CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022567Orig1s000

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: January 18, 2011

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

SUBJECT: Recommendation for approval action for vilazodone tablets as a treatment for major depressive disorder (MDD).

TO: File NDA 22-567
[Note: This overview should be filed with the 3-22-10 original submission of this NDA.]

1.0 BACKGROUND

Vilazodone is a new antidepressant that has been developed for the treatment of MDD. Vilazodone's antidepressant effect is thought to be mediated through its activity as an SSRI and as a partial agonist at the 5HT1A receptor. There are multiple other drugs in the antidepressant class already approved for the treatment of MDD, however, this would be the first with this particular combined activity. This application is based on data from 2 short-term trials. The proposed dose is 40 mg/day, to be given on a qd basis, with food. Vilazodone is available as 10, 20, and 40 mg immediate release tablets.

The studies in support of this application were conducted under IND 54613. Several meetings were held with the various sponsors over the course of its development. The IND has been held by several different sponsors over its long course. The IND was initially submitted 11-21-97. An early EOP2 meeting was held with the sponsor on 12-20-05, however, this was clearly premature. This meeting focused on a proposed design for the first phase 3 study. Subsequent meetings were held on 8-7-06, 8-20-07, and 5-11-09. The 8-7-06 meeting was another early meeting to discuss CMP, OCP, and pharm/tox issues. The 8-20-07 meeting was focused on their genetic analysis plan, since at that time the sponsor hoped to utilize biomarkers in their development program. The 5-11-09 meeting was to discuss their second phase 3 study and again their plans for genetic analyses. A preNDA meeting was planned for June, 2009, however, this was cancelled since the sponsor found our preliminary comments sufficient to answer all of their questions. Ultimately, they dropped their plans to include analyses of genetic data as part of this NDA.

The primary clinical reviewer for this application was Dr. Cheri Lindberg and the primary statistical reviewer was Dr. Philip Dinh. A secondary review of this application was conducted by Dr. Robert Levin.

2.0 CHEMISTRY

The CMC review was conducted by Drs. Pei-I Chu, Ph.D. and Tien-Mien Chen, Ph.D., and they have recommended approval. Rik Lostritto, Ph.D., has written a Division Director memo confirming that all CMC issues have been resolved, and has also recommended an approval action. The preapproval inspections have been satisfactorily completed. The proposed name, Viibryd, has been accepted by DMEPA.

3.0 PHARMACOLOGY

The pharm/tox review was conducted by Violetta Klimek, Ph.D. and supervisory overviews were provided by Linda Fossom, Ph.D., Barry Rosloff, Ph.D, and Paul Brown, Ph.D.. All pharm/tox questions and issues have been resolved, including agreement on the pharm/tox sections of final labeling. (b) (4)

Nevertheless, they have now finally accepted our proposed language for mechanism of action in section 12.1. (b) (4) The pharm/tox group does not have any other concerns that would preclude a final approval action for this application.

The 2 major human metabolites of vilazodone (M10 and M17) do not appear to have important serotonergic activity. Both have been adequately assessed for toxicity, however, it is unclear if one (M17) has been assessed for embryofetal toxicity, since its presence was not confirmed in the rat or rabbit studies. The sponsor has agreed to explore this issue post-approval.

Specifications for several genotoxic or potentially genotoxic impurities have been limited so that human exposure will be no more than (b) (4) µg of each per day at the MRHD of 40 mg/day.

The sponsor has agreed to conduct a juvenile animal study in rats prior to conducting pediatric studies in children less than 13 years of age.

Teratogenicity, carcinogenicity, mutagenicity, and fertility findings with vilazodone can be summarized as follows:

-Vilazodone caused some developmental toxicity in rats and rabbits at doses that were several multiples of the maximum recommended human dose (MHRD), but not at lower multiples, i.e., 10 times the MRHD for rats and 4 times the MRHD for rabbits. Vilazodone was not teratogenic in either species.
-Two-year carcinogenicity studies were conducted in B6C3F1 mice and Wistar rats. There were no findings in the rat study. In mice, hepatocellular carcinomas and mammary gland adenocarcinomas were observed at doses that were several multiples of the maximum recommended human dose (MHRD), but not at lower multiples, i.e., 5.5 times the MRHD for the hepatocellular carcinomas and 1.8 times the MRHD for the mammary gland adenocarcinomas. The clinical significance of these findings for humans is unknown.
-Mutagenicity assays were mixed, with negative findings in two in vitro assays, but positive findings in two in vitro clastogenicity assays. Findings were negative, however, in two in vivo clastogenicity assays, and in an in vivo/in vitro unscheduled DNA synthesis assay.
-A fertility assay in rats revealed positive findings in males at 40 times the MRHD, but not at 6 times the MHRD.

4.0 BIOPHARMACEUTICS

The OCP review was conducted by Drs. Bei Yu, Huixia Zhang, Jee Eun Lee, Atul Bhattaram, Yaning Wang, Issam Zineh, and Li Zhang.

There were 24 phase 1 studies in the vilazodone program, including 9 bioavailability/bioequivalence studies, a mass balance study, 2 food effect studies, renal and hepatic impairment studies, an elderly study, 2 drug-drug interaction studies, and 7 special studies. The 7 special studies included: PET study; REM suppression study; thorough QT study; ethanol interaction study; gastric pH study; a sleep EEG study; and a study on ejaculatory effects. There were also 9 in vitro studies.

PET Study

Study 255 was conducted to evaluate occupancy for the 5HT1A receptor. Single vilazodone doses of 20 and 40 mg were assessed. There was little evidence for occupancy at the 20 mg dose, however, 5HT1A occupancy at the 40 mg dose was found to be in the range of 15-35%. This study was considered part of the basis for the 40 mg dose selection for the definitive phase III trials. It might be argued, however, that multiple dose studies would have been preferable, given the relatively long elimination half-life of vilazodone (around 26 hours) with an accumulation ratio of approximately 1.8.

Pharmacokinetic Profile for Vilazodone

Vilazodone's clinical effects are thought to be due primarily to the parent drug. Its pharmacokinetic properties are summarized in the following table, from the OCP review:

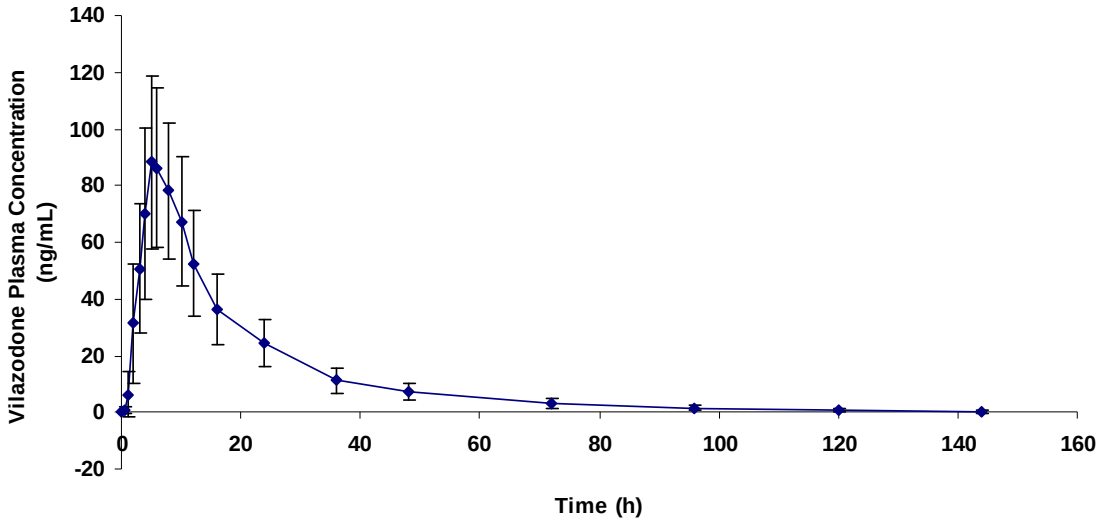
Table 1: Important PK properties of vilazodone

PK Property	PK Parameter	
Dose-proportionality	PK dose-proportional for doses 5 – 80 mg	
Absorption	Tmax (median), hour	4-5
	T1/2, hour	~25
	Absolute Bioavailability (with food), %	72
	Food Effect	High fat/light meal increased C_{max} and AUC by ~2-fold.
Distribution	Protein Binding, %	96-99
Metabolism	Pathways	CYP (3A4 is the primary isoenzyme, with the minor contributions from CYP2C19 and 2D6) and non-CYP (possibly by carboxylesterase). No active metabolites.
Excretion	A mass balance study for vilazodone showed ~85% of the administered radioactivity was recovered in the urine (~20%) and feces (~65%) combined, while ~ 3% of the administered dose of vilazodone was recovered as unchanged drug (~1% in urine, and ~2% in feces).	

Accumulation of vilazodone is predictable from single dose data (accumulation factor of about 1.8), does not vary with dose, and steady state is achieved in about 3 days. The steady state mean Cmax value after daily dosing with vilazodone 40 mg under fed conditions is 156 ng/mL.

The following figure from the OCP review illustrates the time-concentration profile for vilazodone following a single 40 mg dose:

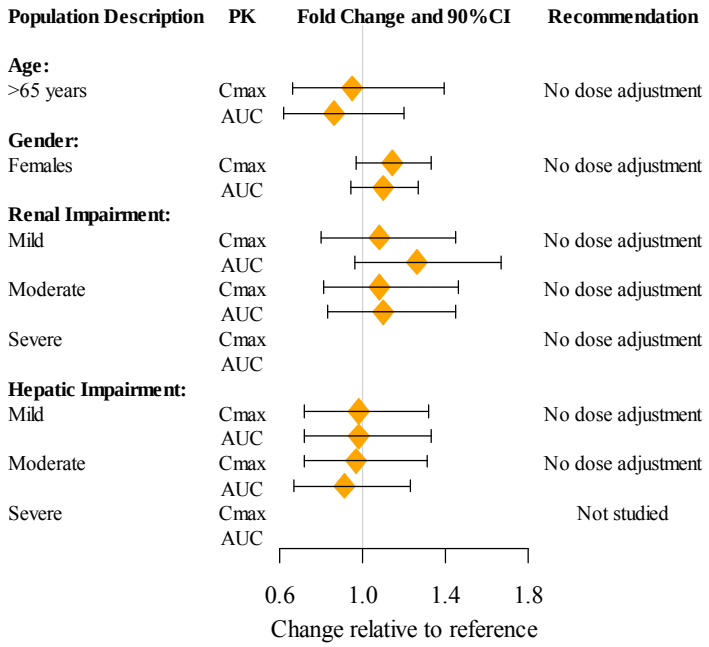
Figure 1. Mean (± SD) vilazodone plasma concentration versus time profile after oral single dose of 40 mg vilazodone tablet under fed conditions.



The Effect of Intrinsic and Extrinsic Factors on Vilazodone's Pharmacokinetics

Effect of Intrinsic Factors: The study of various intrinsic factors on vilazodone's pharmacokinetics suggest that no dosage adjustment is needed based on age, gender, renal, or hepatic impairment (See Figure 2, from the OCP review). Patients with severe renal or hepatic impairment have not been studied. Given the mechanisms for clearance of vilazodone, a study in patients with severe renal impairment would not be needed, however, it would be informative to have a study in patients with severe hepatic impairment.

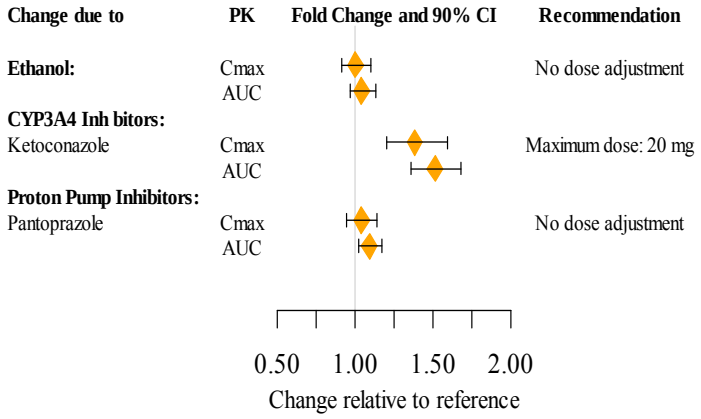
Figure 2. Impact of intrinsic factors on vilazodone PK



The data shown for elderly subjects (>65 years) are relative to subjects (24-55 years).
The data shown for female subjects are relative to male subjects.
The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.

Effect of Other Drugs: The study of several drugs in combination with vilazodone revealed a concern for pharmacokinetic interactions only with strong 3A4 inhibitors (see Figure 3 to follow; from OCP review). Based on the finding with ketoconazole, the vilazodone dose should be reduced to 20 mg when used in combination with CYP3A4 strong inhibitors. Although the interaction of vilazodone with CYP3A4 inducers has not been evaluated, it can be expected that such inducers could result in inadequate vilazodone concentrations and may diminish effectiveness. Concomitant administration of vilazodone with inhibitors of CYP2C19 and CYP2D6 is not expected to alter plasma concentrations of vilazodone. These isoforms are minor elimination pathways in the metabolism of vilazodone. *In vitro* studies have shown that CYP1A2, CYP2A6, CYP2C9 and CYP2E1 have minimal contribution to the metabolism of vilazodone.

Figure 3. Impact of other drugs on vilazodone PK



Effect of Vilazodone on Other Drugs: Coadministration of vilazodone with substrates for CYP1A2, CYP2C9, CYP3A4, or CYP2D6 is unlikely to result in clinically significant changes in the concentrations of the CYP substrates. A study in healthy subjects found that vilazodone (20 mg/day for 8-10 days) had no effect on the pharmacokinetics of caffeine, flurbiprofen, nifedipine or debrisoquine, probes for CYP1A2, CYP2C9, CYP3A4, and CYP2D6, respectively. Vilazodone coadministration with mephenytoin to healthy subjects resulted in a small (11%) increase in mephenytoin biotransformation, suggestive of a minor induction of CYP2C19. *In vitro* studies have shown that vilazodone is a moderate inhibitor of CYP2C19 and CYP2D6.

Thorough QT Study: Treatment with vilazodone does not prolong the QTc interval. The effect of vilazodone (20, 40, 60, and 80 mg) on the QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg), parallel-group, thorough QTc study in 157 healthy subjects. The study demonstrated an ability to detect small effects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10 msec for vilazodone, based on the individual correction method (QTcI). This is below the threshold for clinical concern. However, it is unknown whether 80 mg is adequate to represent a high clinical exposure condition.

5.0 CLINICAL DATA

5.1 Efficacy Data

Phase II Dose Finding Trials

Five dose-finding trials were conducted as part of the Phase II program for vilazodone. Three of these trials were of flexible dose design (244, 245, and 247) and two were of fixed dose design (246 and 248). These were all double-blind, randomized, placebo-controlled, 8-week, parallel group trials in outpatients meeting DSM-IV criteria for MDD. The HAM-D-17 was the primary efficacy assessment and change from baseline to endpoint on the HAM-D-17 total score was the primary endpoint in all five trials. Three of these trials included an active comparator for assay sensitivity. Dosing in these trials was as follows:

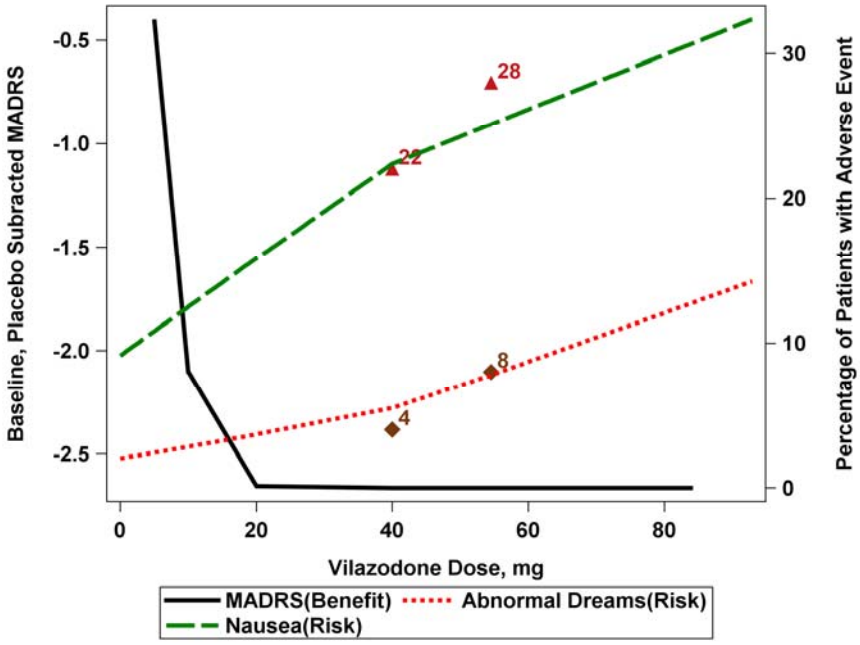
Table 2: Dosing in Phase II Dose-Finding Trials					
Trial Number	Vilazodone Dosing (mg/day)				Active Comparators (mg/day)
	Flexible-Dose Trials	Fixed-Dose Trials			
		5	10	20	
244	20-100				Fluoxetine 20
245	10-20; 40-60-; 80-100				Fluoxetine 20
246	---		X	X	Citalopram 20
247	5-20				---
248	---	X	X	X	---

In none of these five trials was there a significant finding of superiority for any of the vilazodone trial arms vs. placebo on the primary endpoint, nor were any of the three active comparator arms shown to be superior to placebo on the primary endpoint. Thus, the three trials that included active control arms were judged to be "failed" trials, and the two vilazodone alone trials were judged to be "negative" trials. Although these trials were either failed or negative on the primary endpoint, the two fixed dose trials did reveal findings on the MADRS, a secondary endpoint, that were at least suggestive of efficacy at the 20 mg/day dose for vilazodone. Both trials included substantial sample sizes, i.e., about 120 per arm for study 246 and about 130 per arm for study 248. The efficacy data for the MADRS total score are summarized in Table 3:

Table 3: Summary of Efficacy Results for Fixed Dose Phase 2 Trials on MADRS (Difference between vilazodone and placebo in least square mean change from baseline using an LOCF approach)			
Trial	Dose	Difference (Vilazodone-Pbo)	P-Value
246	10	-2.3	P=0.123
	20	-2.8	P=0.059
248	5	-0.4	P=0.725
	10	-1.9	P=0.158
	20	-2.5	P=0.062

The phase 2 trials also revealed a dose response for adverse events within this broad vilazodone dose range, with increasingly poor tolerability as the dose was pushed above 40 mg/day. Figure 4 (from the OCP review) depicts the dose-MADRS and AE relationships in these phase 2 trials. The depression symptoms decrease with increasing dose. Doses beyond 20 mg do not offer additional reduction in MADRS. However, certain AEs, e.g., abnormal dreams and nausea, increase with doses between 5 mg – 80 mg.

Figure 4. Dose response findings for efficacy and selected adverse events in phase 2 trials for vilazodone.



Phase III Efficacy Trials

Two nearly identical efficacy trials were conducted in the Phase 3 program for vilazodone (Studies 04 and 07). These were multicenter (all US sites), randomized, double-blind, parallel group, placebo-controlled, short-term (8-week) trials of vilazodone in adult patients (ages 18 to 70) meeting DSM-IV-TR criteria for MDD, single episode or recurrent. Patients were required to have at screening and baseline visits a HAM-D score of $\geq$ 22 on the first 17 items of the 21 item HAM-D, and a HAM-D item 1 (depressed mood) score of $\geq$ 2. Both studies included only a single fixed dose of 40 mg/day. Also in Study 04, patients who could not tolerate the 40 mg dose could be maintained on 20 mg/day. Randomization was 1:1 vilazodone 40 mg/day vs. placebo in both studies. Vilazodone was initiated at 10 mg/day for 7 days, then increased to 20 mg/day for 7 days, and maintained at 40 mg/day for weeks 3 through 8. Vilazodone was taken with food in both studies 04 and 07. The 40 mg/day dose was selected based in part on the finding in the phase 2 trials that 20 mg/day appeared to be on the margin of an effective dose range and the PET study showing that 40 mg/day is required to have any significant occupancy at the 5HT1A receptor. The MADRS was the primary efficacy assessment, and was conducted at baseline and weeks 1, 2, 4, 6, and 8. The primary endpoint was change from baseline to week 8 on the MADRS total score. The primary analysis was analysis of covariance (last observation carried forward) for a modified intent-to-treat (ITT) population. These were the patients who took at least one dose of their assigned treatment and who had baseline and at least one follow-up efficacy assessment. CGI-I and CGI-S were included among several secondary endpoints.

CLDA-07-DP-02 (Study 7): This multicenter (15 sites) US study compared vilazodone 40 mg/day vs placebo (1:1). There were about 230 patients per group (ITT). There were about 19% dropouts (roughly the same for both groups). Placebo had a higher % dropout for lack of efficacy and a lower % dropout for AEs, compared to vilazodone. The mean age for the sample was 42 years and the female:male ratio was 56%:44%. The mean baseline MADRS total score was 32, and the least square mean changes from baseline for MADRS to week 8 were: -10.8 (pbo) and -13.3 (vilazodone). The difference between groups in change from baseline was -2.5 (SE=0.96; 95% CI=-4.4, -0.6; p=0.009). A mixed-effects model for repeated measures (MMRM) analysis also favored vilazodone vs. placebo, as did analyses of CGI-S and CGI-I.

GNSC-04-DP-02 (Study 4): This multicenter (18 sites) US study compared vilazodone 40 mg/day vs placebo (1:1). Patients who could not tolerate the 40 mg dose could be reduced to 20 mg/day. There were about 204 patients per group (ITT). There were about 25% dropouts (roughly the same for both groups). Placebo had a higher % dropout for lack of efficacy and a lower % dropout for AEs, compared to vilazodone. The mean age for the sample was 40 years and the female:male ratio was 63%:37%. The mean baseline MADRS total score was 31, and the least square mean changes from baseline for MADRS to week 8 were: -9.7 (pbo) and -12.9 (vilazodone). The difference between groups in change from baseline was -3.2 (SE=0.99; 95% CI=-5.1, -1.2; p=0.001). A mixed-effects model for repeated measures (MMRM) analysis also favored vilazodone vs. placebo, as did analyses of CGI-S and CGI-I.

Forty-one patients were maintained on the middle dose due to reasons of intolerability, i.e., 20 mg in the vilazodone group and 2 placebo pills for the placebo group. There were 28 such patients in the vilazodone group and 13 in the placebo group. Thirteen of these patients completed the study, i.e., 6 on vilazodone and 5 on placebo. The drug minus placebo difference in least square mean change from baseline on the MADRS total score was -4.3 (95% CI -11.6,2.9; P=0.23).

Onset of Effect: FDA conducted mixed model repeated measures (MMRM) analyses for trials 7 and 4 as sensitivity analyses. These analyses provide results by treatment visit over the course of these 8-week trials, as illustrated in Table 4:

Table 4: Time of Onset of Statistically Significant Treatment Effect in Trials 7 and 4 (Difference between drug and placebo in change from baseline in MADRS total score, based on MMRM Analyses)

	Trial 7		**Trial 4**	
Visit Week	**Difference**	**P-Value**	**Difference**	**P-Value**
1	**-0.4**	**P=0.347**	**-1.7**	**P=0.0001**
2	**-1.0**	**P=0.087**	**-1.7**	**P=0.0063**
4	**-1.6**	**P=0.050**	**-2.9**	**P=0.0005**
6	**-2.3**	**P=0.017**	**-4.1**	**P<0.0001**
8	**-2.9**	**P=0.006**	**-3.6**	**P=0.0007**

Whether or not the nominally statistically significant vilazodone-placebo treatment differences observed at these earlier time points (week 4 for Trial 7 and week 1 for Trial 4) represent clinically relevant treatment effects is unknown.

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

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

-Efficacy Conclusions: I agree with Drs. Dinh, Lindberg, and Levin that the sponsor has demonstrated efficacy for vilazodone in the treatment of MDD at a dose of 40 mg/day. The sponsor has not conducted a maintenance study in MDD, but they have committed to conducting such a study. In addition, they have committed to conducting a pediatric MDD study (ages 7-17), and a study at 20 mg in adults.

Genetic Data

Genotype data were available for assessment of the relationships between genetic variations in CYP2C19, CYP2D6, and ACE with vilazodone response in the two phase 3 studies. There were no meaningful associations with MADRS by responder analyses or change at 8 weeks. There were also no robust associations with discontinuation rates or failure to reach target dose that could explain the similar responses in CYP2C19 UMs and PMs. Genotype data were not available for all pivotal studies in which DNA was collected. Given the complicated vilazodone metabolic pathway, it is uncertain whether genetic variation on pharmacokinetic-related genes would likely result in clinically meaningful differences in either response or adverse events.

5.2 Safety Data

The development program for vilazodone in MDD included data from 24 phase 1 studies, 5 phase 2 studies, and 3 phase 3 studies, all in adults. These 32 studies included a total of 2898 adult subjects exposed to one or more doses of vilazodone. The 24 phase 1 program involved 721 subjects exposed to vilazodone doses ranging from 1 to 80 mg in single and repeat dose studies. FDA's safety review focused primarily on the 8 phase 2-3 studies, involving 2177 patients exposed to vilazodone. Seven of these were placebo-controlled, 8-week studies that included 1578 patients with MDD exposed to vilazodone. The eighth study was an open label study involving 599 patients exposed to vilazodone for up to one year. Overall, the vilazodone exposure was 552 subject-years. The phase 2-3 studies included only 37 patients $\geq$ 65 years old and only 272 in the 55 to 64 year old age range. There were no pediatric patients exposed to vilazodone in this program.

Deaths: There were 3 deaths in the development program, including a homicide in a phase 1 study, and 2 suicides in later studies. Neither suicide occurred in a patient exposed to vilazodone.

Nonfatal Serious Adverse Events (SAEs): Overall, 81 patients experienced a nonfatal SAE, including 5 in phase 1 studies and 76 in phase 2-3 studies.
-Phase 1: Of these 5 patients with SAEs, 4 occurred in vilazodone patients, and one in an active control patient. Of the 4 vilazodone events, 2 were psychiatric (1 occurred 5 days after stopping

drug), 1 was a fracture, and 1 was a seizure, possibly related to vasovagal syncope occurring during a blood draw. The other psychiatric event may have been drug-related, however, it was not clear that this patient was actually a "healthy volunteer". Overall, the proportion of SAEs was similarly low in vilazodone [4/721(0.6%)] and placebo patients [0/132(0%)].
-Phase 2: There were 37 patients with SAEs in the phase 2 program, including 21 vilazodone patients, 13 placebo patients, and 3 active control patients. Of the 21 events in vilazodone patients, 6 were psychiatric, 5 were "pregnancy", 1 was "medication missing", and the remaining 9 were isolated events that are all common background events: diarrhea; hypertension; tremor, migraine; TIA; fracture; atrial fibrillation; cervicitis; pneumonia. Diarrhea and tremor are established adverse reactions with vilazodone; the remaining 7 events were not, in view, plausibly drug-related. Overall, the proportion of SAEs was similar in vilazodone [21/1137(1.8%)] and placebo patients [13/562(2.3%)]. There was a similar broad scattering of events among vilazodone and placebo patients, with no pattern implicating vilazodone as a cause of any other than the two already established events.
-Phase 3 Controlled Trials: There were 16 patients with SAEs in the two controlled trials in the phase 3 program, including 9 in vilazodone patients and 7 in placebo patients. Of the 9 events in vilazodone patients, 2 were psychiatric and 7 were isolated common background events: prostate cancer; concussion; lymphoma; CAD; pleural effusion; chest pain; and cholecyctitisis, none of which were plausibly drug-related, in my view. Overall, the proportion of SAEs was similar in vilazodone [9/436(2.0%)] and placebo patients [7/433(1.6%)]. There was a similar broad scattering of events among vilazodone and placebo patients, with no pattern implicating vilazodone as a cause of any of the SAEs in these 2 trials.
-Phase 3 Open Label Trial: There were 23 patients with SAEs in the open label phase 3 trial. Three of these were psychiatric events, and the remaining covered the spectrum of non-psychiatric events. With the exception of 2 instances of pneumonia, these were isolated, common background events, with no pattern implicating vilazodone as a cause for any of these.

These events are difficult to assess for causality. Overall, however, for the phase 2-3 studies, the proportions of patients experiencing SAEs appeared to be similar for vilazodone and placebo patients. Many of the SAEs were psychiatric events that likely represented worsening of the underlying condition being treated, and are expected in any psychiatric drug development program. The others were common background events, with no pattern of findings suggesting any particular event was more common in patients exposed to vilazodone than those exposed to placebo.

Dropouts for Adverse Events: In the placebo controlled trials with vilazodone, there was no single adverse event leading to discontinuation in > 1% of patients. Approximately 7% of vilazodone-exposed patients discontinued due to an adverse event compared to 3% of placebo-exposed patients. The most common adverse events leading to discontinuation were gastrointestinal, psychiatric, and neurological.

Predicted Adverse Events: Given that vilazodone is an SSRI, certain adverse events might be predicted, and several of these were observed:
-Serotonin Syndrome: The database was searched for terms suggestive of possible serotonin toxicity. Two subjects were identified with such events, including one patient in the long-term

open label phase 3 study. This patient took an overdose of approximately 240 mg of vilazodone. The other patient had received a vilazodone dose of 80 mg in a phase 2 study.
-Mania/Hypomania: A search of the database discovered 6 patients with likely treatment-emergent mania or hypomania, including 5 taking vilazodone and 1 taking placebo.
-Bleeding: Although bleeding events were identified in the vilazodone database, the proportions of patients experiencing such events were similar in vilazodone and placebo groups, i.e., approximately 3% for each.

Common Adverse Events: The following table (Table 5), derived from a pooling of the two phase 3 trials, includes adverse events occurring at a rate of at least 5% on vilazodone and having a rate at least twice the placebo rate, i.e., those FDA considers common and drug-related.

Table 5: Common and Drug-Related Adverse Events

Adverse Event Term	Vilazodone 40 mg	Placebo
Diarrhea	**28%**	**9%**
Nausea	**23%**	**5%**
Vomiting	**5%**	**1%**
Insomnia	**6%**	**2%**

Additional adverse events identified from this pooling as having a rate of at least 2% and at least twice the placebo rate included the following: gastroenteritis, paresthesia, tremor, abnormal dreams, restlessness, libido decreased, orgasm abnormal, delayed ejaculation, erectile dysfunction, feeling jittery, palpitations, and increased appetite. There is strong evidence for dose-relatedness for many of the common adverse events, with doses above 40 mg being poorly tolerated for most patients.

Labs, Vital Signs, Weight, ECGs: Vilazodone was not associated with any clear finding of drug-related changes in laboratory parameters, vital signs, or weight in the placebo-controlled trials. Laboratory testing included routine serum chemistries, thyroid testing, routine hematology testing, and urinalysis. Vital signs included blood pressure, pulse, respiratory rate, and ECGs. A thorough QT study with vilazodone did not reveal QT prolongation or any other important changes in ECG parameters.

Ophthalmological Findings: Concern about ophthalmological toxicity with vilazodone was initially based on a finding of transient corneal opacities in a dog study. Longer-term animal studies did not, however, confirm the early signal for corneal pathology. Thus, there was no confirmed signal for corneal pathology in animal studies, and never even a hint of cataract formation in animals. Nevertheless, based on the early animal findings, certain human studies included various ophthalmologic evaluations, i.e., slit lamp exams, dilated fundoscopy, tests of visual acuity, intraocular pressure, and Schirmer's test for decreased lacrimation. These tests were done only in the 5 phase 2 studies and some in the uncontrolled, longer-term phase 3 study.

The only clear finding from the extensive exams in the phase 2 studies was a slight decrease in tear production based on results of Schirmer testing, and this was the likely explanation for at least some of the reports of blurred vision and the few reports of corneal abnormalities. The small number of reports of retinal or vitreous findings in these phase 2 studies were not

suggestive of any drug related problem in these areas. A question had been raised in a 5-7-01 review by our ophthalmological consultant, Dr. Wiley Chambers, regarding a possible signal for treatment-emergent cataract formation from 2 of the phase 2 studies, however, in retrospect, Dr. Chambers has now acknowledged that the actual increase in cataracts was observed in the active control arm, while the vilazodone arms had cataract findings similar to the placebo arm.

Eye-related adverse events for the year-long open label study included dry eye (4.7%) and blurred vision (4.0%), and these were like related to the dry eye problem detected in phase 2 studies. Of interest, these problems did not emerge as drug-related in the 2 phase 3 studies. There were other much less common ophthalmological adverse events reported in this open label study, but with a pattern and frequency consistent with the background rate observed in this population. The only other finding of interest in this open label study was a 13% rate of cataract progression over 1 year, i.e., detectable worsening of existing cataracts. Dr. Chambers considered this progression rate somewhat high, but it is hard to interpret in the absence of a control group. On the other hand, we did find a reference for a study that used an LOCSII approach at 6-month intervals to assess the rate of progression for patients with cataracts (LOCSII was also used in the 52-week vilazodone study). After 6 months, worsening could be detected in 38% of patients with nuclear cataracts and 34% of patients with cortical cataracts.[1] Thus, the 13% rate over 1 year observed in the 52-week vilazodone study does not seem at all unexpected, in fact, seems low. There were 4 patients in the 52-week vilazodone study who had new lens changes compared to apparently normal lenses at baseline. Using a denominator of 110 (this was the number of patients who had slit lamp exams at both baseline and 52 weeks) yields a 1-year rate of new cataract occurrence of roughly 4%. Unfortunately, we don't have an age-adjusted background rate of new cataract detection to compare this to. While this may simply represent the background rate, a conservative approach would be to mention in labeling cataracts as a possible adverse reaction. The sponsor has reluctantly accepted this approach.

Dr. Chambers, in his final consult on this NDA (dated 1-7-2011), indicates that the sponsor has adequately assessed the ophthalmological safety profile of vilazodone. He concludes that the dry eye observed with vilazodone is likely drug-related. He notes what he believes is a somewhat high rate of cataract progression observed in the year-long study, but acknowledges the difficulty in interpreting this finding in the absence of a control group. He further notes that a very long-term controlled trial would be needed to determine whether or not cataract induction and/or progression is associated with vilazodone use, but stops short of suggesting that we require such a study post-approval. He further indicates that the ophthalmological risks can be managed through labeling. He has not, however, suggested any specific labeling. Dr. Levin, the clinical team leader, in his supervisory memo (dated 1-5-2011), has recommended that we require warning language for cataracts, and that we require an 18-month active controlled trial to assess for cataract induction and/or progression.

Comment: I think that the 2 findings of concern, i.e., dry eyes and possible cataract formation, can be noted in the other adverse reactions section of labeling. As noted, however, I think the risk for cataract formation is remote and the changes observed in the 52-week study likely

[1] Benjamin V, Datiles MB, and Lasa SM. Senile cataract progression studies using the lens opacities classification system II. Investigative Ophthalmology & Visual Science 1993;34:2138-2141.

represent the background rate. The dry eyes problem, although likely real, seems to rather minor and did not emerge as drug related in the phase 3 trials. The cataract issue cannot be further assessed without a large, long-term controlled trial. I'm not optimistic that such a study can or will ever be done, and even if done, can be easily interpreted, and, therefore, I don't think there is any justification to ask for such a study. I have discussed Dr. Levin's concerns with him, and in light of the fact that there was no signal for cataract induction from the phase 2 studies and also Dr. Chamber's current views on the findings overall, he has expressed agreement that neither strong labeling nor a phase 4 study is needed regarding the cataract issue. Thus, there is agreement that the term "cataract" can be added to the terms "dry eye and blurred vision" in the Other Events table, under Adverse Reactions.

Sexual Dysfunction: Other SSRIs have been shown to cause sexual dysfunction, and adverse event reporting for vilazodone provides fairly convincing evidence for sexual dysfunction with this drug as well. The sponsor had collected data using specific sexual function scales (ASEX and CSFQ) in 2 of its trials, however, the results were quite inconsistent, showing worsening on some measures and improvement on others. (b) (4) The sponsor had also conducted a phase 1 study assessing the effects of vilazodone on ejaculatory latency. Although that study had fluoxetine as an active control, it was not able to detect a drug/placebo difference for fluoxetine on time to ejaculation. Therefore, the failure to detect a drug/placebo difference for vilazodone on time to ejaculation is uninterpretable.

Pregnancy and Nursing Mothers: There are no controlled human data regarding vilazodone use during pregnancy, and it should be used only if the potential benefits outweigh the potential risks. Similarly, there are no human data regarding vilazodone concentrations in breast milk. Women should breast feed only if the potential benefits outweigh the potential risks. Vilazodone will also receive the standard labeling language regarding possible neonatal complications associated with use of serotonergic antidepressants late in the third trimester.

Pediatric Patients: The safety and effectiveness of vilazodone have not been evaluated in pediatric patients.

Drug Abuse and Dependence: Vilazodone is not a controlled substance. Animal studies did not reveal abuse or dependence potential, however, its abuse potential has not been systematically evaluated in humans. A 1-5-11 memo from the Controlled Substances Staff agrees with our view that vilazodone has a low potential for abuse.

Overdosage: Overdose experience with vilazodone is limited to observations in 5 patients who received doses in the range of 200 to 280 mg. Clinical findings included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation.

Other Safety Issues for Labeling: Although no signal for excess suicidal ideation or behavior was observed in the development program for vilazodone, as an antidepressant, it is expected to have this risk, and will have a box warning in its label for suicidality. Given the finding that

vilazodone's pharmacological profile suggests that it has a prominent SSRI effect, it is expected to have the potential for other typical SSRI risks, including serotonin syndrome or NMS-like reactions, abnormal bleeding, activation of mania, discontinuation symptoms, hyponatremia, and seizures, and will have warning language for all of these risks in its label. Given the concern for serotonin syndrome, vilazodone will need to be used cautiously with other drugs having serotonergic effects, including other SSRIs, SNRIs, triptans, tramadol, buspirone, and tryptophan products. Given the concern for bleeding, vilazodone will need to be used cautiously with aspirin or other NSAIDS, or with warfarin therapy or other anticoagulation drugs. It will also have a contraindication for use with MAOIs. The sponsor has not done a particularly good exploration of discontinuation symptoms with vilazodone. Given its SSRI mechanism, it can be expected to have discontinuation symptoms and will have the standard language regarding discontinuation, i.e., a need to taper. The sponsor can look at discontinuation more systematically in the maintenance study and in the lower dose study they will be doing post-approval.

Conclusions Regarding Safety: Vilazodone has an adverse event profile similar to that seen for other SSRIs. I think the sponsor has adequately characterized this profile, and I agree with Drs. Lindberg and Levin that this adverse event profile can be characterized in labeling.

6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

Vilazodone is another antidepressant with predominantly an SSRI profile, 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 and the agreed upon PMCs and PMRs.

8.0 CONCLUSIONS AND RECOMMENDATIONS

Major Issues in Approval Decision

Efficacy Issues
-No maintenance data: Although the sponsor has demonstrated that vilazodone is effective as an antidepressant in 8-week studies at a dose of 40 mg/day, there are no systematically collected longer-term data to address the question of maintenance efficacy. A maintenance study is needed.
-Dosing information marginal: Although the sponsor has established antidepressant efficacy for vilazodone at a dose of 40 mg/day, the evidence are weaker for lower doses. As noted, there are some data in the program that are supportive of possible efficacy for the 20 mg dose, however, more definitive data are needed regarding this issue. Doses higher than 40 mg are poorly tolerated.

Safety Issues: Vilazodone has a tolerability profile similar to that observed with other SSRIs. There were no safety problems identified that would preclude an approval for this drug.

Phase 4 Commitments and Requirements

Study of 20 mg Dose: The sponsor has committed to conducting an additional efficacy study evaluating the efficacy of vilazodone at a dose of 20 mg/day. This is important because of the dose related adverse events for vilazodone, particularly at doses of 40 mg and higher.

Maintenance Study: The sponsor has not conducted a maintenance study in MDD, but has committed to conducting such a study post-approval.

Pediatric Program: No pediatric patients were studied in the pre-approval program for vilazodone, however, the sponsor has committed to conducting a pediatric program (ages 7-17) in MDD. This would include early tolerability/PK studies and also definitive phase 3 trials in pediatric depression.

3A4 Inducer Study: CYP3A4 is the major pathway for metabolism of vilazodone, and it has been shown that strong inhibitors of 3A4 roughly double exposures to this drug. It is likely that 3A4 inducers reduce exposures to vilazodone, and it is important to have systematic data regarding this issue. The sponsor has committed to conducting a drug-drug interaction study of vilazodone with a 3A4 inducer, e.g., carbamazepine.

Severe Hepatic Impairment: Vilazodone is extensively cleared by hepatic metabolism, and hepatic impairment studies have been conducted in hepatic patients with mild and moderate impairment. Although these studies have not demonstrated any overall reduction in clearance in these patients, it would, nevertheless, be useful to obtain such information in hepatic patients with severe impairment. The sponsor has committed to conducting such a study.

PgP Interaction: Information on the effect of PgP on the pharmacokinetics of vilazodone and the effect of vilazodone on PgP was not included in this development program. This information

would be useful in fully understanding the metabolism of vilazodone, and the sponsor has committed to conducting an in vitro study to evaluate whether vilazodone is a substrate or inhibitor of PgP.

Human Metabolite M17: Because the major human metabolite M17 was not demonstrated to be present in plasma of either rats or rabbits, the embryo-fetal reproductive toxicity studies with vilazodone did not adequately assess the toxicity of M17. Consequently, we have asked the sponsor to commit to assessing the reproductive toxicity of metabolite M17 in an embryo-fetal study, if necessary. Because M17 was formed by hepatocytes isolated from rabbits, it is possible that M17 is present in plasma of rabbits treated with vilazodone. If the systemic exposure to M17 at the doses of vilazodone that were used in the original embryo-fetal study is demonstrated to be equal to or greater than the exposure in humans at the MRHD, the original rabbit study would be considered to have adequately assessed the embryo-fetal toxicity for M17. Otherwise, an embryo-fetal study in either rats or rabbits where M17 is administered by a route that will produce systemic exposure equal to or greater than the exposure in humans at the MRHD will be required. The sponsor has agreed to fully explore this issue post-approval.

Key Issues for Clinical Use of Vilazodone

Vilazodone is a new antidepressant for the treatment of MDD. If approved, it would be the first in the class to have as its prominent pharmacological characteristics both selective serotonin reuptake inhibition (SSRI) and 5-HT_{1A} partial agonism. Vilazodone's profile of adverse events is similar to that seen with other SSRIs, in particular, prominent GI adverse effects, and it is unknown whether or not it has any advantages compared to other drugs in the antidepressant class. If approved, it will have warning language in its label for serious adverse events observed with other antidepressants, including suicidal ideation and behavior, serotonin syndrome, abnormal bleeding, and activation of mania, and a contraindication for use with MAOIs. The recommended dose is 40 mg per day, and vilazodone needs to be taken with food to ensure adequate exposure. There are preliminary data suggesting that a 20 mg dose may be effective in some patients, however, more data would be needed to provide confirmation of efficacy before this lower dose could generally be recommended. Although there are no systematic data regarding longer-term efficacy with vilazodone, it is standard practice with antidepressants to continue patients who have improved during short-term treatment. It takes about 3 days to reach steady state concentrations with vilazodone, and when stopping therapy, the dose should be tapered gradually. No dose adjustment is needed based on age, gender, renal, or hepatic impairment. It is recommended that the vilazodone dose be reduced to 20 mg when taken with strong CYP3A4 inhibitors, e.g., ketoconazole. Vilazodone is not expected to have important effects on the clearance of other drugs that are CYP substrates.

Recommendation

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

cc:
Orig NDA 22-567
ODE-I/RTemple/EUnger
HFD-130/TLaughren/MMathis/RLevin/CLindberg/WBender
DOC: Laughren_Vilazodone_MDD_NDA22567_AP Memo.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 P LAUGHREN
01/18/2011