Vilazodone: Clinical Basis for the US Food and Drug Administration's Approval of a New Antidepressant

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ABSTRACT

Objective: Vilazodone was recently approved by the US Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD). The purpose of this review is to summarize the FDA's approach to its review of the clinical pharmacology and the clinical efficacy and safety data for this new drug application, important issues in its decision-making, and its conclusions.

Data Sources: The data sources for this review were the original raw data sets for all clinical trials included in the development program for vilazodone, as well as the sponsor's original analyses of these data.

Study Selection: Data were available from 24 human trials involving vilazodone, and included a total of 2,898 human subjects exposed to 1 or more doses of this drug.

Data Extraction: The FDA had access to original raw data sets for these trials.

Results: Vilazodone is effective in treating MDD at a dose of 40 mg/d, but it needs to be incrementally adjusted to this dose to minimize gastrointestinal symptoms. It needs to be taken with food to ensure adequate plasma concentrations. Vilazodone's profile of adverse events is similar to that seen with selective serotonin reuptake inhibitors. No dose adjustment is needed based on age, gender, or renal or hepatic impairment. It is recommended that the vilazodone dose be reduced to 20 mg when it is taken with strong cytochrome P450 (CYP) 3A4 inhibitors, eg, ketoconazole. Vilazodone is not expected to have important effects on the clearance of other drugs that are cytochrome P450 substrates.

Conclusions: Vilazodone is a new treatment for MDD, but it is unknown whether it has any advantages compared to other drugs in the antidepressant class.

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Vilazodone was approved by the US Food and Drug Administration (FDA) on January 21, 2011, for the treatment of major depressive disorder (MDD). It is an indolalkylamine that binds with high affinity to the serotonin reuptake site (Ki = 0.1 nM) but not to the norepinephrine (Ki = 56 nM) or dopamine (Ki = 37 nM) reuptake sites. It potently and selectively inhibits reuptake of serotonin (IC_{50} = 1.6 nM); ie, it is a selective serotonin (5-HT) reuptake inhibitor (SSRI). Vilazodone also binds with high affinity to 5-HT_{1A} receptors and is a 5-HT_{1A} receptor partial agonist at this receptor (IC_{50} = 2.1 nM). As is the case for all antidepressants, the mechanism of vilazodone's antidepressant effect is not known but is thought to be related to enhancement of serotonergic activity in the central nervous system through its SSRI effect. Although vilazodone is a partial agonist at 5-HT_{1A} receptors, the net effect of this activity on serotonergic transmission is not known. Whether the partial agonist activity enhances vilazodone's antidepressant effect has not been explored, eg, by studying vilazodone in nonresponders to SSRIs.

This article summarizes selected aspects of the FDA's review of the vilazodone New Drug Application, particularly the clinical pharmacology and the clinical efficacy and safety data. It discusses data that were important to decisions made during drug development for vilazodone and data important to the FDA's approval decision and its determination of how best to characterize the drug in labeling and of what additional data to obtain postmarketing. The primary source documents for this article are the FDA's reviews and memoranda for the vilazodone New Drug Application, and these can be accessed for more detailed information at the FDA's Web site.[1]

PHARMACOKINETIC PROFILE OF VILAZODONE

Basic Pharmacokinetics of Vilazodone

Peak plasma vilazodone concentrations are reached at about 4 to 5 hours after dosing when the drug is taken with food. Vilazodone's elimination half-life is about 25 hours, and steady state is achieved in about 3 days. Vilazodone has an accumulation factor of about 1.8; ie, peak plasma vilazodone concentration at steady state is 1.8 times that observed after a single dose. Vilazodone pharmacokinetics show a prominent food effect; ie, peak plasma vilazodone concentration and area under the concentration time curve are increased about 2-fold when the drug is taken with food, even a light meal. For this reason, vilazodone should be taken with food to ensure adequate plasma concentrations. Vilazodone is extensively metabolized through cytochrome P450 (CYP) and non-CYP (probably by carboxylesterase) pathways, with only ~3% excreted unchanged in the urine and feces. CYP3A contributes significantly to the metabolism via CYP pathways; CYP2C19 and 2D6 pathways have a minor role in

vilazodone's metabolism. Genetic variation in CYP2C19 and 2D6 has not been observed to affect vilazodone's plasma levels significantly. Vilazodone has no active metabolites; ie, its clinical effects are thought to be due primarily to the parent drug.

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

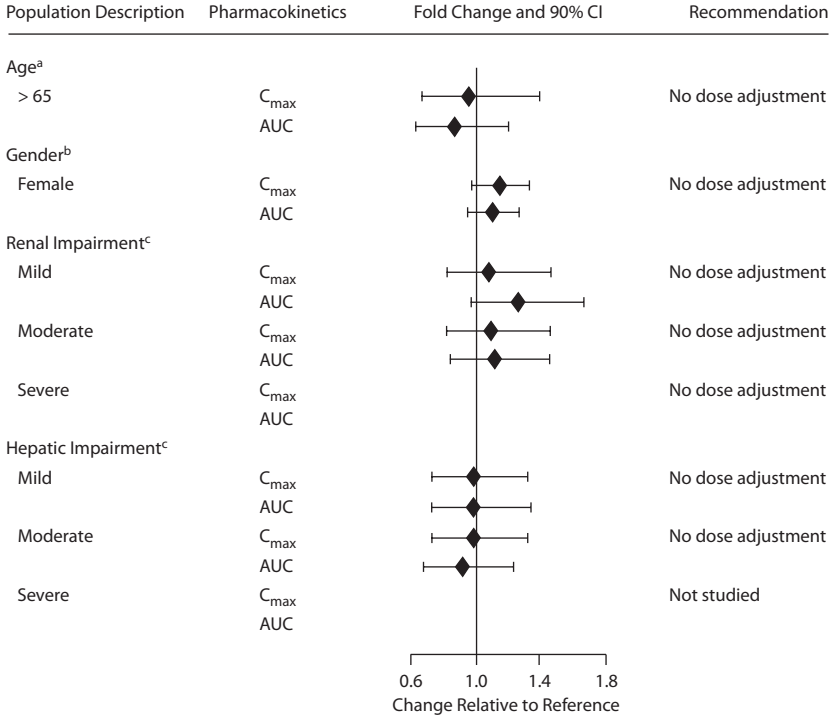
Effect of patient characteristics on vilazodone (intrinsic factors). The studies[1] of various intrinsic factors on vilazodone's pharmacokinetics suggest that no dosage adjustment is needed based on age, gender, or the presence of mild to moderate hepatic impairment (Figure 1). Of course, factors other than pharmacokinetics may necessitate more cautious dosing in certain populations, eg, the elderly. Patients with severe hepatic impairment have not yet been studied; however, the pharmaceutical sponsor has agreed to perform a pharmacokinetic study as a postmarketing commitment. Because vilazodone is extensively metabolized and not renally excreted, renal impairment is not expected to have an important effect on vilazodone's clearance, and no effect was observed in patients with mild to moderate renal impairment.

Effects of other drugs on vilazodone (extrinsic factors). In vitro studies[1] of several drugs in combination with vilazodone revealed a significant pharmacokinetic interaction only with a strong CYP3A4 inhibitor (Figure 2), which increased plasma concentrations by about 50%. On the basis of the finding with ketoconazole, the vilazodone dose should be reduced to 20 mg when it is used in combination with strong CYP3A4 inhibitors. Although the interaction of vilazodone with CYP3A4 inducers has not been evaluated, it can be expected that such inducers could result in decreased vilazodone concentrations and possible diminished effectiveness. The CYP2C19 and CYP2D6 isoenzymes are minor elimination pathways in the metabolism of vilazodone, and concomitant administration of inhibitors of these isoenzymes is not thought to be important. In vitro studies have shown that CYP1A2, CYP2A6, CYP2C9, and

Clinical Points

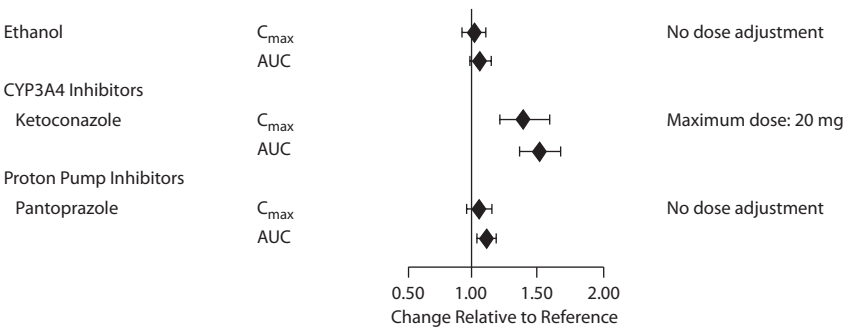
- Vilazodone is a new antidepressant recently approved by the US Food and Drug Administration for the treatment of major depressive disorder.
- Although its prominent pharmacologic effects include both selective serotonin (5-HT) reuptake inhibition and partial agonism at 5-HT_{1A} receptors, its clinical profile is most similar to other selective serotonin reuptake inhibitors.
- It is unknown whether vilazodone has any advantages compared to other drugs in the antidepressant class.

Figure 1. Impact of Intrinsic Factors on Vilazodone Pharmacokinetics



[a]The data shown for elderly subjects (> 65 years) are relative to younger subjects (24–55 years).
[b]The data shown for female subjects are relative to male subjects.
[c]The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.
Abbreviations: AUC = area under the concentration time curve, C_{max} = peak plasma vilazodone concentration.

Figure 2. Impact of Other Drugs on Vilazodone Pharmacokinetics



Abbreviations: AUC = area under the concentration time curve, C_{max} = peak plasma vilazodone concentration.

Table 1. Vilazodone Dosages in Phase 2 Dose-Finding Trials

Trial No.	No. of Subjects Per Arm, Mean	Flexible-Dose Trials, mg/d	Fixed-Dose Trials, mg/d			Active Comparator, mg/d
			5	10	20	
244	90	20–100				Fluoxetine, 20
245	97	10–20, 40–60, 80–100				Fluoxetine, 20
246	122	…		X	X	Citalopram, 20
247	110	5–20				None
248	133	…	X	X	X	None

CYP2E1 make minimal contributions to the metabolism of vilazodone.

Effect of Vilazodone on Other Drugs

In vitro data suggest that coadministration of vilazodone with substrates for CYP1A2, CYP2C9, CYP3A4, or CYP2D6 is unlikely to result in clinically significant changes in the concentrations of substrates for these enzymes.

PHASE 2 DOSE-FINDING TRIALS

Five trials[1] using doses from 5 to 100 mg/d were conducted as part of the phase 2 program for vilazodone, but only 2 used fixed-dose designs (trials 246 and 248) that were informative about dose-response. The other 3 used flexible titration designs (trials 244, 245, and 247). All were double-blind, randomized, placebo-controlled, 8-week, parallel group trials in outpatients meeting *DSM-IV* criteria for MDD and had sample sizes ranging from 86 to 140 patients per treatment arm. The Hamilton Depression Rating Scale (HDRS) was the primary efficacy measure in all 5 trials, and the drug effect was assessed by comparing change from baseline at week 8 on the sum of the scores for the first 17 items (HDRS) in the drug and placebo groups. Missing data were imputed using a last observation carried forward (LOCF) approach. Three of these trials included an active comparator to assess for assay sensitivity (ability of the trial to detect the treatment effect of a drug known to be effective). Dosing in these trials is provided in Table 1.

None of the 5 trials demonstrated a statistically significant treatment effect of vilazodone on its primary endpoint. Moreover, none of the 3 active comparator trials showed the comparator to be statistically distinguishable from placebo, indicating that these trials lacked assay sensitivity for the primary trial endpoint (HDRS) and were uninformative about vilazodone's effect on that endpoint. The 2 trials lacking an active control group could be considered "negative" trials for vilazodone, but this is not certain in the absence of an active control to confirm assay sensitivity.

Although these trials were unsuccessful on their primary endpoints, the 2 fixed-dose trials (246 and 248) showed dose responses for the difference between vilazodone and placebo on a secondary endpoint, the Montgomery-Asberg Depression Rating Scale (MADRS), suggestive of a treatment effect for the 20-mg/d vilazodone groups (the nominal unadjusted *P* values were .06 in both trials). The secondary endpoint data for the MADRS total score are summarized in Table 2.

Table 2. Summary of Efficacy Results for Fixed-Dose Phase 2 Trials on Montgomery-Asberg Depression Rating Scale[a]

Trial No.	Difference (vilazodone–placebo)	*P* Value
246		
Dose, mg/d		
10	−2.3	.12
20	−2.8	.06
248		
Dose, mg/d		
5	−0.4	.73
10	−1.9	.16
20	−2.5	.06

[a]Difference between vilazodone and placebo in least squares mean change from baseline using a last observation carried forward approach.

Overall, for these phase 2 trials, depression symptoms tended to decrease as daily doses increased to 20 mg. There was no useful information from these trials regarding dose response for efficacy at doses above 20 mg/d. The frequency of adverse events increased with dose, and doses above 40 mg/d were poorly tolerated in studies 244 and 245.

PHASE 3 EFFICACY AND SAFETY TRIALS

Two nearly identical efficacy trials[1] were conducted in the phase 3 program for vilazodone (trials 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 years) meeting *DSM-IV-TR* criteria for MDD, single episode or recurrent. Patients were required to have, at screening and baseline visits, an HDRS score of ≥ 22 on the first 17 items of the 21-item HDRS, and an HDRS item 1 (depressed mood) score of ≥ 2. Although these trials included only a single fixed dose of 40 mg/d, in trial 04, patients who did not tolerate the 40-mg dose could be maintained on 20 mg/d. Randomization was 1:1 vilazodone 40 mg/d versus placebo in both trials. Vilazodone was initiated at 10 mg/d for 7 days, then increased to 20 mg/d for 7 days, and maintained at 40 mg/d for weeks 3 through 8. Vilazodone was taken with food in both trials. Neither trial included an active comparator.

Unfortunately, there was no additional dose finding in phase 3. The rationale for the single 40-mg/d dose was based on data that were less than persuasive. The 40-mg/d dose was not specifically evaluated in the phase 2 studies, but the 20-mg/d dose appeared to be at the lower margin of efficacy. Of note, however, because the phase 2 studies with an active control group failed to demonstrate assay sensitivity, they cannot be interpreted as providing adequate assessment of the 20-mg vilazodone dose (or any dose, for that matter).

In addition, 5-HT_{1A} receptor occupancy is thought to correlate with salutary drug effects, and a positron emission tomography study[1] was conducted to assess 5-HT_{1A} receptor occupancy in vivo. There was evidence of modest receptor occupancy with 40-mg vilazodone (15%–35%) but no evidence of occupancy with 20-mg findings interpreted as supportive of the 40-mg dose. The positron emission tomography study was conducted using only single doses of

Table 3. Time of Onset of Statistically Significant Treatment Effect in Trial Numbers 07 and 04[a]

	Trial 07		Trial 04	
Visit Week	Difference	*P* Value	Difference	*P* Value
1	−0.4	.35	−1.7	.0001
2	−1.0	.09	−1.7	.0063
4	−1.6	.05	−2.9	.0005
6	−2.3	.02	−4.1	< .0001
8	−2.9	.006	−3.6	.0007

[a]Difference between drug and placebo in change from baseline in Montgomery-Asberg Depression Rating Scale total score, based on mixed-effects model for repeated-measures analyses.

vilazodone, however, and given vilazodone's relatively long elimination half-life and its accumulation ratio of 1.8, it could be argued that receptor occupancy at steady state, following repeated doses, might have been higher. Thus, neither the phase 2 studies nor the positron emission tomography study provides conclusive evidence that vilazodone at doses less than 40 mg/d are ineffective.

The MADRS was the primary efficacy assessment, and it was conducted at baseline and weeks 1, 2, 4, 6, and 8. The primary endpoint was the difference between drug and placebo in change from baseline to week 8 on the MADRS total score. The primary analysis was analysis of covariance, based on a modified intent-to-treat (ITT) population: patients who took at least 1 dose of their assigned treatment and who had baseline and at least 1 follow-up efficacy assessment. Missing data were imputed using an LOCF approach. Clinical Global Impressions-Improvement (CGI-I) and Severity of Illness (CGI-S) scales were included among several secondary endpoints.

For trial 07, there were approximately 230 patients per group in the ITT population, with approximately 19% dropouts (roughly the same for both groups). Placebo had a higher percentage dropout for lack of efficacy (15% for placebo and 6% for vilazodone) and a lower percentage dropout for adverse events (9% for placebo and 17% for vilazodone), compared to vilazodone. The mean age of the sample was 42 years, and 56% of patients were female. The mean baseline MADRS total score was 32, and the least squares mean changes from baseline to week 8 were −10.8 (placebo) and −13.3 (vilazodone). The difference between groups in change from baseline was −2.5 (standard error [SE] of the mean = 0.96; 95% confidence interval [CI], −4.4 to −0.6; $P = .009$). A mixed-effects model for repeated measures (MMRM) analysis, a widely used and generally preferred alternative to LOCF, also significantly favored vilazodone over placebo on the MADRS, as did analyses with CGI-S and CGI-I.

In trial 04, there were approximately 204 patients per group in the ITT population, with approximately 25% dropouts (roughly the same for both groups). Placebo again had a higher percentage dropout for lack of efficacy (18% for placebo and 8% for vilazodone) and a lower percentage dropout for adverse events (20% for placebo and 36% for vilazodone) compared to vilazodone. The mean age of the sample was 40 years, and 63% of patients were female. The mean baseline MADRS total score was 31, and the least squares mean changes from baseline to week 8 were −9.7 (placebo) and −12.9 (vilazodone). The difference between groups in change from baseline was −3.2 (SE = 0.99; 95% CI, −5.1 to −1.2; $P = .001$). The MMRM analysis also favored vilazodone over placebo on the MADRS, as did analyses with CGI-S and CGI-I. Forty-one patients could not be titrated to the highest dose because of intolerability, and they were maintained on the middle dose, ie, 20 mg in the vilazodone group and 1 placebo pill for the placebo group. There were 28 such patients in the vilazodone group and 13 in the placebo group. Eleven of these patients completed the study, ie, 6 took vilazodone and 5 took placebo. On the basis of an exploratory analysis of this small subgroup taking 20 mg/d, the drug minus placebo difference in least squares mean change from baseline on the MADRS total score was estimated to be −4.3 (95% CI, −11.6 to 2.9), suggesting that explorations of this dose would be worthwhile.

The MMRM analyses for trials 07 and 04 provided results (drug-placebo differences in change from baseline in MADRS total score and unadjusted *P* values) by treatment visit over the course of these 8-week trials, as illustrated in Table 3.

There have been published suggestions that vilazodone may have a rapid onset.[2,3] The available data do not support such a conclusion. First, none of the trials purporting to show an early effect included an active control. Second, the largest effects in both trials are observed only at 6 to 8 weeks, similar to what is seen with other antidepressants. Whether the statistically significant vilazodone-placebo treatment differences observed at the week-1 time point in trial 04 represent a clinically relevant treatment effect is unknown, and it is noteworthy that this finding was not replicated in trial 07.

The only longer term data were from a 1-year open-label trial that could not be interpreted because of the lack of a control group.

SAFETY FINDINGS FOR VILAZODONE

In evaluating the safety of a new drug, the FDA pays particular attention to all deaths, other serious adverse events, and adverse events occurring in patients who dropped out of a study (adverse dropouts). Serious adverse events are defined as deaths, nonfatal life-threatening adverse events, events leading to inpatient hospitalization or prolongation of a hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. The FDA relies on data derived from placebo-controlled trials to establish the common adverse event profile for a new drug. In addition, the FDA evaluates laboratory, vital sign, and electrocardiographic data and data from special studies, eg, a thorough QT study,[4] and assessments to further establish a drug's safety profile.

The development program for vilazodone in MDD included data from 24 phase 1 trials,[1] the 5 phase 2 trials[1] noted above, and 3 phase 3 trials (the 2 described

above, and a 1-year open-label trial, all in adults).[1] These 32 trials included a total of 2,898 subjects exposed to 1 or more doses of vilazodone. The 24-trial phase 1 program included 721 subjects exposed to vilazodone doses ranging from 1 to 80 mg in single- and repeat-dose trials. The FDA's safety review focused primarily on the 8 phase 2 and 3 trials, including 2,177 patients exposed to vilazodone. Seven of these were placebo-controlled, 8-week trials that included 1,578 patients with MDD exposed to vilazodone. The eighth trial was an uncontrolled, open-label trial involving 599 patients exposed to vilazodone for up to 1 year. Overall, the vilazodone exposure was 552 patient-years. The phase 2 and 3 trials included only 309 patients aged 55 years or older and only 37 patients aged 65 years and older, respectively, a common pattern but one that largely omits potentially vulnerable populations (elderly and patients with concomitant illness). There were no pediatric patients exposed to vilazodone in this program.

Deaths, Other Serious Adverse Events, and Adverse Dropouts

There were no deaths in the vilazodone program in normal subjects or patients taking vilazodone. Overall, 81 patients experienced a nonfatal serious adverse event, including 5 in phase 1 studies and 76 in phase 2 and 3 studies. These events are difficult to assess for causality. Overall, however, in the phase 2 and 3 studies, the proportions of patients experiencing nonfatal serious adverse events appeared to be similar for vilazodone and placebo patients. Many of the serious adverse events were psychiatric in nature and probably represented worsening of the underlying condition being treated; such events are expected and observed in any psychiatric drug development program. The others were common background events, such as pneumonia, prostate cancer, and cholecystitis, with no pattern of findings suggesting that any particular event was more common in patients exposed to vilazodone than in those exposed to placebo. In the placebo-controlled trials, approximately 7% of vilazodone-exposed patients discontinued because of an adverse event compared to 3% of placebo-exposed patients, although there was no single adverse event leading to discontinuation in > 1% of patients. The most common adverse events leading to discontinuation were diarrhea, nausea, palpitations, and fatigue.

Predicted Adverse Events of Special Interest

Certain adverse events are expected in SSRI-treated patients and were of particular interest in the vilazodone development program:

- Serotonin syndrome: The New Drug Application database was searched using terms suggestive of possible serotonin toxicity. Two patients were identified with such events, including 1 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 probable treatment-emergent mania or hypomania (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, ie, approximately 3% for each.

Common, Nonserious Adverse Events

On the basis of a pooling of the 2 phase 3 trials, the FDA has identified 4 adverse events that it considers common and drug-related, ie, occurring at a rate of at least 5% with vilazodone and having a rate at least twice the placebo rate. The rates for these 4 adverse events are as follows: diarrhea (28%, vilazodone vs 9%, placebo), nausea (23%, vilazodone vs 5%, placebo), vomiting (5%, vilazodone vs 1%, placebo), and insomnia (6%, vilazodone vs 2%, placebo). The gastrointestinal adverse events and insomnia tended to occur early in treatment. Additional adverse events identified from this pooling as having a rate of at least 2% and at least twice the placebo rate (an approach to judging possible causality) included the following: gastroenteritis, paresthesia, tremor, abnormal dreams, restlessness, decreased libido, abnormal orgasm, delayed ejaculation, erectile dysfunction, feeling jittery, palpitations, and increased appetite. There is strong evidence for dose relatedness for many of these common adverse events, with poor tolerability of doses above 40 mg for most patients.

Sexual Dysfunction

Other SSRIs have been shown to cause male and female sexual dysfunction, and adverse events of sexual dysfunction (decreased libido, abnormal orgasm, delayed ejaculation, erectile dysfunction, and sexual dysfunction) were reported more frequently for vilazodone compared to placebo in the phase 2 and 3 studies. The overall percentages of vilazodone-treated patients spontaneously reporting sexual dysfunction were quite low (5% or less), but such low rates are observed with all SSRIs, and it is well-recognized that reporting of sexual dysfunction is severely underreported in trials that do not devote particular attention to eliciting such effects. Indeed, such adverse events were specifically identified in the FDA's gender guidance as needing special attention, particularly in women.[5] Placebo-controlled trials comparing bupropion, a non-SSRI antidepressant, with SSRIs (either sertraline or escitalopram) that used specific approaches to elicit sexual dysfunction demonstrated a high rate of sexual dysfunction with typical SSRIs.[6,7] The pharmaceutical sponsor did collect data using specific sexual function scales (Arizona Sexual Experience Scale [ASEX] and Changes in Sexual Function Questionnaire) in 2 of its trials, but the results were inconsistent, showing worsening on some items and improvement on others, with no clear pattern of change for vilazodone compared to placebo. Unfortunately, these trials did not include an active control SSRI known to cause

dysfunction, so no evidence exists that these trials were capable of detecting such adverse events. Published articles commenting on the trial including the ASEX assessments suggested that vilazodone did not cause sexual dysfunction,[2,3] but these conclusions are not supported by the data. Without an active control that is known to cause sexual dysfunction to demonstrate assay sensitivity, the results from these trials cannot support any conclusion as to the absolute or relative effect of vilazodone on sexual function.

Laboratories, Vital Signs, Weight, Electrocardiograms

Vilazodone was not associated with any clear finding of drug-related changes in laboratory parameters, vital signs, or weight in the placebo-controlled trials.[1] Laboratory testing included routine serum chemistries, thyroid testing, routine hematology testing, urinalysis, and electrocardiograms. Vital signs included blood pressure, pulse, and respiratory rate. A thorough QT study[1] with vilazodone revealed that it does not prolong the QTc interval or cause any other important changes in electrocardiogram parameters. Vilazodone was tested in this study at doses up to 80 mg. The study demonstrated appropriate assay sensitivity, and the baseline-corrected QTc interval was < 10 milliseconds for vilazodone, below the threshold generally considered to indicate clinical concern.

Overdose

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.

Risk Information for Vilazodone's Label

Although no signal for excess suicidal ideation or behavior was observed in the development program for vilazodone, its labeling bears the box warning for suicidality, which all antidepressants have, based on findings from meta-analyses for drugs in this class.[8,9] As vilazodone's pharmacologic profile shows a prominent SSRI effect, it is expected to have the potential for other typical SSRI risks, including serotonin syndrome or neuroleptic malignant syndrome–like reactions, abnormal bleeding, activation of mania, discontinuation symptoms, hyponatremia, and seizures, and has warning language for all of these risks on its label. Given the concern for serotonin syndrome, vilazodone will need to be used cautiously with other drugs having serotonergic effects, including other SSRIs, serotonin-norepinephrine reuptake inhibitors, triptans, tramadol, buspirone, and tryptophan products. The concern for bleeding suggests that vilazodone will need to be used cautiously with aspirin or other nonsteroidal anti-inflammatory drugs, or with warfarin and other anticoagulants. It also carries a contraindication for use with monoamine oxidase inhibitors (MAOIs). There was no systematic assessment for discontinuation-emergent signs and symptoms, but given that such symptoms are expected with SSRIs, vilazodone labeling recommends tapering when it is discontinued.

Standard animal reproduction studies of vilazodone did not indicate teratogenic potential. Nevertheless, because there are no controlled human data regarding vilazodone use during pregnancy, its label advises use during pregnancy only if the potential benefits outweigh the potential risks. Similarly, because there are no human data regarding vilazodone concentrations in breast milk, women are advised to breast-feed only if the potential benefits outweigh the potential risks. Vilazodone also has standard labeling language regarding possible neonatal complications associated with use of serotonergic antidepressants late in the third trimester.

Vilazodone is not classified as a controlled substance. Animal studies did not reveal abuse or dependence potential; however, labeling acknowledges that its abuse potential has not been systematically evaluated in humans.

MAJOR ISSUES IN APPROVAL DECISION

Although the FDA was satisfied that vilazodone has been shown to be an effective antidepressant in 8-week studies at a dose of 40 mg/d, there were no systematically collected longer-term controlled data to address the question of maintenance efficacy. These data are needed, as all antidepressants are used for long-term maintenance, and are ordinarily obtained after initial approval through randomized withdrawal trials in patients successfully treated for several months. There is also a question about the optimal dose for vilazodone. Some data in the program are suggestive of efficacy for the 20-mg dose, but more definitive data are needed. This is particularly relevant given that vilazodone is to be incrementally dose adjusted to the target of 40 mg and that it is most likely some patients will not receive the 40-mg dose because of side effects, notably gastrointestinal effects. Doses higher than 40 mg are poorly tolerated, and the incidence of certain adverse events is substantial even at 40 mg. Vilazodone has a tolerability profile similar to that observed with other SSRIs, however, and there were no safety problems identified that precluded an approval for this drug.

PHASE 4 COMMITMENTS AND REQUIREMENTS

It is common for the FDA to obtain commitments from a sponsor to procure additional data for a new drug following the initial approval. In some instances, where trials involve a safety concern, such data can be required. The FDA has obtained the pharmaceutical sponsor's agreement to conduct the following studies postapproval:

- Study of 20-mg dose—A study evaluating the efficacy of vilazodone at a dose of 20 mg/d. This is important because of the dose-related adverse events for vilazodone, particularly at doses of 40 mg and higher, and the limited study of the efficacy of 20 mg/d from the phase 2 trials (expected date for final report, January 31, 2014).

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- Maintenance study—A longer term randomized withdrawal trial to assess maintenance efficacy for vilazodone in MDD (expected date for final report, January 31, 2016).
- Pediatric program—A pediatric program (ages 7–17 years) in MDD (expected date for final report, January 31, 2016).
- CYP3A4 inducer study—A drug-drug interaction study of vilazodone with a 3A4 inducer, eg, carbamazepine (expected date for final report, January 31, 2013).
- Severe hepatic impairment—A pharmacokinetic study in patients with severe hepatic impairment (expected date for final report, February 28, 2013).
- P-glycoprotein interaction—An in vitro study to evaluate whether vilazodone is a substrate or inhibitor of P-gp (expected date for final report, December 31, 2011).

LESSONS LEARNED

There are always lessons to be learned from completed drug development programs, and the vilazodone program is no exception. For vilazodone, there are 3 issues in particular that deserve comment.

Dose Response

The dose-response characterization of vilazodone might have been handled differently. It appears that the phase 2 dose-response trials were neither optimally designed nor fully utilized in the design of the phase 3 trials. Early fixed-dose trials should be the optimal source for selecting doses for subsequent studies. Only 2 of the 5 phase 2 trials, however, had fixed-dose designs. Although 2 of the remaining 3 phase 2 trials did explore doses up to 100 mg/d, the flexible-dose designs did not provide an opportunity for useful dose-response information to guide phase 3 dose selection. Nevertheless, the 2 fixed-dose phase 2 trials did provide a rationale for evaluating a dose of 40 mg/d in phase 3 trials. The other source of support for the 40-mg dose was the positron emission tomography trial; however, that trial was also not optimal, as it did not look at receptor occupancy at steady-state plasma concentrations. A steady-state approach might have been more useful given that receptor occupancy was marginal after a single dose, ie, 15%–35%, and might have been improved with the doubling of concentration at steady state. A repeat dose trial would also have provided an opportunity to explore a relationship between receptor occupancy and clinical response. In any case, although it was reasonable to study 40 mg, the phase 2 data gave no reason not to further study 20 mg (given the failure of active controls) and the sponsor missed an opportunity to definitively study the 20-mg dose by not including such an arm in these trials.

Early Onset

Recent publications have implied that vilazodone might have an early onset[2,3]; but the phase 3 trials were not designed to examine this possibility. These trials did not test hypotheses on time of onset, nor did they include other antidepressant treatment arms for comparison in time of onset. Both would have been necessary to support such a claim. In addition, it would have been necessary to replicate a finding of early onset of response.

Sexual Dysfunction

As noted, it has also been suggested that vilazodone may have advantages over other antidepressants with regard to causing sexual dysfunction.[2,3] The sponsor's goal was to demonstrate *no difference* for vilazodone versus placebo on sexual dysfunction. Importantly, the inability to find a statistically significant difference between the vilazodone and placebo groups on sexual dysfunction would not prove that there is no difference. A true demonstration of "no difference" would require a "noninferiority" approach,[10] and possibly a larger sample size. In this case, a study intended to demonstrate "no difference" would also need to include a group randomized to a drug that is known to cause sexual dysfunction (ie, an active control) in order to establish assay sensitivity, the ability to detect sexual dysfunction. The larger sample size might have been accomplished by a prior hypothesis-testing strategy involving pooling data for the 2 phase 3 trials. All of this ideally would have involved prior discussions with the Division of Psychiatry Products on how best to plan the studies to accomplish this important goal.

CLINICAL SUMMARY

Vilazodone was recently approved by the FDA for the treatment of MDD. Vilazodone is available in 10-, 20- and 40-mg immediate release tablets. The recommended dose is 40 mg per day, and vilazodone needs to be taken with food to ensure adequate plasma concentrations. The dose is incrementally adjusted to 40 mg, ie, 10 mg once daily for 7 days, then 20 mg once daily for the next 7 days, and finally 40 mg once daily, to allow for adaptation to gastrointestinal symptoms. Although there are as yet no randomized controlled trials that demonstrate longer term efficacy with vilazodone, it is standard practice with antidepressants to continue treatment of patients who have improved during short-term treatment. Vilazodone's profile of adverse events is similar to that seen with other SSRIs, and it is unknown whether it has any advantages compared to other drugs in the antidepressant class. Consistent with the FDA's practice of including class effects in labeling, vilazodone has warning language in its label for serious adverse events observed with other antidepressants, including suicidal ideation and behavior, serotonin syndrome, abnormal bleeding, activation of mania, and a contraindication for use with MAOIs. It takes about 3 days for vilazodone to reach steady-state concentrations, and when stopping therapy, the dose should be tapered gradually to avoid discontinuation symptoms. Pharmacokinetic findings suggest that dose adjustment is not needed based on age, gender, or renal or hepatic impairment. Other factors, however, may, of course, lead to more cautious

dosing in certain patients. It is recommended that the vilazodone dose be reduced to 20 mg when it is taken with strong CYP3A4 inhibitors, eg, ketoconazole. Vilazodone is not expected to have important effects on the clearance of other drugs that are CYP450 substrates.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), fluoxetine (Prozac and others), ketoconazole (Ketozole, Nizoral, and others), pantoprazole (Protonix and others), tramadol (Ultram, Ryzolt, and others), vilazodone (Viibryd), warfarin (Coumadin, Jantoven, and others).

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