the schizophrenic subgroup or all patients, it does not provide evidence of efficacy for iloperidone. Furthermore, in the sponsor's preferred analysis including all patients, haloperidol is clearly superior to placebo and appears to be statistically significantly superior to iloperidone.

- For study 3004, the analysis including all patients does show superiority of iloperidone over placebo, a finding that is not seen for the analysis including only schizophrenic patients. In both instances, however, risperidone appears to be statistically significantly superior to iloperidone.
- For study 3005, only the analysis focused on the schizophrenic subgroup shows superiority of iloperidone over placebo. In the sponsor's preferred analysis, iloperidone fails to show superiority to placebo and, at the same time, risperidone appears to be statistically significantly superior to iloperidone.

2.5 Comment on 9-10-08 Meeting with Sponsor

I refer to the final minutes for this meeting for complete details on the proceedings and outcome.

The sponsor made a number of arguments in favor of iloperidone, several of which we acknowledged had some plausibility and encouraged them to elaborate on in their complete response: (1) their contention that the apparent inferiority of iloperidone to the active comparators risperidone and haloperidol is only temporary due to differences in the time it takes to get patients to effective exposures for iloperidone, (2) their contention that this early difference does not represent a significant risk to patients, and (3) their contention that there are certain safety advantages that iloperidone has over other antipsychotic drugs in the class that tend to mitigate this early disadvantage in efficacy. We did not accept their argument about the need for multiplicity adjustments for the comparisons of active control drugs to iloperidone. Using a sequential approach, there still remain 2 illustrations of an apparent disadvantage for iloperidone in efficacy.

There remained a concern, however, about the primary source of evidence for the efficacy of iloperidone.
-We still considered study 3101 the only unambiguously positive study.
-We remained concerned about the sponsor's focus on study 3004 as a primary source of evidence, since this study was based on the all-randomized patients analysis. We found this problematic because of the striking differences in outcomes for the schizophrenic and schizoaffective subgroups, and the analysis focusing only on the schizophrenic subgroup is not positive.
-We continued to consider study 3000 negative overall.
-We continued to consider study 3005 as a possible primary source of support. We favored the analysis focusing on the schizophrenic patients, which we found to be positive. We remained concerned, however, about the geographic disparity in results. The positive findings came almost entirely from non-US sites. Thus, we indicated that they would need to make a convincing argument that this disparity should not be a concern.

3.0 SPONSOR'S 11-6-08 RESPONSE TO 7-25-08 NOT APPROVABLE LETTER

In its 11-6-08 response, the sponsor argues that they have provided positive results for the effectiveness of iloperidone in the acute treatment of schizophrenia in 2 adequate and well-controlled trials, i.e., studies 3101 and 3004. They further argue that studies 3000 and 3005

provide supportive evidence for the acute efficacy of iloperidone and that studies 3001, 3002, and 3003 provide evidence for the maintenance efficacy of iloperidone in schizophrenia. They acknowledge our arguments that they have not provided sufficient evidence for the acute and maintenance efficacy of iloperidone in schizophrenia, but note that they disagree. They indicate that they can show that iloperidone is effective for this indication in the US population, has comparable efficacy to other available antipsychotic agents, and has certain safety advantages over other available antipsychotic agents.

3.1 Evidence of Efficacy for Iloperidone

As noted, the sponsor considers studies 3101 and 3004 as their primary sources of support for the efficacy of iloperidone in the acute treatment of schizophrenia, and studies 3000 and 3005 as supportive sources of evidence. Since we agree that study 3101 is a positive study, I will not comment further on that study (already fully described in previous reviews). I will also not comment further on studies 3001, 3002, and 3003. These were active-controlled maintenance studies that relied on findings of no difference between iloperidone and haloperidol. We have not yet accepted non-inferiority designs as a primary source of support for efficacy claims.

3.1.1 Study 3004

The results for study 3004 are provided in section 2.4, but as noted in section 2.5, we still do not find this study an acceptable source of evidence. Although the results for both dose groups in the all-randomized patients analysis are positive, there is a striking difference in outcomes for the schizophrenic and schizoaffective subgroups. The analysis focusing only on the schizophrenic subgroup is not even close to positive for either dose group ($p=0.306$ for 10-16 mg/day and $p=0.581$ for 4-8 mg/day).

In its response, the sponsor focuses heavily on an argument that we should not distinguish between schizophrenia and schizoaffective disorder. They argue that this is a difficult distinction in the acute setting and that the treatment of psychotic symptoms in the acute setting is the same, regardless of the diagnosis.

> Comment: While these may be true statements, they are irrelevant to this discussion. The investigators had some basis for making the diagnoses they made, and it is highly inappropriate for the sponsor or its consultants to discard these judgments that the protocol required the investigators to make. The more important facts are that these are considered distinct diagnoses by DSM-IV, however difficult it is to distinguish them acutely, and the outcome is strikingly different for the different subgroups.

The sponsor also argues that the finding for the schizoaffective subgroup, making up a mere 22% of the sample, is an "anomaly." They note that the schizoaffective patients on placebo had scores that actually worsened by an average of 5.9 points compared to an improvement of 4.9 points in the schizophrenic placebo sample.

> Comment: This may be an anomaly, however, the problem is not fixed by simply combining all the data to reach a conclusion. The anomaly is what is driving the overall positive result. Given this finding, the entire result should be discarded. This is clearly not just a power problem. We would not have objected if the effects were similar in the

schizophrenic and schizoaffective patients, and the p-value for the schizophrenic subgroup would become significant if the sample size had been increased slightly. Clearly that would not have helped in this situation. Consequently, I am not persuaded by Vanda's arguments for relying on the all patients analysis for study 3004. I do not consider study 3004 a valid source of evidence to support a claim for the acute treatment of schizophrenia.

3.1.2 Study 3000

The sponsor continues to argue that the finding for the 12 mg/day dose arm for the all patients analysis (p=0.047) should be considered supportive evidence.

Comment: As noted under section 2.4, this is a negative study whether considered for the schizophrenic subgroup or the all patients analysis. One is not entitled to look at the 12 mg/day group for the all patients analysis because the combined 8+12 mg/day group is not significant. Thus, this study cannot be considered a primary source of support for the efficacy of iloperidone. Nevertheless, I do agree that the data for the 12 mg dose are consistent with the positive finding in study 3005 for efficacy in a range of 12 to 16 mg/day.

3.1.3 Study 3005

The sponsor concedes that study 3005 is a negative study based on their preferred all patients analysis. Based on several other findings, they feel it can still be considered a source of supportive evidence. In our not approvable letter, we focused on analyses looking at the schizophrenic subgroups in studies 3000, 3004, and 3005. In these subgroup analyses, we found study 3005 to be a positive study (see section 2.4). We did, however, raise 2 concerns about this study. One concern had to do with the apparent inferiority of iloperidone to risperidone in this study. The other concern was the fact that the positive findings appeared to be coming almost entirely from the non-US sites. The issue of comparative efficacy will be addressed in section 3.2. In responding to our concern about the geographic disparity, the sponsor used several arguments:

(1) First, they argued that, in studies 3101 and 3004, subgroup analyses in the US population demonstrated a consistent superiority for iloperidone over placebo.

(2) They also argue that, for the US subgroup in study 3005, neither iloperidone nor risperidone was superior to placebo. Thus, they consider the US subgroup in this study a failed experiment that cannot be interpreted. The following table supporting this assertion was taken from the statistics review:

Table 36. Study ILP3005ST: reviewer's primary efficacy results by region: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 10-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
U.S.A.				
Sample size	75	50	48	53
LS Means *	6.53	6.66	8.99	5.44
Difference from placebo	1.08	1.21	3.54	
(95% confidence interval)	(-3.06, 5.22)	(-3.32, 5.74)	(-0.98, 8.07)	
Unadjusted p-values	0.607	0.599	0.124	
Non-U.S.A.				
Sample size	103	61	71	60
LS Means *	8.33	10.56	13.28	3.45
Difference from placebo	4.89	7.11	9.84	
(95% confidence interval)	(1.02, 8.75)	(2.80, 11.42)	(5.65, 14.02)	
Unadjusted p-values	0.014	0.001	<0.001	

(Source: reviewer's results)
* Reviewer's note: positive changes indicate improvements

(3) Finally, they argue that the non-US sites for study 3005 (i.e., Canada, Germany, Hungary, Poland, Croatia, and Israel) all represent ethnic groups that are also well-represented in the US and, thus, can be considered reasonable surrogates for the US population.

Comment: The geographic disparity was never a major concern for me, and I still consider it reasonable to look primarily at the schizophrenic subgroup as we did in our original analysis of this study. I accept their argument that the data from the US sites are not interpretable, as no effect is shown for either active drug. Study 3101 does provide evidence of efficacy in a US population. Thus, I consider study 3005 a second primary source of evidence for the claim of the acute treatment of schizophrenia. I will address the issue of comparative efficacy in section 3.2.

Efficacy Summary

I am in agreement with the sponsor that study 3101 is one primary source of positive evidence for iloperidone. I disagree with them, however, on study 3004 as a second primary source of evidence. I think the data for that trial are fatally pathological, and one cannot reasonably pool data from the schizophrenic and schizoaffective subgroups. It is not that I fundamentally object to pooling data from schizophrenic and schizoaffective patients (we have accepted this approach many times in the past), but for this study, where the positive finding in the schizoaffective patients is by the sponsor's own admission an "anomaly," there is no justification for such a pooling. Thus, I find this study uninterpretable. Study 3000 also cannot be a primary source of support for iloperidone (but the data for 12 mg are consistent with findings in the 12-16 mg range for study 3005). That leaves only study 3005. As I have indicated, I am now willing to consider study 3005 as a second primary source of evidence for iloperidone. As noted, the 2 objections to the data for this trial were the comparative efficacy findings, which I will address in section 3.2, and the geographic disparity. I am persuaded by the sponsor's argument that the lack of efficacy in the US sites for study 3005 should not rule out this study as a source of evidence. As they point out, risperidone also failed in the US sites, and thus, data from these sites is simply uninterpretable. They have other positive data for US sites, in particular, from

study 3101. Although I do not believe we should rely on the noninferiority findings from the 3 maintenance studies (studies 3001, 3002, and 3003) as support for a maintenance claim for iloperidone, I do believe this additional suggestive evidence of iloperidone's efficacy in schizophrenia can be considered in the overall decision for this drug. Thus, I believe the sponsor has provided data from 2 adequate and well-controlled trials in support of a claim for the acute treatment of schizophrenia.

3.2 Relative Efficacy of Iloperidone vs Other Antipsychotic Drugs

As noted, one of our concerns expressed in the not approvable letter was the rather consistent finding across studies 3000, 3004, and 3005 that iloperidone appeared to be inferior on the primary efficacy assessment to an active control antipsychotic agent. This was true whether or not the study could be considered positive for iloperidone (see section 2.4). The reason we considered this problematic was that such inferiority might represent a risk to schizophrenic patients. In this section, I will consider the sponsor's arguments about comparative efficacy, and in section 3.3 I will consider the sponsor's arguments that, even if true, such an inferiority could not reasonably be considered a risk to patients.

The sponsor proposes 4 arguments for why we should not be concerned about the finding of apparent inferiority of iloperidone to an active control agent in studies 3000, 3004, and 3005:

-Study 3101 (iloperidone vs ziprasidone): The sponsor points out that iloperidone was shown to be equivalent to ziprasidone in study 3101, a placebo-controlled short-term study.

> Comment: I agree that this was the case. However, this was the only one of the 4 short-term placebo controlled trials in which this was the case.

-12 mg/day iloperidone vs haloperidol in studies 3000, 3001, 3002, and 3003: The sponsor points out that the 12 mg/day dose group in study 3000 was not statistically significantly different than the haloperidol arm in that study (p=0.4). They also note that in the acute phase of the 3 haloperidol controlled trials (i.e., no placebo group; studies 3001, 3002, and 3003), iloperidone 12 mg/day was equivalent to haloperidol.

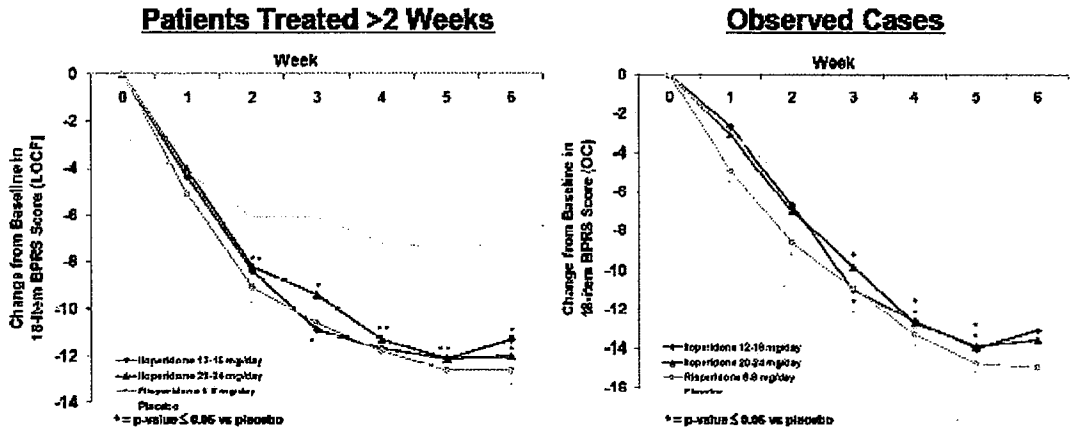
> Comment: Again, I don't disagree with this observation. However, the active control studies (3001, 3002, and 3003) are difficult to interpret. And the 12 mg/day iloperidone arm is only 1 of several iloperidone dose groups in study 3000. The other iloperidone dose groups were inferior to haloperidol. On the other hand, it is true that 12 mg/day appears to be the lower end of the effective dose range for iloperidone.

-Apparent Inferiority as a Result of Titration Differences: The sponsor argues that the apparent inferiority of iloperidone to active control agents in several of their studies can be largely explained by slower titration rates for iloperidone compared to the active control agents in those trials. The result of this slower titration was a higher dropout rate for lack of efficacy in the iloperidone arms. [For example, in study 3005, dropouts for lack of efficacy were 23% in both the 12-16 and the 20-24 mg/day iloperidone arms, compared to 8% for the risperidone arm.] In the LOCF analyses, these higher dropouts resulted in an apparent inferiority. The sponsor argues that, when titration for the control agent was done at a slower, comparable rate to that for iloperidone, efficacy was comparable for iloperidone and the active control agent. The sponsor

cites studies 3101 (a comparison with ziprasidone) and the 12 mg iloperidone vs 15 mg haloperidol comparison in study 3000 as examples of comparable titration where efficacy was also comparable. In both studies, the titration period to achieve the target dose was 7 days for both active agents.

The 2 more problematic studies for iloperidone, in terms of comparative efficacy, were studies 3004 and 3005. In both studies, iloperidone appeared to be inferior to risperidone with regard to the efficacy outcomes. Given my current view that study 3004 has a pathological outcome that renders it completely uninterpretable, I will not consider it further in this discussion of comparative efficacy. That leaves only study 3005. It is true that the time periods to reach an effective target dose of iloperidone and risperidone were strikingly different in study 3005, i.e., 7 days for iloperidone and 2 days for risperidone. Because it takes roughly 5 days to reach steady state concentrations with iloperidone once the target dose is achieved, it would be roughly 2 weeks before patients could achieve steady state concentrations. The sponsor conducted exploratory analyses looking at mean change from baseline to endpoint for the subgroup of patients who remained on assigned treatment for at least 2 weeks, in order to assess how the different active treatments might compare for patients who could achieve an effective steady state concentrations for both active drugs. It is of some interest that this analysis, although post-hoc and clearly exploratory, does show comparable efficacy for both iloperidone dose groups (10-16 and 20-24 mg/day) and risperidone 6-8 mg/day. The following figures (taken from sponsor's 11-6-08 response to the NA letter) illustrate this finding of comparable efficacy for iloperidone and risperidone in study 3005 for patients remaining in treatment for at least 2 weeks, and also in the observed cases analysis for this study:

Figure 11: Study 3005: Mean Change from Baseline in 18-Item BPRS Score - >2 Week LOCF and OC Analysis



Source: Module 2.7.3 Figure 11 and primary data submitted in NDA 22-192

It is noteworthy that our MMRM analysis (an analysis that is perhaps more appropriate in this setting with early dropouts for lack of efficacy) for the schizophrenic subgroup (the group most relevant for this application) suggests a highly significant result in favor of iloperidone for both

dose groups; these results are still numerically inferior to those for risperidone, but the difference are not as large as seen in other analyses.

Table 1. Study ILP3005ST: reviewer's MMRM results: change from endpoint to baseline in BPRS total score (schizophrenia patients)

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8mg	Placebo
LS Means	9.9	10.3	13.0	5.5
Difference from placebo	4.4	4.8	7.5	
(95% confidence interval)	(1.2, 7.7)	(1.3, 8.3)	(4.1, 10.9)	
Unadjusted p-values	0.008	0.008	<0.001	

(Source: reviewer's results. Model terms include baseline BPRS total score, center, treatment, time, and treatment-by-time interaction)
* Reviewer's note: positive changes indicate improvements

-Multiplicity Adjustments: The sponsor also argues that multiplicity adjustments are needed when making the comparisons of active control agent with the various iloperidone dose groups in these studies. They have proposed several different adjustments and argue that there are very few significant comparisons left after making such adjustments.

Comment: I think a more reasonable approach is to begin with the highest iloperidone dose group and move sequentially to lower iloperidone dose groups, only if significance is found at the higher dose groups, without the need for adjustment. Given the earlier discussion, I think the only comparisons left that are of interest come from study 3005. For this study, both iloperidone dose groups appear to be inferior to the risperidone group. However, as noted, if one looks at iloperidone patients who were able to achieve steady state at the target dose, the efficacy differences are less prominent.

Overall Comment on Comparative Efficacy: Given all of the above observations, I am inclined to agree with the sponsor that attempting to make efficacy comparisons of the active treatment arms in these trials is complex and problematic. When all the data are considered, the only differences that stand up are for study 3005, and even those are minimized when patients with optimal exposures to drug are compared. I still think this difference in the ability to titrate drugs like iloperidone and risperidone is meaningful and possibly important in a clinical setting, and might even be noted in labeling. However, I now agree that this difference should not be the basis for a rejection of this application. This conclusion is also importantly influenced by considerations in section 3.3 that the risks associated with such apparent differences in early efficacy that are based on the need for slower titration are difficult to define and may not be clinically meaningful.

3.3 Risks Associated with Relative Inferiority of Iloperidone

The FD&C Act does not require that a new drug has to be more effective than, or even equally effective to, already available treatments for the indication of interest. A new drug merely needs to be effective, i.e., better than placebo. In fact, in the 7-25-08 not approvable letter for iloperidone, we were clear that our concern about a possible inferiority for iloperidone relative to other drugs in this class had to do with the possible risk resulting from such inferiority, rather than the inferiority per se. So, apart from the question of relative inferiority, which the sponsor disputes (see section 3.2), they argue that the inferred risk is also not real. In the sponsor's view,

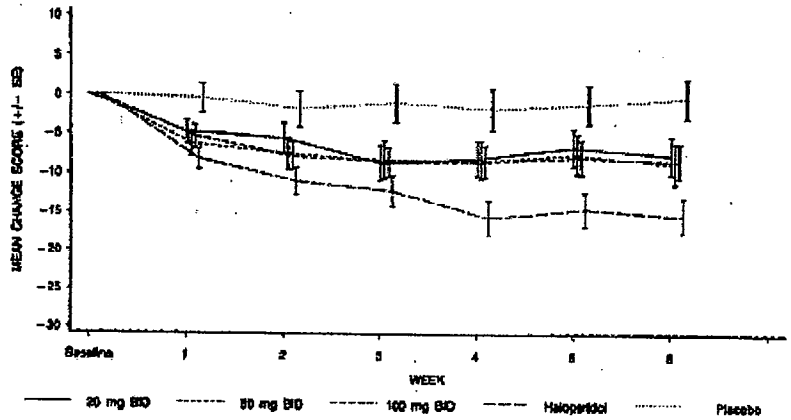
the only problem with iloperidone is the need for a more gradual titration to achieve an effective exposure compared to some other antipsychotic agents. While acknowledging this "problem," they argue that this need for a more gradual titration does not in fact confer any risk in a clinical setting. They make the following arguments to support their case:

-Artificially inflated dropouts for lack of efficacy in placebo-controlled trials: The sponsor cites a paper by Kemmler (Kemmler, et al, 2005) to make the case that placebo-controlled trials (PCTs) result in increased dropouts in patients in the active treatment arms, both overall and for lack of efficacy, compared to active-controlled trials (ACTs). The weighted mean dropout rates overall in the active treatment arms of atypical antipsychotic PCTs were 48%, compared to 28% in ACTs. The weighted mean dropout rates for lack of efficacy in the active treatment arms of atypical antipsychotic PCTs were 26%, compared to 10% in ACTs. The sponsor cites dropout data from the acute phase of 3 of its active-controlled trials (3001, 3002, and 3003) as further support of this problem (about 70-80% of patients completed these trials compared to only 40% completion rates for a similar PCT [study 3000]). Kemmler, et al, argue that this finding is in part due to investigators' concerns that patients in PCTs might be getting placebo and are, therefore, not being effectively managed.

-Equivalent efficacy for iloperidone once effective plasma levels are achieved: As noted in section 3.2, patients in study 3005 who were able to stay in for at least 2 weeks did show comparable efficacy for iloperidone and risperidone.

-Iloperidone is not alone among antipsychotic drugs in having a need for more gradual titration: The sponsor correctly points out, and supports with data, the fact that similar patterns of dropout for lack of efficacy as seen with iloperidone are seen with PCTs of quetiapine and ziprasidone, antipsychotic drugs that also require more gradual titration. For each of these development programs, there was only 1 study using an active comparator drug, haloperidol in both cases. Both quetiapine and ziprasidone appeared to be inferior to haloperidol in these trials, i.e., findings very similar to what is seen with iloperidone. The following figure provides the data from the only ziprasidone study in that NDA including an active control:

Figure 14: Ziprasidone Study 115: PANSS Total Score Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF



Source: Adapted from the Geodon NDA 20-825 Statistical Review

-Important differences between clinical trials and clinical practice: The sponsor argues that PCTs do not mimic clinical practice with regard to dropouts due to lack of efficacy. They argue that current guidelines for the management of exacerbated schizophrenic patients emphasize the need for rapid control of agitation using intramuscular benzodiazepines or atypical antipsychotic drugs in the first few days and then gradually shifting the focus to working with the patient to find an antipsychotic medication for the patient that will be both effective and well-tolerated for the longer term. Unfortunately, medications that are effective acutely may not be well tolerated more chronically, e.g., EPS and weight gain. Switching to a better tolerated antipsychotic agent may mean adjunctive therapy and even cross-titrating for several weeks to maintain control. The sponsor argues that these adjunctive treatments permit patients to remain in treatment during the several weeks it may take to switch patients to a better tolerated medication. Such strategies are not permitted during usual PCTs, resulting in substantial dropouts.

-Absence of demonstrated risk from ineffective antipsychotic treatment even in the artificial context of the placebo-controlled trial: The sponsor also argues that, even in the context of PCTs with antipsychotic drugs, as artificial a setting as this is, there is no evidence of excess risk from ineffective treatment. They cite a paper that I authored several years ago (Laughren, 2001) in which I looked at suicides occurring in the context of PCTs in schizophrenia. I did not find any excess suicides associated with placebo assignment, and I argued that such a finding provides support for the continued use of placebo in these trials. In fact, we rarely see suicides occurring in the controlled phase of antipsychotic trials in schizophrenic patients. Suicides are actually not uncommon in antipsychotic development programs. However, they almost all occur during longer-term open extensions in patients who are already stabilized and are taking what would be expected to be effective doses of antipsychotic agents. This finding is in fact consistent with the widely held clinical view that the period of greatest risk for suicide in schizophrenic patients is during the residual phase of the illness, when they are stabilized regarding positive symptoms but still suffering from substantial negative symptoms.

-Overall comments on possible risks associated with a perceived relative inferiority of iloperidone: I think the sponsor has made a reasonable argument that we have not established that there is an actual risk associated with the perceived lesser efficacy of iloperidone compared to other antipsychotic agents. It is likely that the maintenance phase of treatment would be of much greater relevance in terms of any differences in relative efficacy, and what little data we have regarding iloperidone's relative efficacy during chronic use suggests that it is comparable to other antipsychotic agents. Thus, I am inclined to agree that we have not made a good case for risk associated with the perceived inferiority.

3.4 Selection of Dosing Range for Iloperidone (and establishing acceptability of available iloperidone data for safety purposes)

The sponsor argues for a target iloperidone dose of 12 mg/day, and an effective dose range of 12-24 mg/day. They are focused on findings from studies 3101 and 3004 as primary sources, while I consider studies 3101 and 3005 as the most appropriate primary sources. Nevertheless, I agree with their conclusion. The 12-16 mg/day dose range in study 3005 was effective, and the effect size was not so different that that seen for the 20-24 mg/day dose arm in that trial, particularly in the MMRM analysis. As additional evidence, the sponsor cites the 3 maintenance studies (3001, 3002, and 3003) in which the modal iloperidone dose was 12 mg/day. Finally, the sponsor cites their PK-PD modeling in which they find a plateau in the concentration response curve at about 5 ng/ml, which is equivalent to a dose of about 12 mg/day. Generally no additional benefit is observed as the dose is pushed above 12 mg/day in this analysis. [Note: Although this PK-PD modeling is difficult to interpret, there is nothing here to dispute the efficacy of 12 mg/day.] As a result of this assessment, the sponsor argues that the currently available safety data within the dose range of 12-24 mg/day is sufficient to support the safety of iloperidone. I agree.

3.5 Safety Advantages for Iloperidone

The sponsor notes that an important deterrent to compliance with antipsychotic medications is poor tolerability, and they argue that iloperidone has some relative advantages regarding tolerability compared to other atypical antipsychotic medications. In particular, they view iloperidone as having advantages for akathisia, EPS, sedation, and prolactin elevation. Iloperidone's metabolic effects relative to other antipsychotic drugs will also be considered here. The sponsor indicates that these advantages are most prominent at the 12 mg/day dose, another argument for targeting this dose. [Note: I will not be reviewing these data critically, since the sponsor is not making any comparative claims, but rather, assessing whether the data are at least suggestive of possible advantages for iloperidone compared to other antipsychotic drugs. The data were derived from studies 3000, 3004, 3005, and 3001.]

3.5.1 Akathisia

Akathisia was assessed as an adverse event (AE), and using either the Extrapyramidal Symptoms Rating Scale (ESRS) or the Barnes Akathisia Scale (BAS).

-As an AE, akathisia for iloperidone was not distinguishable from placebo in any of the 4 studies, but clearly distinguishable from haloperidol in study 3000, from risperidone in studies 3004 and 3005, and from ziprasidone in study 3101.
-Formal assessments for akathisia using the ESRS in study 3000 and the BAS in studies 3004, 3005, and 3101 generally showed similar results, i.e., iloperidone could not be distinguished from placebo, while there were often signals of akathisia for the comparator drugs.

3.5.2 Extrapyramidal Symptoms (EPS)

EPS were assessed as an adverse event (AE), and using the Extrapyramidal Symptoms Rating Scale (ESRS).
-Muscle rigidity and tremor were dose-related events for iloperidone, but at lower levels than for the active controls haloperidol, risperidone, and even ziprasidone.

3.5.3 Sedation

Sedation was also dose-related for iloperidone, but much superior to that seen with ziprasidone in study 3101, and somewhat superior to sedation with risperidone.

3.5.4 Prolactin Elevation

Iloperidone was prolactin neutral in the short-term trials, and clearly distinguishable from both haloperidol and risperidone in this regard. Ziprasidone was also prolactin neutral in study 3101.

3.5.5 Metabolic Effects (Weight Gain and Effects on Tryglycerides, Cholesterol, and Glucose)

Iloperidone is associated with modest weight gain over the course of short-term trials, similar to that seen with risperidone. Iloperidone appears to fall in the middle among the atypical antipsychotic drugs with regard to weight gain (aripiprazole and ziprasidone at the low end and olanzapine and quetiapine at the higher end). Iloperidone had essentially no impact on triglyceride, cholesterol, or glucose levels in the short-term trials. It's profile was most similar to ziprasidone with regard to the laboratory parameters.

3.5.6 Conclusions Regarding Safety Advantages for Iloperidone

Iloperidone appears to have a reasonably favorable adverse event profile compared to several of the other atypical antipsychotics. Iloperidone does, of course, have a QT prolonging effect (see my 7-11-08 memo), but no worse than is seen with ziprasidone.

3.6 Other Issues in Not Approvable Letter

3.6.1 Data from Gilliam's Site

In the not approvable letter, we noted potential problems with this investigator, and asked the sponsor to evaluate the impact of data coming from this site. Dr. Gilliam was an investigator in

only 1 study, i.e., study 3101, and we had already confirmed that this remained a positive study for iloperidone with data from that site excluded. The sponsor confirmed our findings.

3.6.2 Hepatic Compromise Study

In the not approvable letter, we had asked the sponsor to repeat the hepatic compromise study. In our 9-10-08 meeting with the sponsor, we reached agreement that this could be accomplished as a phase 4 commitment. In the meantime, the sponsor has agreed to labeling that recommends not using iloperidone in patients with hepatic impairment.

3.6.3 P-Gp Interaction Study

In the not approvable letter, we had asked for an in vitro interaction study for iloperidone and P-Gp. In our 9-10-08 meeting, we reached agreement that this could be accomplished as a phase 4 commitment.

4.0 LABELING AND ACTION LETTER

4.1 Labeling

4.2 Foreign Labeling

Iloperidone is not approved anywhere at this time for the treatment of schizophrenia.

4.3 Action Letter

We have reached agreement with the sponsor on final labeling which is included with the approval letter.

We have secured phase 4 commitments to conduct a maintenance study, to repeat the hepatic compromise study, and to conduct an in vitro P-Gp interaction study. The sponsor has also agreed to our requirement to plan and conduct a pediatric program in adolescents with schizophrenia.

5.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC. There are several previously approved atypical antipsychotic agents similar in overall activity to iloperidone, and an evaluation of the safety data for iloperidone did not reveal particular safety issues that were so unexpected for a drug in this class as to justify a PDAC meeting. Furthermore, the design and results of the efficacy trials did not pose any unusual concerns that we could not address within our group. Overall, there were no sufficiently controversial issues that would have benefited, in my view, from advisory committee discussion.

6.0 CONCLUSIONS AND RECOMMENDATIONS

I recommend that we issue an approval letter with our mutually agreed upon final labeling for iloperidone in the acute treatment of schizophrenia.

cc:
Orig NDA 22-192
ODE-I/RTemple
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DOC: AP Memo_Iloperidone_Schiz_Laughren.doc

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

/s/

Thomas Laughren
3/27/2009 01:26:39 PM
MEDICAL OFFICER